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(54) **HIGH-THROUGHPUT DIAGNOSTIC ASSAY FOR THE HUMAN VIRUS CAUSING SEVERE ACUTE RESPIRATORY SYNDROME (SARS)**

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(57) **ABSTRACT**

The present invention relates to a high-throughput diagnostic assay for the virus causing Severe Acute Respiratory Syndrome (SARS) in humans ("hSARS virus"). In particular, the invention relates to a high-throughput reverse transcription-PCR diagnostic test for SARS associated *coronavirus* (SARS-CoV). The present assay is a rapid, reliable assay which can be used for diagnosis and monitoring the spread of SARS and is based on the nucleotide sequences of the N (nucleocapsid)-gene of the hSARS virus. The present method eliminates false negative results and provides increased sensitivity for the assay. The invention also discloses the S (spike)-gene of the hSARS virus. The invention further relates to the deduced amino acid sequences of the N-gene and S-gene products of the hSARS virus and to the use of the N-gene and S-gene products in diagnostic methods. The invention further encompasses diagnostic assays and kits comprising antibodies generated against the N-gene or S-gene product.

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(60) Provisional application No. 60/457,031, filed on Mar. 24, 2003. Provisional application No. 60/457,730, filed on Mar. 26, 2003. Provisional application No. 60/459,931, filed on Apr. 2, 2003. Provisional application No. 60/460,357, filed on Apr. 3, 2003. Provisional application No. 60/461,265, filed on Apr. 8,

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a cag gac gct gta gct tca aaa atc tta gga ttg cct acg cag act gtt 49
  Gln Asp Ala Val Ala Ser Lys Ile Leu Gly Leu Pro Thr Gln Thr Val
  1           5           10          15
gat tca tca cag ggt tct gaa tat gac tat gtc ata ttc aca caa act 97
Asp Ser Ser Gln Gly Ser Glu Tyr Asp Tyr Val Ile Phe Thr Gln Thr
          20          25          30
act gaa aca gca cac tct tgt aat gtc aac cgc ttc aat gtg gct atc 145
Thr Glu Thr Ala His Ser Cys Asn Val Asn Arg Phe Asn Val Ala Ile
          35          40          45
aca agg gca aaa att ggc att ttg tgc ata atg tct gat aga gat ctt 193
Thr Arg Ala Lys Ile Gly Ile Leu Cys Ile Met Ser Asp Arg Asp Leu
          50          55          60
tat gac aaa ctg caa ttt aca agt cta gaa ata cca cgt cgc aat gtg 241
Tyr Asp Lys Leu Gln Phe Thr Ser Leu Glu Ile Pro Arg Arg Asn Val
          65          70          75          80
gct aca tta caa gca gaa aat gta act gga ctt ttt aag gac tgt agt 289
Ala Thr Leu Gln Ala Glu Asn Val Thr Gly Leu Phe Lys Asp Cys Ser
          85          90          95
aag atc att act ggt ctt cat cct aca cag gca cct aca cac ctc agc 337
Lys Ile Ile Thr Gly Leu His Pro Thr Gln Ala Pro Thr His Leu Ser
          100          105          110
gtt gat ata aaa ttc aag act gaa gga tta tgt gtt gac ata cca ggc 385
Val Asp Ile Lys Phe Lys Thr Glu Gly Leu Cys Val Asp Ile Pro Gly
          115          120          125
ata cca aag gac atg acc tac cgt aga ctc atc tct atg atg ggt ttc 433
Ile Pro Lys Asp Met Thr Tyr Arg Arg Leu Ile Ser Met Met Gly Phe
          130          135          140
aaa atg aat tac caa gtc aat ggt tac cct aat atg ttt atc acc cgc 481
Lys Met Asn Tyr Gln Val Asn Gly Tyr Pro Asn Met Phe Ile Thr Arg
          145          150          155          160
gaa gaa gct att cgt cac gtt cgt gcg tgg att ggc ttt gat gta gag 529
Glu Glu Ala Ile Arg His Val Arg Ala Trp Ile Gly Phe Asp Val Glu
          165          170          175
ggc tgt cat gca act aga gat gct gtg ggt act aac cta cct ctc cag 577
Gly Cys His Ala Thr Arg Asp Ala Val Gly Thr Asn Leu Pro Leu Gln
          180          185          190
cta gga ttt tct aca ggt gtt aac tta gta gct gta ccg act ggt tat 625
Leu Gly Phe Ser Thr Gly Val Asn Leu Val Ala Val Pro Thr Gly Tyr
          195          200          205
gtt gac act gaa aat aac cta 646
Val Asp Thr Glu Asn Asn Leu
          210          215

```

FIG. 1

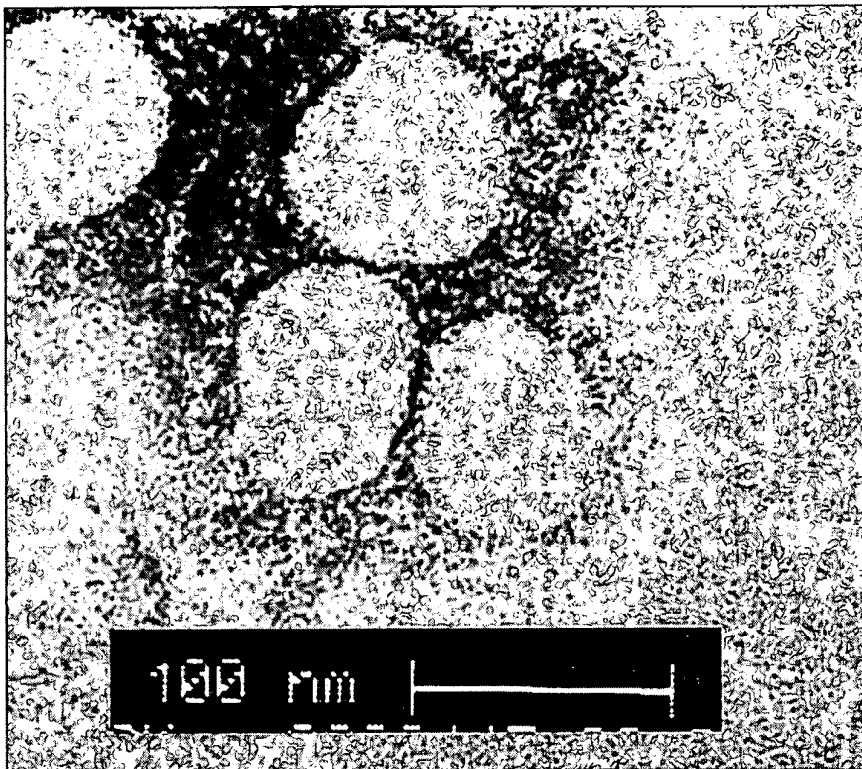


FIG. 2



FIG. 3

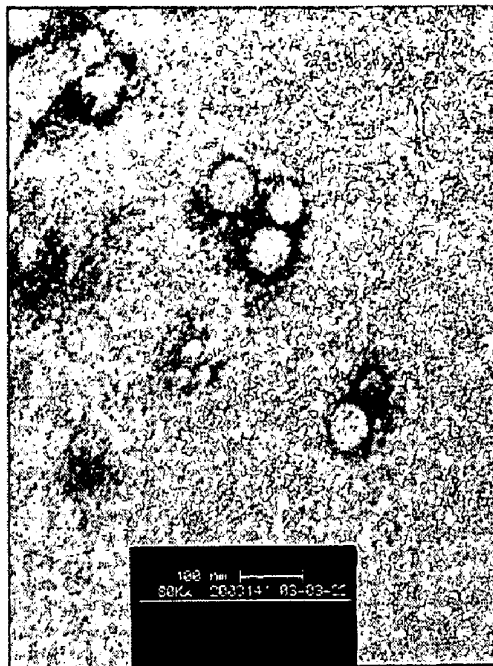


FIG. 4

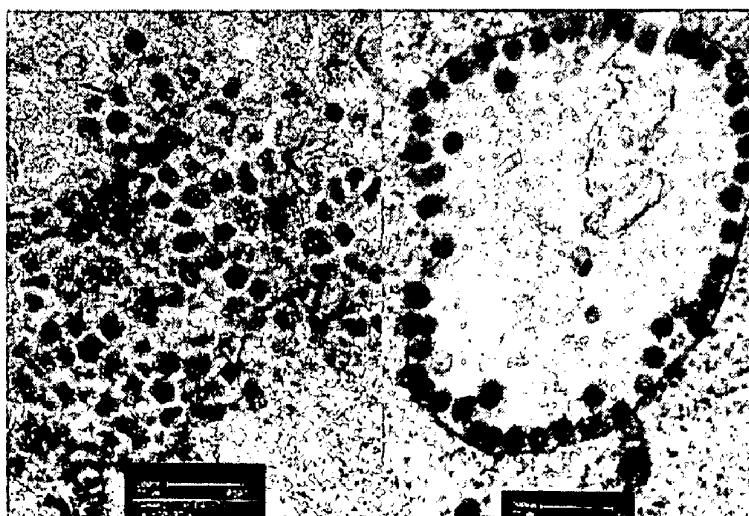


FIG. 5A

FIG. 5B

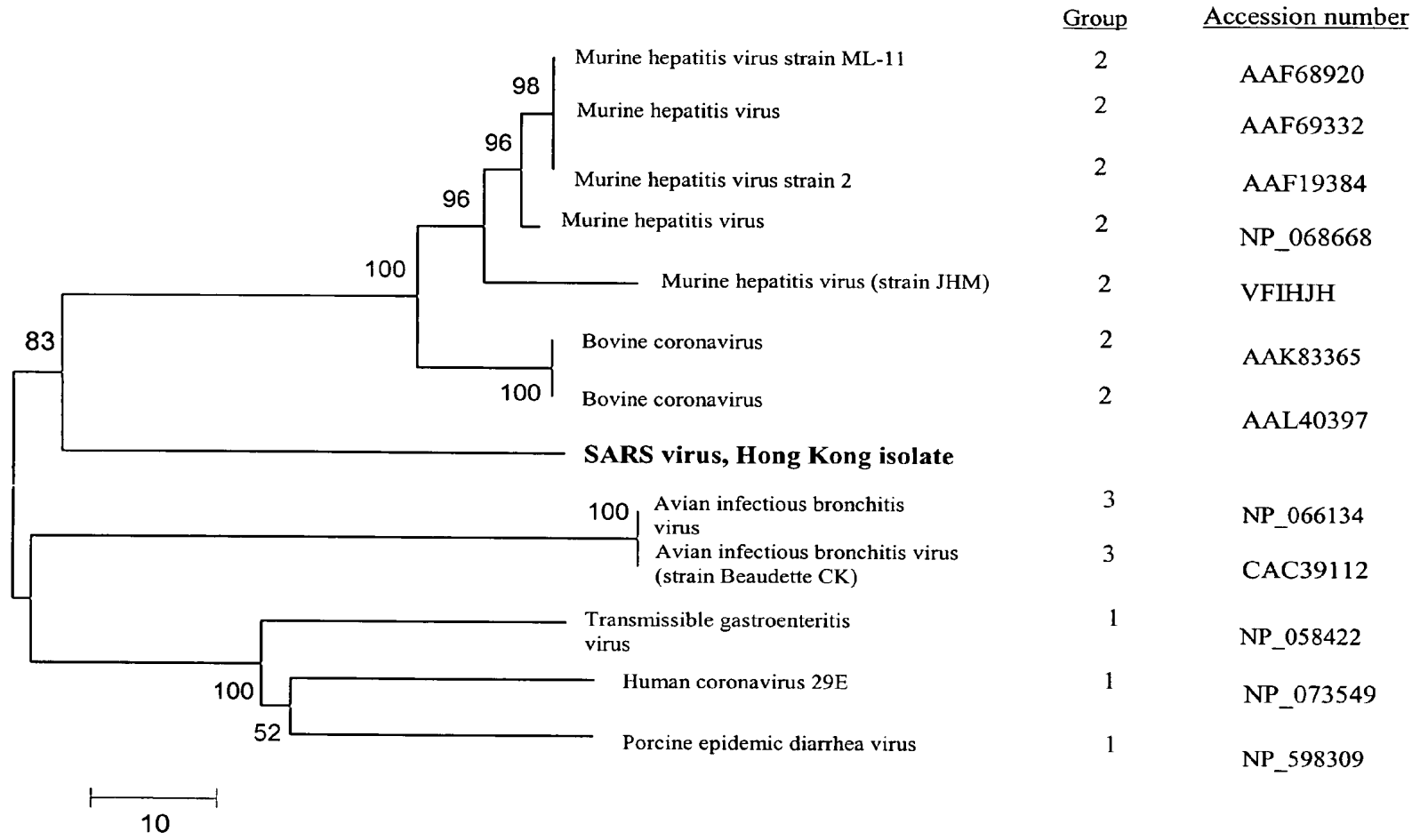


FIG. 6

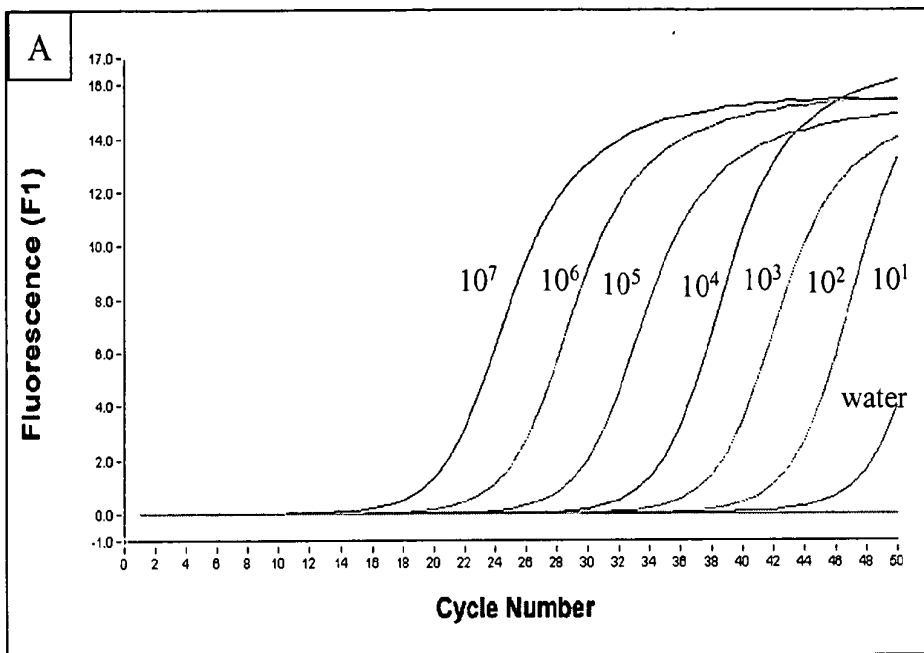


FIG. 7A

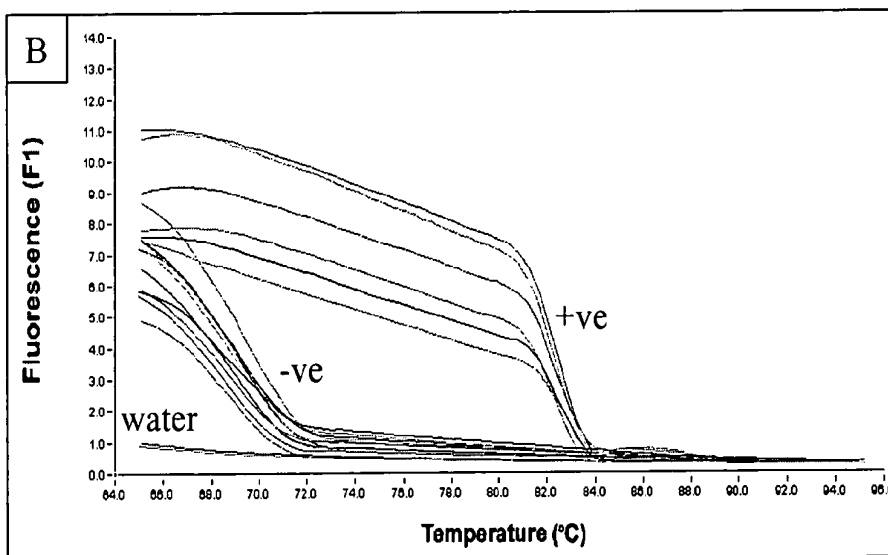


FIG. 7B

t	aaa	tgt	agt	aga	atc	ata	cct	gcg	cgt	gcg	cgc	gta	gag	tgt	ttt	gat	49
	Lys	Cys	Ser	Arg	Ile	Ile	Pro	Ala	Arg	Ala	Arg	Val	Glu	Cys	Phe	Asp	
1				5					10						15		
aaa	ttc	aaa	gtg	aat	tca	aca	cta	gaa	cag	tat	gtt	ttc	tgc	act	gta		97
Lys	Phe	Lys	Val	Asn	Ser	Thr	Leu	Glu	Gln	Tyr	Val	Phe	Cys	Thr	Val		
			20					25					30				
aat	gca	ttg	cca	gaa	aca	act	gct	gac	att	gta	gtc	ttt	gat	gaa	atc		145
Asn	Ala	Leu	Pro	Glu	Thr	Thr	Ala	Asp	Ile	Val	Val	Phe	Asp	Glu	Ile		
		35					40					45					
tct	atg	gct	act	aat	tat	gac	ttg	agt	gtt	gtc	aat	gct	aga	ctt	cgt		193
Ser	Met	Ala	Thr	Asn	Tyr	Asp	Leu	Ser	Val	Val	Asn	Ala	Arg	Leu	Arg		
	50					55					60						
gca	aaa	cac	tac	gtc	tat	att	ggc	gat	cct	gct	caa	tta	cca	gcc	ccc		241
Ala	Lys	His	Tyr	Val	Tyr	Ile	Gly	Asp	Pro	Ala	Gln	Leu	Pro	Ala	Pro		
65					70				75					80			
cgc	aca	ttg	ctg	act	aaa	ggc	aca	cta	gaa	cca	gaa	tat	ttt	aat	tca		289
Arg	Thr	Leu	Leu	Thr	Lys	Gly	Thr	Leu	Glu	Pro	Glu	Tyr	Phe	Asn	Ser		
			85					90						95			
gtg	tgc	aga	ctt	atg	aaa	aca	ata	ggt	cca	gac	atg	ttc	ctt	gga	act		337
Val	Cys	Arg	Leu	Met	Lys	Thr	Ile	Gly	Pro	Asp	Met	Phe	Leu	Gly	Thr		
			100				105						110				
tgt	cgc	cgt	tgt	cct	gct	gaa	att	gtt	gac	act	gtg	agt	gct	tta	gtt		385
Cys	Arg	Arg	Cys	Pro	Ala	Glu	Ile	Val	Asp	Thr	Val	Ser	Ala	Leu	Val		
		115				120						125					
tat	gac	aat	aag	cta	aaa	gca	cac	aag	gag	aag	tca	gct	caa	tgc	ttc		433
Tyr	Asp	Asn	Lys	Leu	Lys	Ala	His	Lys	Glu	Lys	Ser	Ala	Gln	Cys	Phe		
	130					135					140						
aaa	atg	ttc	tac	aaa	ggt	gtt	att	aca	cat	gat	gtt	tca	tct	gca	atc		481
Lys	Met	Phe	Tyr	Lys	Gly	Val	Ile	Thr	His	Asp	Val	Ser	Ser	Ala	Ile		
145				150					155					160			
aac	aga	cct	caa	ata	ggc	gtt	gta	aga	gaa	ttt	ctt	aca	cgc	aat	cct		529
Asn	Arg	Pro	Gln	Ile	Gly	Val	Val	Arg	Glu	Phe	Leu	Thr	Arg	Asn	Pro		
			165					170					175				
gct	tgg	aga	aaa	gct	gtt	ttt	atc	tca	cct	tat	aat	tca	cag	aac	gct		577
Ala	Trp	Arg	Lys	Ala	Val	Phe	Ile	Ser	Pro	Tyr	Asn	Ser	Gln	Asn	Ala		
			180					185					190				
gta	gct	tca	aaa	atc	tta	gga	ttg	cct	acg	cag	act	gtt	gat	tca	tca		625
Val	Ala	Ser	Lys	Ile	Leu	Gly	Leu	Pro	Thr	Gln	Thr	Val	Asp	Ser	Ser		
		195				200						205					
cag	ggt	tct	gaa	tat	gac	tat	gtc	ata	ttc	aca	caa	act	act	gaa	aca		673
Gln	Gly	Ser	Glu	Tyr	Asp	Tyr	Val	Ile	Phe	Thr	Gln	Thr	Thr	Glu	Thr		
	210					215					220						

FIG. 8

gca cac tct tgt aat gtc aac cgc ttc aat gtg gct atc aca agg gca	721
Ala His Ser Cys Asn Val Asn Arg Phe Asn Val Ala Ile Thr Arg Ala	
225	230 235 240
aaa att ggc att ttg tgc ata atg tct gat aga gat ctt tat gac aaa	769
Lys Ile Gly Ile Leu Cys Ile Met Ser Asp Arg Asp Leu Tyr Asp Lys	
	245 250 255
ctg caa ttt aca agt cta gaa ata cca cgt cgc aat gtg gct aca tta	817
Leu Gln Phe Thr Ser Leu Glu Ile Pro Arg Arg Asn Val Ala Thr Leu	
	260 265 270
caa gca gaa aat gta act gga ctt ttt aag gac tgt agt aag atc att	865
Gln Ala Glu Asn Val Thr Gly Leu Phe Lys Asp Cys Ser Lys Ile Ile	
	275 280 285
act ggt ctt cat cct aca cag gca cct aca cac ctc agc gtt gat ata	913
Thr Gly Leu His Pro Thr Gln Ala Pro Thr His Leu Ser Val Asp Ile	
	290 295 300
aaa ttc aag act gaa gga tta tgt gtt gac ata cca ggc ata cca aag	961
Lys Phe Lys Thr Glu Gly Leu Cys Val Asp Ile Pro Gly Ile Pro Lys	
	305 310 315 320
gac atg acc tac cgt aga ctc atc tct atg atg ggt ttc aaa atg aat	1009
Asp Met Thr Tyr Arg Arg Leu Ile Ser Met Met Gly Phe Lys Met Asn	
	325 330 335
tac caa gtc aat ggt tac cct aat atg ttt atc acc cgc gaa gaa gct	1057
Tyr Gln Val Asn Gly Tyr Pro Asn Met Phe Ile Thr Arg Glu Glu Ala	
	340 345 350
att cgt cac gtt cgt gcg tgg att ggc ttt gat gta gag ggc tgt cat	1105
Ile Arg His Val Arg Ala Trp Ile Gly Phe Asp Val Glu Gly Cys His	
	355 360 365
gca act aga gat gct gtg ggt act aac cta cct ctc cag cta gga ttt	1153
Ala Thr Arg Asp Ala Val Gly Thr Asn Leu Pro Leu Gln Leu Gly Phe	
	370 375 380
tct aca ggt gtt aac tta gta gct gta ccg act ggt tat gtt gac act	1201
Ser Thr Gly Val Asn Leu Val Ala Val Pro Thr Gly Tyr Val Asp Thr	
	385 390 395 400
gaa aat aac cta	1213
	Glu Asn Asn Leu

FIG. 8 Con't

c aga acc atg cct aac atg ctt agg ata atg gcc tct ctt gtt ctt gct 49
 Arg Thr Met Pro Asn Met Leu Arg Ile Met Ala Ser Leu Val Leu Ala
 1 5 10 15

cgc aaa cat aac act tgc tgt aac tta tca cac cgt ttc tac agg tta 97
 Arg Lys His Asn Thr Cys Cys Asn Leu Ser His Arg Phe Tyr Arg Leu
 20 25 30

gct aac gag tgt gcg caa gta tta agt gag atg gtc atg tgt ggc ggc 145
 Ala Asn Glu Cys Ala Gln Val Leu Ser Glu Met Val Met Cys Gly Gly
 35 40 45

tca cta tat gtt aaa cca ggt gga aca tca tcc ggt gat gct aca act 193
 Ser Leu Tyr Val Lys Pro Gly Gly Thr Ser Ser Gly Asp Ala Thr Thr
 50 55 60

gct tat gct aat agt gtc ttt aac att tgt caa gct gtt aca gcc aat 241
 Ala Tyr Ala Asn Ser Val Phe Asn Ile Cys Gln Ala Val Thr Ala Asn
 65 70 75 80

gta aat gca ctt ctt tca act gat ggt aat aag ata gct gac aag tat 289
 Val Asn Ala Leu Leu Ser Thr Asp Gly Asn Lys Ile Ala Asp Lys Tyr
 85 90 95

gtc cgc aat cta caa cac agg ctc tat gag tgt ctc tat aga aat agg 337
 Val Arg Asn Leu Gln His Arg Leu Tyr Glu Cys Leu Tyr Arg Asn Arg
 100 105 110

gat gtt gat cat gaa ttc gtg gat gag ttt tac gct tac ctg cgt aaa 385
 Asp Val Asp His Glu Phe Val Asp Glu Phe Tyr Ala Tyr Leu Arg Lys
 115 120 125

cat ttc tcc atg atg att ctt tct gat gat gcc gtt gtg tgc tat aac 433
 His Phe Ser Met Met Ile Leu Ser Asp Asp Ala Val Val Cys Tyr Asn
 130 135 140

agt aac tat gcg gct caa ggt tta gta gct agc att aag aac ttt aag 481
 Ser Asn Tyr Ala Ala Gln Gly Leu Val Ala Ser Ile Lys Asn Phe Lys
 145 150 155 160

gca gtt ctt tat tat caa aat aat gtg ttc atg tct gag gca aaa tgt 529
 Ala Val Leu Tyr Tyr Gln Asn Asn Val Phe Met Ser Glu Ala Lys Cys
 165 170 S 175

tgg act gag act gac ctt act aaa gga cct cac gaa ttt tgc tca cag 577
 Trp Thr Glu Thr Asp Leu Thr Lys Gly Pro His Glu Phe Cys Ser Gln
 180 185 190

cat aca atg cta gtt aaa caa gga gat gat tac gtg tac ctg cct tac 625
 His Thr Met Leu Val Lys Gln Gly Asp Asp Tyr Val Tyr Leu Pro Tyr
 195 200 205

cca gat cca tca aga ata tta ggc gca ggc tgt ttt gtc gat gat att 673
 Pro Asp Pro Ser Arg Ile Leu Gly Ala Gly Cys Phe Val Asp Asp Ile
 210 215 220

gtc aaa cag atg gta cac tta tga ttg aaa ggt tcc gtg tca ctg gct 721
 Val Lys Gln Met Val His Leu
 225 230

att gat gc 729

FIG. 9

```

1 atattaggtt tttacctacc caggaaaagc caaccaacct c gatctcttg tagatctgtt
61 ctctaaacga actttaaaat ctgtgtagct gtcgctcggc tgcatgccta gtgcacctac
121 gcagtataaa caataataaa ttttactgtc gttgacaaga aacgagtaac tcgtccctct
181 tctgcagact gcttacgggt tcgtccgtgt tgcagtcgat catcagcata cctaggtttc
241 gtccgggtgt gaccgaaagg taagatggag agccttgttc ttggtgtcaa cgagaaaaa
301 cacgtccaac tcagtttgcc tgccttcag gttagagacg tgctagtgcg tggcttcggg
361 gactctgtgg aagaggccct atcggaggca cgtgaacacc tcaaaaatgg cacttgtggt
421 ctagtagagc tggaaaagg cgtactgcc cagcttgac agccctatgt gttcattaaa
481 cgttctgatg ccttaagcac caatcacggc cacaaggctg ttgagctggt tgcagaaatg
541 gacggcattc agtacggtcg tagcgggtata acactgggag tactcgtgcc acatgtgggc
601 gaaaccccaa ttgcataccg caatgttctt cttcgtaga acggtataa gggagccggt
661 ggtcatagct atggcatcga tctaaagtct tatgacttag gtgacgagct tggcactgat
721 cccattgaag attatgaaca aactggaac actaagcatg gcagtgggac actccgtgaa
781 ctcaactcgt agctcaatgg agtgcgctc actcgctatg tcgacaaca tttctgtggc
841 ccagatgggt accctcttga ttgcatcaaa gattttctcg cacgcgctgg caagtcaatg
901 tgcactcttt ccgaacaact tgattacatc gagtcaaga gaggtgtcta ctgctgccgt
961 gaccatgagc atgaaattgc ctggttcact gagcgtctcg ataagagcta cgagcaccag
1021 acacccttcg aaattaagag tgccaagaaa tttgacactt tcaaaaggga atgcccaaag
1081 tttgtgtttc ctcttaactc aaaagtcaaa gtcattcaac cacgtgttga aaagaaaaag
1141 actgagggtt tcatggggcg tatacgtctt .gtgtacctg ttgcatctcc acaggagtgt
1201 aacaatatgc acttgtctac cttgatgaaa tgtaatcatt gcgatgaagt ttcattggca
1261 acgtgcgact ttctgaaagc cacttgtgaa cattgtggca ctgaaaattt agttattgaa
1321 ggactacta actgtgggta cctacctact aatgctgtag tgaaaatgcc atgtcctgcc
1381 tgtcaagacc cagagattgg acctgagcat agtggtgagc attatcaca ccactcaaac
1441 attgaaactc gactccgcaa gggaggtagg actagatggt ttggaggctg tgtgtttgcc
1501 tatgttggct gctataataa gcgtgcctac tgggttctc gtgctagtgc tgatattggc
1561 tcaggccata ctggcattac tggtgacaat gtggagacct tgaatgagga tctccttgag
1621 aactgagtc gtgaacgtgt taacattaac attgttggcg attttcattt gaatgaagag
1681 gttgccatca ttttggcate tttctctgct tctacaagt cctttattga cactataaag
1741 agtcttgatt acaagtcttt caaaaccatt gttgagtcct gcggtaaacta taaagttacc
1801 aagggaaagg ccgtaaaagg tgcttggaa attggacaac agagatcagt ttaaacacca
1861 ctgtgtgggt ttcctcaca ggctgctggt gttatcagat caatttttgc cgcacactt
1921 gatgcagcaa accactcaat tctgatttg caaagagcag ctgtcaccat acttgatggt
1981 atttctgaac agtcattacg tcttgtcgac gccatggttt ataactcaga cctgctcacc
2041 aacagtgtca ttattatggc atatgtaact ggtggtcttg tacaacagac tctcagtggt
2101 ttgtctaatc ttttgggcac tactgttgaa aaactcaggc ctatcttga atggattgag
2161 gcgaaactta gtgcaggagt tgaatttctc aaggatgctt gggagattct caaatttctc
2221 attacaggtg tttttgacat cgtcaagggt caaatacagg ttgcttcaga taacatcaag
2281 gattgtgtaa aatgcttcat tgatgttgtt aacaaggcac tcgaaatgtg cattgatcaa
2341 gtcactatcg ctggcgcaa gttgcgatca ctcaacttag gtgaagtctt catcgtctca
2401 agcaaggac tttaccgtca gttatacgt ggcaaggagc agctgcaact actcatgcct
2461 cttaaggcac caaaagaagt aacctttctt gaagggtatt cacatgacac agtacttacc
2521 tctgaggagg ttgttctcaa gaacggtgaa ctgcaagcac tcgagacgcc cgttgatagc
2581 ttcacaaatg gagctatcgt cggcacacca gtctgtgtaa atggcctcat gctcttagag
2641 attaaggaca aagaacaata ctgcgcattg tctcctggtt tactggctac aaacaatgtc
2701 tttcgcttaa aaggggtgct accaattaaa ggtgtaacct ttggagaaga tactgtttgg
2761 gaagttcaag gttacaagaa tgtgagaatc acatttgagc ttgatgaacg tgttgacaaa
2821 gtgcttaatg aaaagtgctc tgtctacact gttgaatccg gtaccgaagt tactgagttt
2881 gcatgtgttg tagcagaggc tgttgtgaag actttacaac cagtttctga tctccttacc
2941 aacatgggta ttgatcttga tgagtggagt gtagctacat tctacttatt tgatgatgct
3001 ggtgaagaaa acttttcatc acgtatgtat tgttctttt accctccaga tgaggaagaa
3061 gaggacgatg cagagtgtga ggaagaagaa attgatgaaa cctgtgaaca tgagtacggt
3121 acagaggatg attatcaagg tctccctctg gaatttgggt cctcagctga aacagttcga
3181 gttgaggaag aagaagagga agactggctg gatgatacta ctgagcaatc agagattgag
3241 ccagaaccag aacctacacc tgaagaacca gttaatcagt ttactgggta tttaaaactt
3301 actgacaatg ttgccattaa atgtgttgac atcgtttaag aggcacaaa tgctaactct

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FIG. 10

3361 atggtgattg taaatgctgc taacatacac ctgaaacatg gtggtggtgt agcagggtgca
 3421 ctaacaagc caaccaatgg tgccatgcaa aaggagagtg atgattacat taagctaaat
 3481 ggcctcttta cagtaggagg gtcttgtttg ctttctggac ataatcttgc taagaagtgt
 3541 ctgcatgttg ttggacctaa cctaaatgca ggtgaggaca tccagcttct taaggcagca
 3601 tatgaaaatt tcaattcaca ggacatctta cttgcacatg tgttgcagc aggcataattt
 3661 ggtgctaaac cacttcagtc tttacaagtg tgcgtgcaga cggttcgtac acaggtttat
 3721 attgcagtca atgacaaaagc tctttatgag caggttgtca tggattatct tgataacctg
 3781 aagcctagag tgaagcacc taaacaagag gagccacca acacagaaga ttccaaaact
 3841 gaggagaaat ctgtcgtaca gaagcctgtc gatgtgaagc caaaaattaa ggcctgcatt
 3901 gatgaggtta ccacaacact ggaagaaact aagtttctta ccaataagt actcttgttt
 3961 gctgatatca atggtaagct ttaccatgat tctcagaaca tgcttagagg tgaagatatg
 4021 tctttccttg agaaggatgc accttcatag gtaggtgatg ttatcactag tggatgatc
 4081 acttgtgttg taataccctc caaaaaggct ggtggcacta ctgagatgct ctcaagagct
 4141 ttgaagaaag tgccagttga tgagtatata accacgtacc ctggacaagg atgtgctggt
 4201 tatakacttg aggaagctaa gactgctctt aagaaatgca aatctgcatt ttatgacta
 4261 ccttcagaag cacctaagtc taaggaaagc attctaggaa ctgtatcctg gaatttgaga
 4321 gaaatgcttg ctcatgctga agagacaaga aaattaatgc ctatatgcat ggatgttaga
 4381 gccataatgg caaccatcca acgtaagtat aaaggaatta aaattcaaga gggcatcggt
 4441 gactatgggt tccgattctt cttttatact agtaaagagc ctgtagcttc tattattacg
 4501 aagctgaact ctctaaatga gccgctgtc acaatgccaa ttggttatgt gacacatggt
 4561 tttaatcttg aagaggctgc gcgctgtatg cgttctctta aagctcctgc cgtagtgtca
 4621 gtatcatcac cagatgctgt tactacatat aatggatacc tcaactcgtc atcaaagaca
 4681 tetgaggagc actttgtaga aacagtttct ttggctggct cttacagaga ttggctctat
 4741 tcaggactgg gtacagagtt aggtgttgaa tttcttaagc gtggtgacaa aattgtgtac
 4801 cacactctgg agagccccgt cgagttctat cttgacgggt aggttctttc acttgacaaa
 4861 ctaaaagatc tcttatccct gcgggagggt aagactataa aagtgttcac aactgtggac
 4921 aacactaatc tccacacaca gcttgtggat atgtctatga catatggaca gcagtttggg
 4981 ccaacatact tggatgggtc tgatgttaca aaaattaaac ctcatgtaa tcatgagggg
 5041 aagactttct ttgtactacc tagttagtac aactacgta gtgaagcttt cgagtactac
 5101 catactcttg atgagagttt tcttggtagg tacatgtctg ctttaaacca cacaaagaaa
 5161 tggaaatttc ctcaagttgg tggtttaact tcaattaaat gggctgataa caattgttat
 5221 ttgtctagtg ttttattagc acttcaacag cttgaagtca aattcaatgc accagcactt
 5281 caagaggctt attatagagc ccgtgctggt gatgctgcta acttttgtgc actcactc
 5341 gcttacagta ataaaactgt tggcgagctt ggtgatgtca gagaaactat gacccatctt
 5401 ctacagcatg ctaatttggc atctgcaaaag cgagttctta atgtgggtgtg taaacattgt
 5461 ggtcagaaaa ctactacctt aacgggtgta gaagctgtga tgtatatggg tactctatct
 5521 tatgataatc ttaagacagg tgtttccatt ccatgtgtgt gtggtcgtga tgctacacaa
 5581 tatctagtac aacaagagtc ttcttttgtt atgatgtctg caccacctgc tgagtataaa
 5641 ttacagcaag gtacattctt atgtgcgaat gactacactg gtaactatca gtgtggtcat
 5701 tacactcata taactgctaa ggagaccctc tatcgtattg acggagctca ccttacaagg
 5761 atgtcagagt acaaaggacc agtgactgat gttttctaca aggaaacatc ttacactaca
 5821 accatcaagc ctgtgtcgtc taaactcgat ggagttactt acacagagat tgaacccaaa
 5881 ttggatgggt attataaaaa ggataatgct tactatacag agcagcctat agaccctgta
 5941 ccaactcaac cattaccaa tgcgagtttt gataatttca aactcacatg ttctaacaca
 6001 aaatttgctg atgatttaaa tcaaatgaca ggcttcacaa agccagcttc acgagagcta
 6061 tctgtccatc tcttcccaga cttgaatggc gatgtagtgg ctattgacta tagacactat
 6121 tcagcgagtt tcaagaaagg tgctaaatta ctgcataagc caattgtttg gcacattaac
 6181 caggctacaa ccaagacaac gttcaacca aacacttggg gtttacgttg tctttggagt
 6241 acaaagccag tagatacttc aaattcattt gaagtctctg cagtagaaga cacacaagga
 6301 atggacaatc ttgcttgtga aagtcaacaa cccacctctg aagaagtgtg ggaatcct
 6361 accatacaga aggaagtcat agagtgtgac gtgaaaacta ccgaagtgtg aggcaatgct
 6421 atacttaaac catcagatga aggtgttaa gtaacacaag agttaggtca tgaggatctt
 6481 atggctgctt atgtggaaaa cacaagcatt accattaaga aacctaatga gctttcacta
 6541 gccttagggt taaaaacaat tgccactcat ggtattgctg caattaatag tgttcttgg
 6601 agtaaaatth ttgcttatgt caaaccttc ttaggacaag cagcaattac aacatcaaat
 6661 tgcgctaaga gattagcaca acgtgtgttt aacaattata tgccttatgt gtttacatta

FIG. 10 Con't

6721 ttgttccaat tgtgtacttt tactaaaagt accaattcta gaattagagc ttcactacct
 6781 acaactattg ctaaaaaatag tgtaagagtg gttgctaaat tatgtttgga tgccggcatt
 6841 aattatgtga agtcacccaa attttctaaa ttgttcacaa tcgctatgtg gctattgttg
 6901 ttaagtattt gcttaggttc tctaactctgt gtaactgctg cttttggtgt actcttatct
 6961 aattttggtg ctccctctta ttgtaatggc gttagagaat tgtatcttaa ttcgctaac
 7021 gttactacta tggatttctg tgaaggttct tttccttgca gcatttgttt aagtggatta
 7081 gactcccttg attcttatcc agctcttgaa accattcagg tgacgatttc atcgtacaag
 7141 ctagacttga caattttagg tctggccgct gagtgggttt tggcatatat gttgttcaca
 7201 aaattctttt atttattagg tctttcagct ataatgcagg tgttctttgg ctattttgct
 7261 agtcatttca tcagcaattc ttggctcatg tggtttatca ttagtattgt acaaatggca
 7321 cccgtttctg caatgggttag gatgtacatc ttctttgctt ctttctacta catatggaag
 7381 agctatgttc atatcatgga tgggtgcacc tcttcgactt gcatgatgtg ctataagcgc
 7441 aatcgtgcca cacgcgttga gtgtacaact attgttaatg gcatgaagag atctttctat
 7501 gtctatgcaa atggaggccg tggcttctgc aagactcaca attggaattg tctcaattgt
 7561 gacacatttt gcaactgtag tacattcatt agtgatgaag ttgctcgtga tttgtcactc
 7621 cagtttaaaa gaccaatcaa ccctactgac cagtcacgt atattgttga tagtgtgct
 7681 gtgaaaaatg ggcgcttca cctctacttt gacaaggctg gtcaaaagac ctatgagaga
 7741 catcgcctct cccattttgt caatttagac aatttgagag ctaacaacac taaaggttca
 7801 ctgcctatta atgtcatagt ttttgatggc aagtccaaat gcgacgagtc tgcttctaag
 7861 tctgcttctg tgtactacag tcagctgatg tgccaaccta ttctgttgc tgcaccaagct
 7921 cttgtatcaa acgttggaga tagtactgaa gtttccgta agatgttga tgcttatgct
 7981 gacacctttt cagcaacttt tagtgttct atggaaaaac ttaaggcact tttgtctaca
 8041 gctcagcagc agttagcaaa ggggttagct ttagatggtg tcctttctac attcgtgca
 8101 gctgcccagc aagggtgttgt tgataccgat gttgacacaa aggatgttat tgaatgtctc
 8161 aaactttcac atcactctga cttagaagtg acaggtgaca gttgtaacaa tttcatgctc
 8221 acctataata aggttgaaaa catgacgcc agagatcttg gcgcatgat tgcactgta
 8281 gcaaggcata tcaatgcca agtagcaaaa agtcacaatg tttcactcat ctggaatgta
 8341 aaagactaca tgtctttatc tgaacagctg cgtaaacaaa ttcgtagctg tgccaagaag
 8401 aacaacatac cttttacact aacttgtgct acaactagac aggttgtcaa tgcataact
 8461 actaaaatct cactcaaggg tggtaagatt gttagtactt gttttaaact tatgcttaag
 8521 gccacattat tgtgcgttct tctgcattg gtttgttata tcgttatgcc agtacataca
 8581 ttgtcaatcc atgatggtta cacaatgaa atcattggtt acaaagccat tcaggatggt
 8641 gtcactcgtg acatcatttc tactgatgat tgttttgcaa ataaacatgc tggttttgac
 8701 gcatggttta gccagcgtgg tggttcatac aaaaatgaca aaagctgccc tgtagtagct
 8761 gctatcatta caagagagat tggtttcata gtgcctggct taccgggtac tgtgctgaga
 8821 gcaatcaatg gtgacttctt gcattttcta cctcgtggtt ttagtgctgt tggcaacatt
 8881 tgctacacac cttccaaact cattgagtat agtgattttg ctacctctgc ttgcgttctt
 8941 gctgctgagt gtacaatttt taaggatgct atgggcaaac ctgtgccata ttgttatgac
 9001 actaatttgc tagaggggtc tatttcttat agtgagcttc gtccagacac tcgttatgtg
 9061 cttatggatg gtccatcat acagtttctt aacacttacc tggagggttc tgttagagta
 9121 gtaacaactt ttgatgctga gtactgtaga catggtacat gcgaaaggtc agaagtaggt
 9181 atttgcctat ctaccagtgg tagatgggtt ctttaaatg agcattacag agctctatca
 9241 ggagttttct gtggtgttga tgcgatgaat ctcatagcta acatctttac tctcttgg
 9301 caacctgtgg gtgctttaga tgtgtctgct tcagtagtgg ctgggtggtat tattgccata
 9361 ttggtgactt gtgctgcta ctactttatg aaatcagac gtgtttttgg tgagtacaac
 9421 catgttgttg ctgctaatgc acttttgttt ttgatgtctt tcaactatact ctgtctggta
 9481 ccagcttaca gctttctgcc gggagtctac tcagtctttt acttgtactt gacattctat
 9541 ttcaccaatg atgtttcatt cttggctcac cttcaatggt ttgccatggt ttctctatt
 9601 gtgcctttt ggataacagc aatctatgta ttctgtatt ctctgaagca ctgccattgg
 9661 ttctttaaca actatcttag gaaaagagtc atgtttaatg gagttacatt tagtacctc
 9721 gaggaggctg ctttgtgtac ctttttctc aacaaggaaa tgtacctaaa attcgtgac
 9781 gagacactgt tgccacttac acagtataac aggtatcttg ctctatataa caagtacaag
 9841 tatttcagtg gagccttga tactaccagc tctcgtgaag cagcttctg ccacttagca
 9901 aaggctctaa atgacttttag caactcaggt gctgatgttc tctaccaacc accacagaca
 9961 tcaatcactt ctgctgttct gcagagtgtt tttaggaaaa tggcattccc gtcaggcaaa
 10021 gttgaagggt gcatggtaca agtaacctgt ggaactacaa ctcttaatgg attgtggtg

FIG. 10 Con't

10081 gatgacacag tatactgtcc aagacatgtc atttgacacag cagaagacat gcttaatcct
 10141 aactatgaag atctgtctcat tcgcaaatcc aaccatagct ttcttggtca ggctggcaat
 10201 gttcaacttc gtgttattgg ccatttctatg caaaattgtc tgcttaggct taaagttgat
 10261 acttctaacc ctaagacacc caagtataaa tttgtccgta tccaacctgg tcaaacattt
 10321 tcagttctag catgctacaa tggttcacca tctgggtgtt atcagtggtc catgagacct
 10381 aatcatacca ttaaagggtc tttccttaat ggatcatgtg gtagtgttgg ttttaacatt
 10441 gattatgatt gcggtgtcttt ctgctatatg catcatatgg agcttccaac aggagtacac
 10501 gctgggtactg acttagaagg taaattctat ggtccatttg ttgacagaca aactgcacag
 10561 gctgcaggta cagacacaac cataacatta aatgttttgg catggctgta tgctgtgtt
 10621 atcaatgggtg ataggtgggt tcttaataga ttcaccacta ctttgaatga ctttaacctt
 10681 acacttggtt acaaagctca tgaaccttg acacaagatc atgttgacat attgggacct
 10741 ctttctgctc aaacaggaat tggcgtctta gatatgtgtg ctgctttgaa agagctgctg
 10801 cagaatggta tgaatggctg tactatcctt ggtagcacta ttttagaaga tgagtttaca
 10861 ccatttgatg ttgttagaca atgctctgggt gttaccttcc aaggttaagt caagaaaatt
 10921 gtttaagggca ctcatcattg gatgctttta actttcttga catcactatt gattcttgtt
 10981 caaagtacac agtggctact gtttttcttt gtttacgaga atgctttctt gccatttact
 11041 cttgggtatta tggcaattgc tgcattgtgt atgctgcttg ttaagcataa gcacgcattc
 11101 ttgtgcttgt ttctgttacc ttctcttgca acagttgctt actttaatat ggtctacatg
 11161 cctgctagct ggggtgatgcg tatcatgaca tggcttgaat tggctgacac tagcttgtct
 11221 ggttataggc ttaaggattg tgttatgtat gcttcagctt tagtttggct tattctcatg
 11281 acagctcgca ctgtttatga tgatgctgct agacgtgttt ggacactgat gaatgtcatt
 11341 acacttggtt acaaagctca ctatggtaat gctttagatc aagctatttc catgtgggcc
 11401 ttagttatct ctgtaacctc taactattct ggtgtcgtta cgactatcat gtttttagct
 11461 agagctatag tgtttgtgtg tgttgagtat taccattgt tatttattac tggcaacacc
 11521 ttacagtgta tcatgcttgt ttattgtttc ttaggctatt gttgctgctg ctactttggc
 11581 cttttctgtt tactcaaccg ttacttcagg cttactcttg gtgtttatga ctacttggct
 11641 tctacacaag aatttaggta tatgaactcc caggggcttt tgcctcctaa gtagtagtatt
 11701 gatgctttca agcttaacat taagttgttg ggtattggag gtaaaccatg tatcaaggtt
 11761 gctactgtac agtctaaaat gtctgacgta aagtgcacat ctgtggtact gctctcggtt
 11821 cttaacaac tttagagtaga gtcatcttct aaattgtggg cacaatgtgt acaactccac
 11881 aatgatattc ttcttgcaaa agacacaact gaagcttctg agaagatggt ttctcttttg
 11941 tctgttttgc tatccatgca ggggtgctga gacattaata ggttgtgca ggaatgctc
 12001 gtaaacogtg ctactcttca ggctattgct tcagaattta gttctttacc atcatatgcc
 12061 gcttatgcca ctgccagga ggccatgag caggctgtag ctaatggtga ttctgaagtc
 12121 gttctcaaaa agttaaagaa atctttgaat gtggctaaat ctgagtttga ccgtgatgct
 12181 gccatgcaac gcaagttgga aaagatggca gatcaggcta tgacccaaat gtacaacag
 12241 gcaagatctg aggacaagag ggcaaaagta actagtgcta tgcaaaacat gctcttact
 12301 atgcttagga agcttgataa tgatgcactt aacaacatta tcaacaatgc gcgtgatggt
 12361 tgtgttcac tcaacatcat accattgact acagcagcca aactcatggt tgttgcctt
 12421 gattatggta cctacaagaa cacttgtgat ggtaacacct ttacatatgc atctgcactc
 12481 tgggaaatcc agcaagttgt tgatgcggt agcaagattg ttcaacttag tgaattaac
 12541 atggacaatt caccaaattt ggcttggcct cttattgtta cagcttaag agccaactca
 12601 gctgttaaac tacagaataa tgaactgagt ccagtagcac tacgacagat gtctgtgcg
 12661 gctggtacca cacaaacagc ttgtactgat gacaatgcac ttgcctacta taacaattcg
 12721 aaggagggta ggtttgtgct ggcattacta tcagaccacc aagatctcaa atgggctaga
 12781 tccctaaga gtgatggtac aggtacaatt tacacagaac tggaaaccacc ttgtaggtt
 12841 gttacagaca caccaaaagg gcctaaagt aaatacttgt acttcatcaa aggcttaaac
 12901 aacctaata gaggtatggt gctgggcagt ttagctgcta cagtacgtct tcaggctgga
 12961 aatgctacag aagtacctgc caattcaact gtgctttcct tctgtgctt tgcagtagac
 13021 cctgctaaag catataagga ttacctagca agtggaggac aaccaatcac caactgtgtg
 13081 aagatgttgt gtacacacac tgggtacagga caggcaatta ctgtaacacc agaagctaac
 13141 atggaccaag agtcctttgg tgggtcttca tgttgtctgt attgtagatg ccacattgac
 13201 catccaaatc ctaaaggatt ctgtgacttg aaagtaagt acgtccaaat acctaccact
 13261 tgtgctaag acccagtggt ttttactt agaaacacag tctgtaccgt ctgcggaatg
 13321 tggaaagggt atggctgtag ttgtgaccaa ctccgcgaac ccttgatgca gctgctggat
 13381 gcatcaactg ttttaacgg gtttgcggtg taagtgcagc ccgtcttaca ccgtgcgga

FIG. 10 Con't

13441 caggcactag tactgatgtc gtctacaggg cttttgatat ttacaacgaa aaaagtgctg
 13501 gttttgcaaa gttcctaaaa actaattgct gtcgcttcca ggagaaggat gaggaaggca
 13561 atttattaga ctcttacttt gtagttaaga ggcatactat gtctaactac caacatgaag
 13621 agactattta taacttggtt aaagattgtc cagcggttgc tgtccatgac tttttcaagt
 13681 ttagagtaga tggtgacatg gtaccacata tatcacgtca gcgtctaact aaatacacia
 13741 tggctgattt agtctatgct ctacgtcatt ttgatgaggg taattgtgat acattaaaag
 13801 aaatactcgt cacatacaat tgctgtgatg atgattattt caataagaag gattgggatg
 13861 acttcgtaga gaatcctgac atcttacgcg tatatgctaa cttaggtgag cgtgtacgcc
 13921 aatcattatt aaagactgta caattctcgc atgctatgcg tgatgcaggc attgtaggcg
 13981 tactgacatt agataatcag gatcttaatg ggaactggta cgatttcggt gatttcgtac
 14041 aagtagcacc aggctgcgga gttcctattg tggattcata ttactcattg ctgatgccca
 14101 tcctcacttt gactagggca ttggctgctg agtcccatat ggatgctgat ctcgcaaac
 14161 cacttattaa gtgggatttg ctgaaatag attttacgga agagagactt tgtctctcg
 14221 accgttattt taaatattgg gaccagacat accatcccaa ttgtattaac tgtttggatg
 14281 atagggtgat ccttcattgt gcaaacttta atgtgttatt ttctactgtg tttccaccta
 14341 caagttttgg accactagta agaaaaatat ttgtagatgg tgttcctttt gttgtttcaa
 14401 ctggatacca ttttcgtgag ttaggagtcg tacataatca ggatgtaaac ttacatgact
 14461 cgcgtctcag tttcaaggaa cttttagtgt atgctgctga tccagctatg catgcagctt
 14521 ctggcaattt attgctagat aaacgcacta catgcttttc agtagctgca ctaacaaaca
 14581 atgttgcttt tcaaactgtc aaaccggta attttaataa agacttttat gactttgctg
 14641 tgtctaaagg tttctttaag gaaggaagt ctgttgaact aaaacacttc tttcttgctc
 14701 aggatggcaa cgctgctatc agtgattatg actattatcg ttataatctg ccaacaatgt
 14761 gtgatatcag acaactccta ttcgtagtgt aagttgttga taaatacttt gattgttacg
 14821 atggtggctg tattaatgcc aaccaagtaa tctgtaacaa tctggataaa tcagctggtt
 14881 tcccatttaa taaatggggt aaggctagac tttattatga ctcaatgagt tatgaggatc
 14941 aagatgcact tttcgcgtat actaagcgtg atgtcatccc tactataact caaatgaatc
 15001 ttaagtatgc cattagtgca aagaatagag ctgcaccgt agctgggtgc tctatctgta
 15061 gtactatgac aaatagacag tttcatcaga aattattgaa gtcaatagcc gccactagag
 15121 gagctactgt ggtaattgga acaagcaagt tttacgggtg ctggcataat atgttaaaaa
 15181 ctgtttacag tgatgtagaa actccacacc ttatgggttg ggattatcca aaatgtgaca
 15241 gagccatgcc taacatgctt aggataatgg cctctcttgt tcttgctcgc aaacataaca
 15301 cttgctgtaa cttatcacac cgtttctaca ggtagctaa cgagtgtgcg caagtattaa
 15361 gtgagatgg catgtgtggc ggctcactat atgttaaac agtggaaca tcatccggtg
 15421 atgctacaac tgcttatgct aatagtgtct ttaacatttg tcaagctgtt acagccaatg
 15481 taaatgcact tctttcaact gatggtaata agatagctga caagtatgct cgcaatctac
 15541 aacacaggct ctatgagtgt ctctatagaa atagggatgt tgatcatgaa tctcgtgatg
 15601 agttttacgc ttacctgctt aaacatttct ccatgatgat tctttctgat gatgccgtg
 15661 tgtgctataa cagtaactat gcggctcaag gtttagtagc tagcattaag aactttaagg
 15721 cagttcttta ttatcaaaat aatgtgttca tgtctgaggc aaaatggttg actgagactg
 15781 accttactaa aggacctcac gaattttgct cacagcatac aatgctagtt aaacaaggag
 15841 atgattacgt gtacctgctt taccagatc catcaagaat attaggcgca ggctgttttg
 15901 tcatgatgat tgcataaaca gatggtacac ttatgattga aaggttcgtg tcaactggcta
 15961 ttgatgctta ccacttaca aaacatccta atcaggagta tgcctgatgct tttcactgtt
 16021 atttacaata cattagaaag ttacatgatg agcttactgg ccacatggtg gacatgtatt
 16081 ccgtaatgct aactaatgat aacacctcac ggtactggga acctgagttt tatgaggcta
 16141 tgtacacacc acatacagtc ttgcaggctg taggtgcttg tgtattgtgc aattcacaga
 16201 cttcacttcg ttgcggtgcc tgtattagga gaccattcct atgttgcaag tgcgtctatg
 16261 accatgtcat ttcaacatca cacaaattag tgttctctgt taatccctat gtttgcaatg
 16321 ccccagggtg tgatgtcact gatgtgacac aactgtatct aggaggtatg agctattatt
 16381 gcaagtcaca taagcctccc attagttttc cattatgtgc taatggctag gtttttggtt
 16441 tatacaaaaa cacatgtgta ggcagtgaca atgtcactga cttcaatgcy atagcaacat
 16501 gtgattggac taatgctggc gattacatac ttgccaacac ttgtactgag agactcaagc
 16561 ttttcgcagc agaaacgctc aaagccactg aggaaacatt taagctgtca tatggattg
 16621 ccactgtacg cgaagtactc tctgacagag aattgcatct ttcattggag gttggaaaac
 16681 ctgaccacc attgaacaga aactatgtct ttactggtta ccgtgtaact aaaaatagta
 16741 aagtagatgac tggagagtac acctttgaaa aaggtgacta tggtagtgc tttgtgtaca

FIG. 10 Con't

16801 gaggtactac gacatacaag ttgaatggtg gtgattactt tgtgttgaca tctcacactg
 16861 taatgccact tagtgcacct actctagtgc cacaagagca ctatgtgaga attactggct
 16921 tgtaccacaac actcaacatc tcagatgagt tttctagcaa tgttgcaaat tatcaaaagg
 16981 tcggcatgca aaagtactct acactccaag gaccacctgg tactggtaag agtcattttg
 17041 ccatcggact tgctctctat taccatctcg ctgcgatagt gtatacggca tgctctcatg
 17101 cagctgttga tgccctatgt gaaaaggcat taaaatattt gcccatagat aaatgtagta
 17161 gaatcatacc tgcgcgtgcg cgcgtagagt gttttgataa attcaaagtg aattcaacac
 17221 tagaacagta tgtttctctg actgtaaagt cattgccaga aacaactgct gacattgtag
 17281 tctttgatga aatctctatg gctactaatt atgacttgag tgttgtcaat gctagacttc
 17341 gtgcaaaaca ctacgtctat attggcgatc ctgctcaatt accagcccc cgcacattgc
 17401 tgactaaagg cacactagaa ccagaatatt ttaattcagt gtgcagactt atgaaaacaa
 17461 taggtccaga catgttcctt ggaacttgtc gccgtgtgcc tgctgaaatt gtgcaactg
 17521 tgagtgcttt agtttatgac aataagctaa aagcacacaa ggataagtca gctcaatgct
 17581 tcaaaatggt ctacaaagggt gttattacac atgatgtttc atctgcaatc aacagacctc
 17641 aaataggcgt tgtaagagaa tttcttacac gcaatcctgc ttggagaaaa gctgttttta
 17701 tctcacctta taattcacag aacgctgtag cttcaaaaat cttaggattg cctacgcaga
 17761 ctgttgattc atcacagggt tctgaatatg actatgtcat attcacacaa actactgaaa
 17821 cagcacactc ttgtaatgtc aaccgcttca atgtggctat cacaagggca aaaattggca
 17881 ttttgtgcat aatgtctgat agagatcttt atgacaaact gcaatttaca agtctagaaa
 17941 taccacgtcg caatgtggct acattacaag cagaaaatgt aactggactt ttttaaggact
 18001 gtagtaagat cactactggg cttcatccta cacaggcacc tacacacctc agcgttgata
 18061 taaaattcaa gactgaagga ttatgtgttg acataccagg cataccaaag gacatgacct
 18121 accgtagact catctctatg atgggtttca aatgaatta ccaagtcaat ggttacccta
 18181 atatgtttat caccocgcaa gaagctattc gtcacgttcg tgcgtggatt ggctttgatg
 18241 tagagggctg tcatgcaact agagatgctg tgggtactaa cctacctctc cagctaggat
 18301 tttctacagg tgtaactta gtagctgtac cgactggtta tgttgacact gaaaataaca
 18361 cagaattcac cagagttaat gcaaaacctc caccagtgga ccagtttaa catcttatac
 18421 cactcatgta taaaggcttg ccctggaatg tagtgcgtat taagatagta caaatgctca
 18481 gtgatacact gaaaggattg tcagacagag tcgtgttcgt cctttgggcg catggctttg
 18541 agcttacatc aatgaagtac tttgtcaaga ttggacctga aagaacgtgt tgtctgtgtg
 18601 acaaactgac aacttgcttt tctacttcat cagatactta tgcctgctgg aatcattctg
 18661 tgggttttga ctatgtctat aaccatttta tgattgatgt tcagcagtg ggttttacgg
 18721 gtaaccttca gagtaacct gaccaacatt gccaggtaaca tggaaatgca catgtggcta
 18781 gttgtgatgc tatcatgact agatgtttag cagtccatga gtgctttggt aagcgcgttg
 18841 attggctctg tgaataacct attataggag atgaactgag ggttaattct gcttgcagaa
 18901 aagtacaaca catggttgtg aagtctgcat tgcttctgta taagtttcca gtcttctatg
 18961 acattggaaa tccaaaggct atcaagtgtg tgcctcaggc tgaagtagaa tggagttct
 19021 acgatgctca gccatgtagt gacaaagctt acaaaataga ggaactcttc tattcttatg
 19081 ctacacatca cgataaattc actgatgggt tttgtttggt ttggaattgt aacgttgatc
 19141 gttaccagc caatgcaatt gtgtgtaggt ttgacacaag agtcttctca aacttgaact
 19201 taccaggctg tgatgggtgt agtttgtatg tgaataagca tgcattccac actccagctt
 19261 tcgataaaag tgcatttact aatttaagc aattgccttt cttttactat tctgatagtc
 19321 cttgtgagtc tcatggcaaa caagttagtg cggatattga ttatgttcca ctcaaactctg
 19381 ctacgtgat tacacgatgc aatttaggtg gtgctgtttg cagacaccat gcaaatgagt
 19441 accgacagta cttggatgca tataatatga tgatttctgc tggatttagc ctatggattt
 19501 acaacaatt tgatacttat aacctgtgga atacatttac caggttacag agtttagaaa
 19561 atgtggctta taatgttgtt aataaaggac actttgatgg acacgccgcg gaagcacctg
 19621 tttccatcat taataatgct gtttacacaa aggtagatgg tattgatgtg gagatctttg
 19681 aaaataagac aacacttctt gttaatgttg catttgagct ttgggctaag cgtaacatta
 19741 aaccagtgcc agagattaag atactcaata atttgggtgt tgatatogct gctaatactg
 19801 taatctggga ctacaaaaga gaagccccag cacatgtatc tacaataggt gctcgcacaa
 19861 tgactgacat tgccaagaaa cctactgaga gtgcttgttc ttcacttact gtcttgtttg
 19921 atggtagagt ggaaggacag gtagaccttt ttagaaacgc ccgtaatggt gttttaataa
 19981 cagaaggttc agtcaaagg ctaaacacctt caaagggacc agcacaagct agcgtcaatg
 20041 gagtcacatt aattggagaa tcagtaaaaa cacagtttaa ctactttaa aaagtagacg
 20101 gcattattca acagttgcct gaaacctact ttactcagag cagagactta gaggatttta

FIG. 10 Con't

20161 agccagatc acaaatggaa actgactttc tcgagctcgc tatggatgaa ttcatacagc
 20221 gatataagct cgagggtat gccttcgaac acatcgttta tggagatttc agtcatggac
 20281 aacttggcgg tcttcattta atgataggct tagccaagcg ctcacaagat tcaccactta
 20341 aattagagga ttttatccct atggacagca cagtgaaaaa ttacttcata acagatgcmc
 20401 aacaggttc atcaaatgt gtgtgttctg tgattgatct tttacttgat gactttgtcg
 20461 agataataaa gtcacaagat ttgtcagtga tttcaaaagt ggtcaagggt acaattgact
 20521 atgctgaaat ttcattcatg ctttgggtga aggatggaca tggttgaaacc tttaccctaa
 20581 aactacaagc aagtcaagcg tggcaaccag gtgttgccgat gcctaacttg tacaagatgc
 20641 aaagaatgct tcttgaaaag tgtgaccttc agaattatgg tgaaaatgct gttatacca
 20701 aaggaataat gatgaatgtc gcaaagtata ctcaactgtg tcaatactta aatacactta
 20761 ctttagctgt accctacaac atgagagtta ttcactttgg tgctggctct gataaaggag
 20821 ttgcaccagg tacagctgtg ctcagacaat ggttgccaac tggcacacta cttgtcgatt
 20881 cagatcttaa tgacttcgtc tccgacgcag attctacttt aattggagac tgtgcaacag
 20941 tacatacggc taataaatgg gaccttatta ttagcgatat gtatgacctt aggaccaaac
 21001 atgtgacaaa agagaatgac tctaaagaag ggtttttcac ttatctgtgt ggattataa
 21061 agcaaaaact agcctgggt ggtctatag ctgtaaagat aacagagcat tcttggatg
 21121 ctgaccttta caagcttatg ggccatttct catgggtggac agcttttgtt acaaatgtaa
 21181 atgcatcatc atcggaagca tttttaattg gggctaacta tcttggcaag ccgaaggaac
 21241 aaattgatgg ctataccatg catgctaact acattttctg gaggaacaca aatcctatcc
 21301 agttgtcttc ctattcactc tttgacatga gcaaatttcc tcttaaatta agaggaactg
 21361 ctgtaatgtc tcttaaggag aatcaaatca atgatatgat ttattctctt ctggaaaaag
 21421 gtaggttat cattagagaa aacaacagag ttgtggtttc aagtgatatt cttgtaaca
 21481 actaaacgaa catgtttatt tcttattat ttcttactct cactagtggg agtgaccttg
 21541 accggtgcac cacttttgat gatgttcaag ctcttaatta cactcaacat acttcatcta
 21601 tgaggggggt ttactatcct gatgaaatth ttagatcaga cactctttat ttaactcagg
 21661 atttatttct tccattttat tctaatgtta cagggtttca tactattaat catacgtttg
 21721 gcaaccctgt catacctttt aaggatggta tttattttgc tgccacagag aatcaaatg
 21781 ttgtccgtgg ttgggttttt ggtctacca tgaacaacaa gtcacagctg gtgattatta
 21841 ttaacaattc tactaatgtt gttatacagag catgtaactt tgaattgtgt gacaaccctt
 21901 tctttgctgt ttctaaacct atgggtacac agacacatac tatgatattc gataatgat
 21961 ttaattgcac tttogagtac atatctgatg ccttttctgct tgatgtttca gaaaagtcag
 22021 gtaattttaa acacttaoga gattttgtgt ttaaaaaata agatgggttt ctctatgttt
 22081 ataagggtcta tcaacctata gatgtagttc gtgatctacc ttctggtttt aacactttga
 22141 aacctatttt taagttgcct cttggtatta acattacaaa ttttagagcc attcttacag
 22201 ccttttcacc tgetcaagac atttggggca cgctcagctgc agcctatttt gttggctatt
 22261 taaagccaac tacatttatg ctcaagtatg atgaaaatgg tacaatcaca gatgctgttg
 22321 attgttctca aatccactt gctgaactca aatgctctgt taagagcttt gagattgaca
 22381 aaggaattta ccagacctct aatttcaggg ttgttccctc aggagatggt gtgagattcc
 22441 ctaatattac aaacttgggt ccttttggag aggtttttta tgctactaaa ttccttctg
 22501 tctatgcatg ggagagaaaa aaaatttcta atgtgttgc tgattactct gtgctctaca
 22561 actcaacatt ttttcaacc ttttaagtgt atggcgtttc tgccactaag ttgaatgatc
 22621 tttgcttctc caatgtctat gcagattcct ttgtagtcaa gggagatgat gtaagacaaa
 22681 tagcggcagg acaaaactggt gttattgctg attataatta taaattgcca gatgattca
 22741 tgggttgtgt ccttgcctgg aatactagga acattgatgc tacttcaact ggtaattata
 22801 attataaata taggtatctt agacatggca agcttaggcc ctttgagaga gacatatcta
 22861 atgtgccttt ctcccctgat ggcaaacctt gcacccacc tgctcttaat tgttattggc
 22921 cattaaatga ttatggtttt tacaccacta ctggcatttg ctaccaacct tacagagttg
 22981 tagtactttc ttttgaactt ttaaatgcac cggccacggt ttgtggacca aaattatcca
 23041 ctgaccttat taagaaccag tgtgtcaatt ttaattttta tggactcact ggtactgggtg
 23101 tgttaactcc ttcttcaaa agatttcaac catttcaaca atttggccgt gatgtttctg
 23161 atttcactga ttccgttoga gatcctaaaa catctgaaat attagacatt tcacctgtct
 23221 cttttggggg tgtaagtga attacactg gaacaaatgc ttcactgaa gttgctgttc
 23281 tatatcaaga tgttaactgc actgatgttt ctacagcaat tcatgcagat caactcacac
 23341 cagcttggcg catatattct actggaaaca atgtattcca gactcaagca ggctgtctta
 23401 taggagctga gcatgtcgac acttcttatg agtgcgacat tctatttga gctggcattt
 23461 gtgctagtta ccatacagtt tctttattac gtagtactag ccaaaaatct attgtggctt

FIG. 10 Con't

23521 atactatgtc tttaggtgct gatagttcaa ttgcttactc taataacacc attgctatac
 23581 ctactaactt ttcaattagc attactacag aagtaatgcc tgtttctatg gctaaaacct
 23641 ccgtagattg taatatgtac atctgcgag attctactga atgtgctaat ttgcttctcc
 23701 aatatggtag cttttgcaca caactaaatc gtgcactctc aggtattgct gctgaacagg
 23761 atcgcaacac acgtgaagtg ttcgctcaag tcaaacaaat gtacaaaacc ccaacttga
 23821 aatatttttg tggttttaat ttttcacaaa tattacctga ccctctaaag ccaactaaga
 23881 ggtcttttat tgaggacttg ctctttaata aggtgacact cgctgatgct ggcttcatga
 23941 agcaatatgg cgaatgccta ggtgatatta atgctagaga tctcatttgt gcgcagaagt
 24001 tcaatggact tacagtgttg ccacctctgc tcaactgatga tatgattgct gcctacactg
 24061 ctgctctagt tagtggtagt gccactgctg gatggacatt tgggtgctggc gctgctcttc
 24121 aaataccttt tgctatgcaa atggcatata ggttcaatgg cattggagtt acccaaaatg
 24181 ttctctatga gaaccaaaaa caaatcgcca accaatttaa caaggcgatt agtcaaattc
 24241 aagaatcact tacaacaaca tcaactgcat tgggcaagct gcaagacgtt gttaaccaga
 24301 atgctcaagc attaaacaca cttgttaaac aacttagctc taattttggt gcaatttcaa
 24361 gtgtgctaaa tgatatacctt tcgcgacttg ataaagtcga ggcgaggta caaattgaca
 24421 ggtaattac aggcagactt caaagccttc aaacctatgt aacacaaca ctaatcaggg
 24481 ctgctgaaat cagggcttct gctaactctg ctgctactaa aatgtctgag tgtgttcttg
 24541 gacaatcaaa aagagttgac ttttggtaa agggctacca ccttatgtcc tcccacaag
 24601 cagccccgca tgggtgttgc ttccatcatg tcacgtatgt gccatcccag gagaggaact
 24661 tcaccacagc gccagcaatt tgctcatgaag gcaaagcata cttccctcgt gaaggtgttt
 24721 ttgtgtttaa tggcacttct tggtttatta cacagaggaa cttcttttct ccacaaataa
 24781 ttactacaga caatacattt gtctcaggaa attgtgatgt cgttattggc atcattaaca
 24841 acacagttta tgatcctctg caacctgagc ttgactcatt caaagaagag ctggacaagt
 24901 acttcaaaaa tcatacatca ccagatgttg atcttggcga catttcaggc attaacgctt
 24961 ctgtcgtcaa cattcaaaaa gaaattgacc gcctcaatga ggtcgctaaa aatttaaatg
 25021 aatcactcat tgaccttcaa gaattggaa aatatgagca atataataaa tggccttggg
 25081 atgtttggct cggttctatt gctggactaa ttgccatcgt catgggtaca atcttgcctt
 25141 gttgcatgac tagttgttgc agttgcctca aggggtcatg ctcttgtggt tcttgcgca
 25201 agtttgatga ggatgactct gagccagttc tcaaggggtg caaattacat tacacataaa
 25261 cgaacttatg gatttgttta tgagattttt tactcttggg tcaattactg cacagccagt
 25321 aaaaattgac aatgcttctc ctgcaagtac tgttcatgct acagcaacga taccgctaca
 25381 agcctcactc ctttctggat ggcttgttat tggcgttgca tttcttgcgt ttttctagag
 25441 cgctacaaaa ataattgcgc tcaataaaag atggcagcta gccctttata agggctcca
 25501 gttcatttgc aatttactgc tgctatttgt taccatctat tcacatcttt tgcttgcgc
 25561 tgcaggtaag gaggcgcaat ttttgtacct ctatgccttg atataatttc tacaatgcat
 25621 caacgcattg agaattatta tgagatgttg gctttgttgg aagtgcaaat ccaagaacc
 25681 attactttat gatgccaaact actttgtttg ctggcacaca cataactatg actactgtat
 25741 accatataac agtgtcacag atacaattgt cgttactgaa ggtgacggca tttcaacacc
 25801 aaaactcaaa gaagactacc aaattgggtg ttattctgag gataggcact caggtgttaa
 25861 agactatgtc gttgtacatg gctatttcac cgaagtttac taccagcttg agtctacaca
 25921 aattactaca gacactggta ttgaaaatgc tacattcttc atctttaaca agcttgttaa
 25981 agaccaccg aatgtgcaaa tacacacaat cgacggctct tcaggagtgt ctaatccagc
 26041 aatggatcca atttatgatg agccgacgac gactactagc gtgcctttgt aagcacaaga
 26101 aagtgagtac gaacttatgt actcattcgt ttcggaagaa acaggtacgt taatagttaa
 26161 tagcgtactt ctttttcttg ctttctggtt attcttgcta gtcacactag ccatccttac
 26221 tgcgcttcca ttgtgtgcgt actgctgcaa tattgttaac gtgagtttag taaaaccaac
 26281 ggtttacgct tactcgcgct ttaaaaatct gaactcttct gaaggagtcc ctgatcttct
 26341 ggctaaaacg aactaactat tattattatt ctgtttgtaa ctttaacatt gcttatcatg
 26401 gcagacaacg gtactattac cgttgaggag cttaacaac tcctggaaca atggaaccta
 26461 gtaataggtt tcctattcct agcctggatt atgttactac aatttgccta ttctaactcg
 26521 aacaggtttt tgtacataat aaagcttgtt ttccctctggc tcttgtggcc agtaacactt
 26581 gcttgttttg tgcttgcgtg tgtctacaga attaattggg tgactggcgg gattgcgatt
 26641 gcaatggctt gtattgtagg cttgatgtgg cttagctact tcggtgcttc cttcaggctg
 26701 tttgctcgta cccgctcaat gtggctcatt aaccagaaa caaacattct tctcaatgtg
 26761 cctctccggg ggacaattgt gaccagaccg ctcattgaaa gtgaacttgt cattggtgct
 26821 gtgatcattc gtggctcact gcgaatggcc ggacactccc tagggcgctg tgacattaag

FIG. 10 Con't

26881 gacctgccaa aagagatcac tgtggtaca tcacgaacgc tttottatta caaattagga
 26941 gcgtcgcagc gtgtaggcac tgattcaggt tttgctgcat acaaccgcta ccgtattgga
 27001 aactataaat taaatacaga ccacgccggt agcaacgaca atattgcttt gctagtacag
 27061 taagtgacaa cagatgtttc atcttggtga cttccagggt acaatagcag agatattgat
 27121 tatcattatg aggactttca ggattgctat ttggaatcct gacgttataa taagttcaat
 27181 agtgagacaa ttatttaagc ctctaactaa gaagaattat tccggagttag atgatgaaga
 27241 acctatggag ttagattatc cataaaacga acatgaaaat tattctcttc ctgacattga
 27301 ttgtatttac atcttgccgag ctatatcact atcaggagtg tgtagagggt acgactgtac
 27361 tactaaaaga acctgcccc tcaggaacat acgagggcaa ttcaccattt caccctcttg
 27421 ctgacaataa atttgcaacta acttgcaacta gcacacactt tgcttttgct tgtgctgacg
 27481 gtactcgaca tacctatcag ctgctgcaa gatcagtttc accaaaactt ttcacagac
 27541 aagaggaggt tcaacaagag ctctactcgc cactttttct cattgttgct gctctagtat
 27601 ttttaatact ttgcttcacc attaagagaa agacagaatg aatgagctca ctttaattga
 27661 cttctatttg tgccttttag cctttctgct attccttggt ttaataatgc ttattatatt
 27721 ttggttttca ctcgaaatcc aggatctaga agaacctgt accaaagtct aaacgaacat
 27781 gaaacttctc attgttttga cttgtatttc tctatgcagt tgcatatgca ctgtagtaca
 27841 gcgctgtgca tctaataaac ctcatgtgct tgaagatcct tgtaaggtag aacactaggg
 27901 gtaatactta tagcactgct tggctttgtg ctctaggaaa ggttttacct tttcatagat
 27961 ggcacactat ggttcaaaaca tgcacaccta atgttactat caactgtcaa gatccagctg
 28021 gtggtgcgct tatagctagg tgttggtacc ttcacgaagg tcaccaaact gctgcattta
 28081 gagacgtact tgttgtttta aataaacgaa caaattaaaa tgtctgataa tggaccccaa
 28141 tcaaaccaac gtagtgcacc cgcattaca tttggtggac ccacagattc aactgacaat
 28201 aaccagaatg gaggacgcaa tggggcaagg ccaaaacagc gccgacccca aggtttacc
 28261 aataatactg cgtcttggtt cacagctctc actcagcatg gcaaggagga acttagattc
 28321 cctcgaggcc agggcgttcc aatcaacacc aatagtggtc cagatgacca aattggctac
 28381 taccgaagag ctacccgacg agttcgtggt ggtgacggca aaatgaaaga gctcagcccc
 28441 agatggtact tctattacct aggaactggc ccagaagctt cacttcccta cggcgctaac
 28501 aaagaaggca tcgatgggt tgcaactgag ggagccttga atacacccaa agaccacatt
 28561 ggcaccgca atcctaataa caatgctgcc accgtgctac aacttcctca aggaacaaca
 28621 ttgccaaaag gcttctacgc agaggggagc agagggcgca gtcaagcctc ttctcgctcc
 28681 tcatcacgta gtgcggtaa ttcaagaaat tcaactcctg gcagcagtag gggaaattct
 28741 cctgctcgaa tggctagcgg aggtggtgaa actgcctcgc cgctattgct gctagacaga
 28801 ttgaaccagc ttgagagcaa agtttctggt aaaggccaac aacaacaagg ccaaactgtc
 28861 actaagaaat ctgctgctga ggcatctaaa aagcctcgcc aaaaacgtac tggcacaata
 28921 cagtacaacg tcaactcaagc atttgggaga cgtgggtccag aacaaacca aggaaatttc
 28981 ggggaccaag acctaactcag acaaggaaact gattacaaac attggccgca aattgcacaa
 29041 tttgctccaa gtgcctctgc attcctttgga atgtcacgca ttggcatgga agtcacacct
 29101 tcgggaacat ggctgactta tcatggagcc attaaattgg atgacaaaga tccacaattc
 29161 aaagacaacg tcaactgct gaacaagcac attgacgcat aaaaacatt cccaccaaca
 29221 gagcctaaaa aggacaaaa gaaaaagact gatgaagctc agcctttgcc gcagagacaa
 29281 aagaagcagc ccaactgtgac tcttcttctc gcgctgaca tggatgattt ctccagacaa
 29341 ottcaaaatt ccatgagtgg agcttctgct gattcaactc aggcataaac actcatgatg
 29401 accacacaag gcagatgggc tatgtaaacg ttttcgcaat tccgtttacg atacatagtc
 29461 tactcttggt cagaatgaat tctcgtact aacagcaca agtaggttta gtttaactta
 29521 atctcatata gcaatcttta atcaatggt aacattaggg aggacttgaa agagccacca
 29581 cattttcatc gaggccagc ggagtacgat cgaggggaca gtgaataatg ctagggagag
 29641 ctgcctatat ggaagagccc taatgtgtaa aattaatttt agtagtgcta tccccatgtg
 29701 attttaatag cttcttagga gaatgacaaa aaaaaaaaaa aa

FIG. 10 Con't

1 - ATATTAGGTTTTTACCTACCCAGGAAAAGCCAACCAACCTCGATCTCTTGTAGATCTGTT - 60
 - I L G F Y L P R K S Q P T S I S C R S V
 - Y * V F T Y P G K A N Q P R S L V D L F
 - I R F L P T Q E K P T N L D L L * I C S
 61 - CTCTAAACGAACTTTAAAATCTGTGTAGCTGTCGCTCGGCTGCATGCCTAGTGCACCTAC - 120
 - L * T N F K I C V A V A R L H A * C T Y
 - S K R T L K S V * L S L G C M P S A P T
 - L N E L * N L C S C R S A A C L V H L R
 121 - GCAGTATAAACATAATAAATTTTACTGTCGTTGACAAGAAACGAGTAACTCGTCCCTCT - 180
 - A V * T I I N F T V V D K K R V T R P S
 - Q Y K Q * * I L L S L T R N E * L V P L
 - S I N N N K F Y C R * Q E T S N S S L F
 181 - TCTGCAGACTGCTTACGGTTTCGTCCTGTTGCAGTCGATCATCAGCATACCTAGGTTTC - 240
 - S A D C L R F R P C C S R S S A Y L G F
 - L Q T A Y G F V R V A V D H Q H T * V S
 - C R L L T V S S V L Q S I I S I P R F R
 241 - GTCGGGTGTGACCGAAAGGTAAGATGGAGAGCCTTGTCTTGGTGTCAACGAGAAAACA - 300
 - V R V * P K G K M E S L V L G V N E K T
 - S G C D R K V R W R A L F L V S T R K H
 - P G V T E R * D G E P C S W C Q R E N T
 301 - CACGTCCAACCTCAGTTTGCCTGCTCCTCAGGTTAGAGACGTGCTAGTGCCTGGCTTCGGG - 360
 - H V Q L S L P V L Q V R D V L V R G F G
 - T S N S V C L S F R L E T C * C V A S G
 - R P T Q F A C P S G * R R A S A W L R G
 361 - GACTCTGTGGAAGAGGCCCTATCGGAGGCACGTGAACACCTCAAAAATGGCACTTGTGGT - 420
 - D S V E E A L S E A R E H L K N G T C G
 - T L W K R P Y R R H V N T S K M A L V V
 - L C G R G P I G R T * T P Q K W H L W S
 421 - CTAGTAGAGCTGGAAAAGGCGTACTGCCCCAGCTTGAACAGCCCTATGTGTTCAATAAA - 480
 - L V E L E K G V L P Q L E Q P Y V F I K
 - * * S W K K A Y C P S L N S P M C S L N
 - S R A G K R R T A P A * T A L C V H * T
 481 - CGTTCTGATGCCTTAAGCACCAATCACGGCCACAAGGTCGTTGAGCTGGTTGCAGAAATG - 540
 - R S D A L S T N H G H K V V E L V A E M
 - V L M P * A P I T A T R S L S W L Q K W
 - F * C L K H Q S R P Q G R * A G C R N G
 541 - GACGGCATTACGTCGTCGTCGTTAGCGGTATAACACTGGGAGTACTCGTGCCACATGTGGGC - 600
 - D G I Q Y G R S G I T L G V L V P H V G
 - T A F S T V V A V * H W E Y S C H M W A
 - R H S V R S * R Y N T G S T R A T C G R
 601 - GAAACCCCAATTGCATACCGCAATGTTCTTCTTTCGTAAGAACGGTAATAAGGGAGCCGGT - 660
 - E T P I A Y R N V L L R K N G N K G A G
 - K P Q L H T A M F F F V R T V I R E P V
 - N P N C I P Q C S S S * E R * * G S R W
 661 - GGTATAGCTATGGCATCGATCTAAAGTCTTATGACTTAGGTGACGAGCTTGGCACTGAT - 720
 - G H S Y G I D L K S Y D L G D E L G T D
 - V I A M A S I * S L M T * V T S L A L I
 - S * L W H R S K V L * L R * R A W H * S
 721 - CCCATTGAAGATTATGAACAAAACCTGGAACACTAAGCATGGCAGTGGTGCCTCCGTGAA - 780
 - P I E D Y E Q N W N T K H G S G A L R E
 - P L K I M N K T G T L S M A V V H S V N
 - H * R L * T K L E H * A W Q W C T P * T
 781 - CTCCTCGTGTAGCTCAATGGAGGTGCAGTCACTCGCTATGTCGACAACAATTTCTGTGGC - 840
 - L T R E L N G G A V T R Y V D N N F C G
 - S L V S S M E V Q S L A M S T T I S V A
 - H S * A Q W R C S H S L C R Q Q F L W P

FIG. 11

841 - CCAGATGGGTACCCTCTTGATTGCATCAAAGATTTTCTCGCACGCGGGCAAGTCAATG - 900
 - P D G Y P L D C I K D F L A R A G K S M
 - Q M G T L L I A S K I F S H A R A S Q C
 - R W V P S * L H Q R F S R T R G Q V N V
 901 - TGCACCTTTCCGAACAACCTTGATTACATCGAGTCGAAGAGAGGTGTCTACTGCTGCCGT - 960
 - C T L S E Q L D Y I E S K R G V Y C C R
 - A L F P N N L I T S S R R E V S T A A V
 - H S F R T T * L H R V E E R C L L L P *
 961 - GACCATGAGCATGAAATTGCCTGGTTCACTGAGCGCTCTGATAAGAGCTACGAGCACCAG - 1020
 - D H E H E I A W F T E R S D K S Y E H Q
 - T M S M K L P G S L S A L I R A T S T R
 - P * A * N C L V H * A L * * E L R A P D
 1021 - ACACCTTCGAAATTAAGAGTGCCAAGAATTTGACACTTCAAAGGGGAATGCCCAAAG - 1080
 - T P F E I K S A K K F D T F K G E C P K
 - H P S K L R V P R N L T L S K G N A Q S
 - T L R N * E C Q E I * H F Q R G M P K V
 1081 - TTTGTGTTTCTCTTAACTCAAAGTCAAAGTCATTCAACCACGTGTTGAAAAGAAAAG - 1140
 - F V F P L N S K V K V I Q P R V E K K K
 - L C F L L T Q K S K S F N H V L K R K R
 - C V S S * L K S Q S H S T T C * K E K D
 1141 - ACTGAGGGTTTCATGGGGCGTATACGCTCTGTGTACCCTGTTGCATCTCCACAGGAGTGT - 1200
 - T E G F M G R I R S V Y P V A S P Q E C
 - L R V S W G V Y A L C T L L H L H R S V
 - * G F H G A Y T L C V P C C I S T G V *
 1201 - AACAAATATGCACCTTGCTACCTTGATGAAATGTAATCATTGCGATGAAGTTTCATGGCAG - 1260
 - N N M H L S T L M K C N H C D E V S W Q
 - T I C T C L P * * N V I I A M K F H G R
 - Q Y A L V Y L D E M * S L R * S F M A D
 1261 - ACGTGGCACTTCTGAAAGCCACTTGTAACATGTGGCACTGAAAATTTAGTTATTGAA - 1320
 - T C D F L K A T C E H C G T E N L V I E
 - R A T F * K P L V N I V A L K I * L L K
 - V R L S E S H L * T L W H * K F S Y * R
 1321 - GGACCTACTACATGTGGGTACCTACCTACTAATGTGTAGTGAAAATGCCATGTCCTGCC - 1380
 - G P T T C G Y L P T N A V V K M P C P A
 - D L L H V G T Y L L M L * * K C H V L P
 - T Y Y M W V P T Y * C C S E N A M S C L
 1381 - TGTCAAAGACCCAGAGATTGGACCTGAGCATAGTGTGCAGATTATACAACCACTCAAAC - 1440
 - C Q D P E I G P E H S V A D Y H N H S N
 - V K T Q R L D L S I V L Q I I T T T Q T
 - S R P R D W T * A * C C R L S Q P L K H
 1441 - ATTGAAACTCGACTCCGCAAGGGAGGTAGGACTAGATGTTTTGGAGGCTGTGTGTTGCC - 1500
 - I E T R L R K G R T R C F G G C V F A
 - L K L D S A R E V G L D V L E A V C L P
 - * N S T P Q G R * D * M F W R L C V C L
 1501 - TATGTTGGCTGCTATAATAAGCGTGCCTACTGGGTCCTCGTGCTAGTGCTGATATTGGC - 1560
 - Y V G C Y N K R A Y W V P R A S A D I G
 - M L A A I I S V P T G F L V L V L I L A
 - C W L L * * A C L L G S S C * C * Y W L
 1561 - TCAGCCATACTGGCATTACTGGTGACAATGTGGAGACCTGAATGAGGATCTCCTTGAG - 1620
 - S G H T G I T G D N V E T L N E D L L E
 - Q A I L A L L V T M W R P * M R I S L R
 - R P Y W H Y W * Q C G D L E * G S P * D
 1621 - ATACTGAGTCGTGAACGTGTTAACAATTAACATTGTTGGCGATTTTCATTGAATGAAGAG - 1680
 - I L S R E R V N I N I V G D F H L N E E
 - Y * V V N V L T L T L L A I F I * M K R
 - T E S * T C * H * H C W R F S F E * R G

FIG. 11 Con't

1681 - GTTGCCATCATTTTGGCATCTTTCTCTGCTTCTACAAGTGCCTTTATTGACACTATAAAG - 1740
 - V A I I L A S F S A S T S A F I D T I K
 - L P S F W H L S L L L Q V P L L T L * R
 - C H H F G I F L C F Y K C L Y * H Y K E
 1741 - AGTCTTGATTACAAGTCTTTCAAACCATTGTTGAGTCCTGCGGTAACATAAAGTTACC - 1800
 - S L D Y K S F K T I V E S C G N Y K V T
 - V L I T S L S K P L L S P A V T I K L P
 - S * L Q V F Q N H C * V L R * L * S Y Q
 1801 - AAGGAAAGCCCGTAAAAGGTGCTTGAACATTGGACAACAGAGATCAGTTTAAACACCA - 1860
 - K G K P V K G A W N I G Q Q R S V L T P
 - R E S P * K V L G T L D N R D Q F * H H
 - G K A R K R C L E H W T T E I S F N T T
 1861 - CTGTGTGGTTTTCCCTCACAGGCTGCTGGTGTATCAGATCAATTTTTCGCGCACACTT - 1920
 - L C G F P S Q A A G V I R S I F A R T L
 - C V V F P H R L L V L S D Q F L R A H L
 - V W F S L T G C W C Y Q I N F C A H T *
 1921 - GATGCAGCAAACCACTCAATTCCTGATTGCAAAGAGCAGCTGTACCATACTTGATGGT - 1980
 - D A A N H S I P D L Q R A A V T I L D G
 - M Q Q T T Q F L I C K E Q L S P Y L M V
 - C S K P L N S * F A K S S C H H T * W Y
 1981 - ATTTCTGAACAGTCATTACGCTTGTGCGACCCATGGTTTATACTTCAGACCTGCTCACC - 2040
 - I S E Q S L R L V D A M V Y T S D L L T
 - F L N S H Y V L S T P W F I L Q T C S P
 - F * T V I T S C R R H G L Y F R P A H Q
 2041 - AACAGTGTCAATTATTATGGCATATGTAAGTGGTCTGTACAACAGACTTCTCAGTGG - 2100
 - N S V I I M A Y V T G G L V Q Q T S Q W
 - T V S L L W H M * L V V L Y N R L L S G
 - Q C H Y Y G I C N W W S C T T D F S V V
 2101 - TTGTCTAATCTTTTGGGCACTACTGTTGAAAACTCAGGCCTATCTTTGAATGGATTGAG - 2160
 - L S N L L G T T V E K L R P I F E W I E
 - C L I F W A L L L K N S G L S L N G L R
 - V * S F G H Y C * K T Q A Y L * M D * G
 2161 - GCGAAACTTAGTGCAGGAGTTGAATTTCTCAAGGATGCTTGGGAGATTCTCAAATTTCTC - 2220
 - A K L S A G V E F L K D A W E I L K F L
 - R N L V Q E L N F S R M L G R F S N F S
 - E T * C R S * I S Q G C L G D S Q I S H
 2221 - ATTACAGGTGTTTTGACATCGTCAAGGGTCAAATACAGGTTGCTTCAGATAACATCAAG - 2280
 - I T G V F D I V K G Q I Q V A S D N I K
 - L Q V F L T S S R V K Y R L L Q I T S R
 - Y R C F * H R Q G S N T G C F R * H Q G
 2281 - GATTGTGTAATGCTTCATTGATGTTGTTAAACAAGGCACTCGAAATGTGCATTGATCAA - 2340
 - D C V K C F I D V V N K A L E M C I D Q
 - I V * N A S L M L L T R H S K C A L I K
 - L C K M L H * C C * Q G T R N V H * S S
 2341 - GTCACTATCGCTGGCGCAAAGTTGCGATCACTCAACTAGGTGAAGTCTTCATCGCTCAA - 2400
 - V T I A G A K L R S L N L G E V F I A Q
 - S L S L A Q S C D H S T * V K S S S L K
 - H Y R W R K V A I T Q L R * S L H R S K
 2401 - AGCAAGGGACTTTACCGTCAGTGTATACGTGGCAAGGAGCAGCTGCAACTACTCATGCCT - 2460
 - S K G L Y R Q C I R G K E Q L Q L L M P
 - A R D F T V S V Y V A R S S C N Y S C L
 - Q G T L P S V Y T W Q G A A A T T H A S
 2461 - CTTAAGGCACCAAAGAAGTAACCTTTCTTGAAGGTGATTACATGACACAGTACTTACC - 2520
 - L K A P K E V T F L E G D S H D T V L T
 - L R H Q K K * P F L K V I H M T Q Y L P
 - * G T K R S N L S * R * F T * H S T Y L

FIG. 11 Con't

2521 - TCTGAGGAGGTTGTTCTCAAGAACGGTGAAGTCTGAAGCACTCGAGACGCCCGTTGATAGC - 2580
 - S E E V V L K N G E L E A L E T P V D S
 - L R R L F S R T V N S K H S R R P L I A
 - * G G C S Q E R * T R S T R D A R * * L
 2581 - TTCACAAATGGAGCTATCGTCGGCACACCAGTCTGTGTAATGGCCTCATGCTCTTAGAG - 2640
 - F T N G A I V G T P V C V N G L M L L E
 - S Q M E L S S A H Q S V * M A S C S * R
 - H K W S Y R R H T S L C K W P H A L R D
 2641 - ATTAAGGACAAAGAACAATACTGCGCATTGTCTCCTGGTTTACTGGCTACAAACAATGTC - 2700
 - I K D K E Q Y C A L S P G L L A T N N V
 - L R T K N N T A H C L L V Y W L Q T M S
 - * G Q R T I L R I V S W F T G Y K Q C L
 2701 - TTTTCGCTTAAAAGGGGGTGCACCAATTAAGGTGTAACTTTGGAGAAGATACTGTTTGG - 2760
 - F R L K G G A P I K G V T F G E D T V W
 - F A * K G V H Q L K V * P L E K I L F G
 - S L K R G C T N * R C N L W R R Y C L G
 2761 - GAAGTTCAAGGTTACAAGAATGTGAGAATCACATTTGAGCTTGATGAACGTGTTGACAAA - 2820
 - E V Q G Y K N V R I T F E L D E R V D K
 - K F K V T R M * E S H L S L M N V L T K
 - S S R L Q E C E N H I * A * * T C * Q S
 2821 - GTGCTTAATGAAAAGTGTCTGTCTACACTGTTGAATCCGGTACCGAAGTTACTGAGTTT - 2880
 - V L N E K C S V Y T V E S G T E V T E F
 - C L M K S A L S T L L N P V P K L L S L
 - A * * K V L C L H C * I R Y R S Y * V C
 2881 - GCATGTGTTGTAGCAGAGGCTGTTGTGAAGACTTTACAACCGTTTCTGATCTCCTTACC - 2940
 - A C V V A E A V V K T L Q P V S D L L T
 - H V L * Q R L L * R L Y N Q F L I S L P
 - M C C S R G C C E D F T T S F * S P Y Q
 2941 - AACATGGGTATTGATCTTGATGAGTGGAGTGTAGCTACATTCTACTTATTGATGATGCT - 3000
 - N M G I D L D E W S V A T F Y L F D D A
 - T W V L I L M S G V * L H S T Y L M M L
 - H G Y * S * * V E C S Y I L L I * * C W
 3001 - GGTGAAGAAAACCTTTTCATCACGTATGTATGTTTCCTTTTACCTCCAGATGAGGAAGAA - 3060
 - G E E N F S S R M Y C S F Y P P D E E E
 - V K K T F H H V C I V P F T L Q M R K K
 - * R K L F I T Y V L F L L P S R * G R R
 3061 - GAGGACGATGCAGAGTGTGAGGAAGAAGAAATTGATGAAACCTGTGAACATGAGTACGGT - 3120
 - E D D A E C E E E E I D E T C E H E Y G
 - R T M Q S V R K K L M K P V N M S T V
 - G R C R V * G R R N * * N L * T * V R Y
 3121 - ACAGAGGATGATTATCAAGGTCTCCCTCTGGAATTTGGTGCCTCAGCTGAAACAGTTCGA - 3180
 - T E D D Y Q G L P L E F G A S A E T V R
 - Q R M I I K V S L W N L V P Q L K Q F E
 - R G * L S R S P S G I W C L S * N S S S
 3181 - GTTGAGGAAGAAGAAGAGGAAAGTGGCTGGATGATACTACTGAGCAATCAGAGATTGAG - 3240
 - V E E E E E E D W L D D T T E Q S E I E
 - L R K K R K T G W M I L L S N Q R L S
 - * G R R R G R L A G * Y Y * A I R D * A
 3241 - CCAGAACCAGAACCTACACCTGAAGAACCAGTTAATCAGTTTACTGGTTATTTAAAACCT - 3300
 - P E P E P T P E E P V N Q F T G Y L K L
 - Q N Q N L H L K N Q L I S L L V I * N L
 - R T R T Y T * R T S * S V Y W L F K T Y
 3301 - ACTGACAATGTTGCCATTAATGTGTTGACATCGTTAAGGAGGCACAAAGTGCTAATCCT - 3360
 - T D N V A I K C V D I V K E A Q S A N P
 - L T M L P L N V L T S L R R H K V L I L
 - * Q C C H * M C * H R * G G T K C * S Y

FIG. 11 Con't

3361 - ATGGTGATTGTAAATGCTGCTAACATACACCTGAAACATGGTGGTGGTGTAGCAGGTGCA - 3420
 - M V I V N A A N I H L K H G G G V A G A
 - W * L * M L L T Y T * N M V V V * Q V H
 - G D C K C C * H T P E T W W W C S R C T
 3421 - CTCAACAAGGCAACCAATGGTGCCATGCAAAGGAGAGTGATGATTACATTAAGCTAAAT - 3480
 - L N K A T N G A M Q K E S D D Y I K L N
 - S T R Q P M V P C K R R V M I T L S * M
 - Q Q G N Q W C H A K G E * * L H * A K W
 3481 - GGCCCTCTTACAGTAGGAGGGTCTGTTTGTCTTCTGGACATAATCTGCTAAGAAGTGT - 3540
 - G P L T V G G S C L L S G H N L A K K C
 - A L L Q * E G L V C F L D I I L L R S V
 - S P Y S R R V L F A F W T * S C * E V S
 3541 - CTGCATGTTGTTGGACCTAACCTAAATGCAGGTGAGGACATCCAGCTTCTTAAGGCAGCA - 3600
 - L H V V G P N L N A G E D I Q L L K A A
 - C M L L D L T * M Q V R T S S F L R Q H
 - A C C W T * P K C R * G H P A S * G S I
 3601 - TATGAAAATTTCAATTCACAGGACATCTTACTTGACACATTGTTGTGTCAGCAGGCATATTT - 3660
 - Y E N F N S Q D I L L A P L L S A G I F
 - M K I S I H R T S Y L H H C C Q Q A Y L
 - * K F Q F T G H L T C T I V V S R H I W
 3661 - GGTGCTAAACCACTTCAGTCTTTACAAGTGTGCGTGCAGACGGTTCGTACACAGGTTTAT - 3720
 - G A K P L Q S L Q V C V Q T V R T Q V Y
 - V L N H F S L Y K C A C R R F V H R F I
 - C * T T S V F T S V R A D G S Y T G L Y
 3721 - ATTGCACTCAATGACAAAGCTCTTTATGAGCAGGTTGTCATGGATTATCTTGATAACCTG - 3780
 - I A V N D K A L Y E Q V V M D Y L D N L
 - L Q S M T K L F M S R L S W I I L I T *
 - C S Q * Q S S L * A G C H G L S * * P E
 3781 - AAGCCTAGAGTGAAGCACCTAAACAAGAGGCCACCAACACAGAAGATTCCAAAACCT - 3840
 - K P R V E A P K Q E E P P N T E D S K T
 - S L E W K H L N K R S H Q T Q K I P K L
 - A * S G S T * T R G A T K H R R F Q N *
 3841 - GAGGAGAAATCTGTCGTACAGAAGCCTGTGATGTGAAGCCAAAATTAAGGCCTGCATT - 3900
 - E E K S V V Q K P V D V K P K I K A C I
 - R R N L S Y R S L S M * S Q K L R P A L
 - G E I C R T E A C R C E A K N * G L H *
 3901 - GATGAGGTTACCACAACACTGGAAGAACTAAGTTTCTTACCAATAAGTTACTCTTGT - 3960
 - D E V T T T L E E T K F L T N K L L L F
 - M R L P Q H W K K L S F L P I S Y S C L
 - * G Y H N T G R N * V S Y Q * V T L V C
 3961 - GCTGATATCAATGGTAAGCTTTACCATGATTCTCAGAACATGCTTAGAGGTGAAGATATG - 4020
 - A D I N G K L Y H D S Q N M L R G E D M
 - L I S M V S F T M I L R T C L E V K I C
 - * Y Q W * A L P * F S E H A * R * R Y V
 4021 - TCTTTCCTTGAGAAGGATGCACCTTACATGGTAGGTGATGTTATCACTAGTGGTGATATC - 4080
 - S F L E K D A P Y M V G D V I T S G D I
 - L S L R R M H L T W * V M L S L V V I S
 - F P * E G C T L H G R * C Y H * W * Y H
 4081 - ACTTGTGTTGTAATACCCCTCCAAAAGGCTGGTGGCACTACTGAGATGCTCTCAAGAGCT - 4140
 - T C V V I P S K K A G G T T E M L S R A
 - L V L * Y P P K R L V A L L R C S Q E L
 - L C C N T L Q K G W W H Y * D A L K S F
 4141 - TTGAAGAAAGTGCCAGTTGATGAGTATATAACCACGTACCCTGGACAAGGATGTGCTGGT - 4200
 - L K K V P V D E Y I T T Y P G Q G C A G
 - * R K C Q L M S I * P R T L D K D V L V
 - E E S A S * * V Y N H V P W T R M C W L

FIG. 11 Con't

4201 - TATACACTTGAGGAAGCTAAGACTGCTCTTAAGAAATGCAAATCTGCATTTTATGTACTA - 4260
 - Y T L E E A K T A L K K C K S A F Y V L
 - I H L R K L R L L L R N A N L H F M Y Y
 - Y T * G S * D C S * E M Q I C I L C T T
 4261 - CCTTCAGAAGCACCTAATGCTAAGGAAGAGATTCTAGGAAGTATCCTGGAATTTGAGA - 4320
 - P S E A P N A K E E I L G T V S W N L R
 - L Q K H L M L R K R F * E L Y P G I * E
 - F R S T * C * G R D S R N C I L E F E R
 4321 - GAAATGCTTGCTCATGCTGAAGAGACAAGAAAATTAATGCCTATATGCATGGATGTTAGA - 4380
 - E M L A H A E E T R K L M P I C M D V R
 - K C L L M L K R Q E N * C L Y A W M L E
 - N A C S C * R D K K I N A Y M H G C * S
 4381 - GCCATAATGGCAACCATCCAACGTAAGTATAAAGGAATTAATAATCAAGAGGGCATCGTT - 4440
 - A I M A T I Q R K Y K G I K I Q E G I V
 - P * W Q P S N V S I K E L K F K R A S L
 - H N G N H P T * V * R N * N S R G H R *
 4441 - GACTATGGTGTCCGATTCTTCTTTTATACTAGTAAAGAGCCTGTAGCTTCTATTATTACG - 4500
 - D Y G V R F F F Y T S K E P V A S I I T
 - T M V S D S S F I L V K S L * L L L L R
 - L W C P I L L L Y * * R A C S F Y Y Y E
 4501 - AAGCTGAAGTCTCTAAATGAGCCGCTTGTCACAATGCCAATGGTTATGTGACACATGGT - 4560
 - K L N S L N E P L V T M P I G Y V T H G
 - S * T L * M S R L S Q C Q L V M * H M V
 - A E L S K * A A C H N A N W L C D T W F
 4561 - TTTAATCTTGAAGAGGCTGCGCGTGTATGCGTTCTTAAAGCTCCTGCCGTAGTGTC - 4620
 - F N L E E A A R C M R S L K A P A V V S
 - L I L K R L R A V C V L L K L L P * C Q
 - * S * R G C A L Y A F S * S S C R S V S
 4621 - GTATCATCACCAGATGCTGTACTACATATAATGGATACCTCACTTCGTATCAAAGACA - 4680
 - V S S P D A V T T Y N G Y L T S S S K T
 - Y H H Q M L L H I M D T S L R H Q R H
 - I I T R C C Y Y I * W I P H F V I K D I
 4681 - TCTGAGGAGCACTTTGTAGAAACAGTTTCTTTGGCTGGCTCTTACAGAGATTGGTCCTAT - 4740
 - S E E H F V E T V S L A G S Y R D W S Y
 - L R S T L * K Q F L W L A L T E I G P I
 - * G A L C R N S F F G W L L Q R L V L F
 4741 - TCAGGACAGCGTACAGAGTTAGGTGTTGAATTTCTTAAAGCGTGGTGACAAAATTGTGTAC - 4800
 - S G Q R T E L G V E F L K R G D K I V Y
 - Q D S V Q S * V L N F L S V V T K L C T
 - R T A Y R V R C * I S * A W * Q N C V P
 4801 - CACACTCTGGAGAGCCCCGTGAGTTTCTTGTGACGGTGAGGTTCTTTCACTTGACAAA - 4860
 - H T L E S P V E F H L D G E V L S L D K
 - T L W R A P S S F I L T V R F F H L T N
 - H S G E P R R V S S * R * G S F T * Q T
 4861 - CTAAAGAGTCTCTTATCCCTGCGGGAGGTTAAGACTATAAAAGTTCACAAGTGTGGAC - 4920
 - L K S L L S L R E V K T I K V F T T V D
 - * R V S Y P C G R L R L * K C S Q L W T
 - K E S L I P A G G * D Y K S V H N C G Q
 4921 - AACACTAATCTCCACACACAGCTTGTGGATATGTCTATGACATATGGACAGCAGTTTGGT - 4980
 - N T N L H T Q L V D M S M T Y G Q Q F G
 - T L I S T H S L W I C L * H M D S S L V
 - H * S P H T A C G Y V Y D I W T A V W S
 4981 - CCAACATACTGGATGGTGTGCTGATGTTACAAAATTAACCTCATGTAATCATGAGGGT - 5040
 - P T Y L D G A D V T K I K P H V N H E G
 - Q H T W M V L M L Q K L N L M * I M R V
 - N I L G W C * C Y K N * T S C K S * G *

FIG. 11 Con't

5041 - AAGACTTTCTTTGTACTACCTAGTGATGACACACTACGTAGTGAAGCTTTCGAGTACTAC - 5100
 - K T F F V L P S D D T L R S E A F E Y Y
 - R L S L Y Y L V M T H Y V V K L S S T T
 - D F L C T T * * * H T T * * S F R V L P
 5101 - CATACTCTTGATGAGAGTTTCTTGGTAGGTACATGTCTGCTTTAAACCACACAAAGAAA - 5160
 - H T L D E S F L G R Y M S A L N H T K K
 - I L L M R V F L V G T C L L * T T Q R N
 - Y S * * E F S W * V H V C F K P H K E M
 5161 - TGGAAATTTCTCAAGTTGGTGGTTTAACTTCAATTAATGGGCTGATAACAATTGTTAT - 5220
 - W K F P Q V G G L T S I K W A D N N C Y
 - G N F L K L V V * L Q L N G L I T I V I
 - E I S S S W W F N F N * M G * * Q L L F
 5221 - TTGTCTAGTGTTTATTAGCACTTCAACAGCTTGAAGTCAAATTCATGCACCAGCACTT - 5280
 - L S S V L L A L Q Q L E V K F N A P A L
 - C L V F Y * H F N S L K S N S M H Q H F
 - V * C F I S T S T A * S Q I Q C T S T S
 5281 - CAAGAGGCTTATTATAGAGCCCGTGTGGTGTGCTGCTAACTTTGTGCACTCATACTC - 5340
 - Q E A Y Y R A R A G D A A N F C A L I L
 - K R L I I E P V L V M L L T F V H S Y S
 - R G L L * S P C W * C C * L L C T H T R
 5341 - GCTTACAGTAATAAACTGTTGGCGAGCTTGGTGTGTCAGAGAACTATGACCCATCTT - 5400
 - A Y S N K T V G E L G D V R E T M T H L
 - L T V I K L L A S L V M S E K L * P I F
 - L Q * * N C W R A W * C Q R N Y D P S S
 5401 - CTACAGCATGCTAATTTGGAATCTGCAAAGCGAGTCTTAATGTGGTGTGTAACATTGT - 5460
 - L Q H A N L E S A K R V L N V V C K H C
 - Y S M L I W N L Q S E F L M W C V N I V
 - T A C * F G I C K A S S * C G V * T L W
 5461 - GGTCAGAAACTACTACCTTAACGGGTGTAGAAGCTGTGATGTATATGGGTACTCTATCT - 5520
 - G Q K T T T L T G V E A V M Y M G T L S
 - V R K L L P * R V * K L * C I W V L Y L
 - S E N Y Y L N G C R S C D V Y G Y S I L
 5521 - TATGATAATCTTAAGACAGGTGTTTCCATTCCATGTGTGTGGTGTGATGCTACACAA - 5580
 - Y D N L K T G V S I P C V C G R D A T Q
 - M I I L R Q V F P F H V C V V V M L H N
 - * * S * D R C F H S M C V W S * C Y T I
 5581 - TATCTAGTACAACAAGAGTCTTCTTTTGTATGATGCTGCACCACCTGCTGAGTATAAAA - 5640
 - Y L V Q Q E S S F V M M S A P P A E Y K
 - I * Y N K S L L L L * C L H H L L S I N
 - S S T T R V F F C Y D V C T T C * V * I
 5641 - TTACAGCAAGGTACATTCTTATGTGCGAATGAGTACACTGGTAACTATCAGTGTGGTCAT - 5700
 - L Q Q G T F L C A N E Y T G N Y Q C G H
 - Y S K V H S Y V R M S T L V T I S V V I
 - T A R Y I L M C E * V H W * L S V W S L
 5701 - TACACTCATATAACTGCTAAGGAGACCTCTATCGTATTGACGGAGCTCACCTTACAAAG - 5760
 - Y T H I T A K E T L Y R I D G A H L T K
 - T L I * L L R R P S I V L T E L T L Q R
 - H S Y N C * G D P L S Y * R S S P Y K D
 5761 - ATGTCAGAGTACAAAGGACCAGTGACTGATGTTTTCTACAAGGAAACATCTTACTACTACA - 5820
 - M S E Y K G P V T D V F Y K E T S Y T T
 - C Q S T K D Q * L M F S T R K H L T L Q
 - V R V Q R T S D * C F L Q G N I L H Y N
 5821 - ACCATCAAGCCTGTGTCGTATAAACTCGATGGAGTTACTTACACAGAGATTGAACCAAAA - 5880
 - T I K P V S Y K L D G V T Y T E I E P K
 - P S S L C R I N S M E L L T Q R L N Q N
 - H Q A C V V * T R W S Y L H R D * T K I

FIG. 11 Con't

5881 - TTGGATGGGTATTATAAAAAGGATAATGCTTACTATACAGAGCAGCCTATAGACCTTGTA - 5940
 - L D G Y Y K K D N A Y Y T E Q P I D L V
 - W M G I I K R I M L T I Q S S L * T L Y
 - G W V L * K G * C L L Y R A A Y R P C T
 5941 - CCAACTCAACCATTACCAAATGCGAGTTTGGATAATTTCAAACCTCACATGTTCTAACACA - 6000
 - P T Q P L P N A S F D N F K L T C S N T
 - Q L N H Y Q M R V L I I S N S H V L T Q
 - N S T I T K C E F * * F Q T H M F * H K
 6001 - AAATTTGCTGATGATTTAAATCAAATGACAGGCTTCACAAAGCCAGCTTCACGAGAGCTA - 6060
 - K F A D D L N Q M T G F T K P A S R E L
 - N L L M I * I K * Q A S Q S Q L H E S Y
 - I C * * F K S N D R L H K A S F T R A I
 6061 - TCTGTCACATTCTCCAGACTTGAATGGCGATGTAGTGGCTATTGACTATAGACACTAT - 6120
 - S V T F F P D L N G D V V A I D Y R H Y
 - L S H S S Q T * M A M * W L L T I D T I
 - C H I L P R L E W R C S G Y * L * T L F
 6121 - TCAGCGAGTTTCAAGAAAGGTGCTAAATTACTGCATAAGCCAAATGTTTGGCACATTAAC - 6180
 - S A S F K K G A K L L H K P I V W H I N
 - Q R V S R K V L N Y C I S Q L F G T L T
 - S E F Q E R C * I T A * A N C L A H * P
 6181 - CAGGCTACAACCAAGACAACGTTCAAACCAAACACTGGTGTTCAGTTGCTTTGGAGT - 6240
 - Q A T T K T T F K P N T W C L R C L W S
 - R L Q P R Q R S N Q T L G V Y V V F G V
 - G Y N Q D N V Q T K H L V F T L S L E Y
 6241 - ACAAGCCAGTAGATACTTCAAATTCATTTGAAGTCTGGCAGTAGAAGACACACAAGGA - 6300
 - T K P V D T S N S F E V L A V E D T Q G
 - Q S Q * I L Q I H L K F W Q * K T H K E
 - K A S R Y F K F I * S S G S R R H T R N
 6301 - ATGGACAATCTTGCTTGTGAAAGTCAACAACCCACCTCTGAAGAAGTAGTGAAAATCCT - 6360
 - M D N L A C E S Q Q P T S E E V V E N P
 - W T I L L V K V N N P P L K K * W K I L
 - G Q S C L * K S T T H L * R S S G K S Y
 6361 - ACCATACAGAAGGAAGTCATAGAGTGTGACGTGAAAACCTACCGAAGTTGTAGGCAATGTC - 6420
 - T I Q K E V I E C D V K T T E V V G N V
 - P Y R R K S * S V T * K L P K L * A M S
 - H T E G S H R V * R E N Y R S C R Q C H
 6421 - ATACTTAAACCATCAGATGAAGGTGTTAAAGTAACACAAGAGTTAGGTCATGAGGATCTT - 6480
 - I L K P S D E G V K V T Q E L G H E D L
 - Y L N H Q M K V L K * H K S * V M R I L
 - T * T I R * R C * S N T R V R S * G S Y
 6481 - ATGGCTGCTTATGTGAAAACACAAGCATTACCATTAAGAAACCTAATGAGCTTTCACTA - 6540
 - M A A Y V E N T S I T I K K P N E L S L
 - W L L M W K T Q A L P L R N L M S F H *
 - G C L C G K H K H Y H * E T * * A F T S
 6541 - GCCTTAGGTTTAAAAACAATTGCCACTCATGGTATTGCTGCAATTAATAGTGTTCCTTGG - 6600
 - A L G L K T I A T H G I A A I N S V P W
 - P * V * K Q L P L M V L L Q L I V F L G
 - L R F K N N C H S W Y C C N * * C S L E
 6601 - AGTAAAATTTGGCTTATGTCAAACCATTCTTAGGACAAGCAGCAATTACAACATCAAT - 6660
 - S K I L A Y V K P F L G Q A A I T T S N
 - V K F W L M S N H S * D K Q Q L Q H Q I
 - * N F G L C Q T I L R T S S N Y N I K L
 6661 - TGCGCTAAGAGATTAGCACAACGTGTGTTAACAATTATATGCCTTATGTGTTTACATTA - 6720
 - C A K R L A Q R V F N N Y M P Y V F T L
 - A L R D * H N V C L T I I C L M C L H Y
 - R * E I S T T C V * Q L Y A L C V Y I I

FIG. 11 Con't

6721 - TTGTTCCAATTGTGTA CTTTTACTAAAAGTACCAATTCTAGAATTAGAGCTTCACTACCT - 6780
 - L F Q L C T F T K S T N S R I R A S L P
 - C S N C V L L L K V P I L E L E L H Y L
 - V P I V Y F Y * K Y Q F * N * S F T T Y
 6781 - ACAACTATTGCTAAAAATAGTGTTAAGAGTGTGCTAAATTATGTTTGGATGCCGGCATT - 6840
 - T T I A K N S V K S V A K L C L D A G I
 - Q L L L K I V L R V L L N Y V W M P A L
 - N Y C * K * C * E C C * I M F G C R H *
 6841 - AATTATGTGAAGTCACCCAAATTTCTAAATTGTTTCAATCGCTATGTGGCTATTGTTG - 6900
 - N Y V K S P K F S K L F T I A M W L L L
 - I M * S H P N F L N C S Q S L C G Y C C
 - L C E V T Q I F * I V H N R Y V A I V V
 6901 - TTAAGTATTGCTTAGGTTCTCTAATCTGTGTAAGTGTGCTTTTGGTGTACTCTTATCT - 6960
 - L S I C L G S L I C V T A A F G V L L S
 - * V F A * V L * S V * L L L L V Y S Y L
 - K Y L L R F S N L C N C C F W C T L I *
 6961 - AATTTTGGTGTCTCTTCTTATTGTAATGGCGTTAGAGAATTGTATCTTAATTCGTCTAAG - 7020
 - N F G A P S Y C N G V R E L Y L N S S N
 - I L V L L L I V M A L E N C I L I R L T
 - F W C S F L L * W R * R I V S * F V * R
 7021 - GTTACTACTATGGATTCTGTGAAGTTCTTTTCTGCAGCATTTGTTAAGTGGATTA - 7080
 - V T T M D F C E G S F P C S I C L S G L
 - L L L W I S V K V L F L A A F V * V D *
 - Y Y L Y G F L * R F F S L Q H L F K W I R
 7081 - GACTCCCTTGATTCTTATCCAGCTCTTGAACCATTCAGGTGACGATTCATCGTACAAG - 7140
 - D S L D S Y P A L E T I Q V T I S S Y K
 - T P L I L I Q L L K P F R * R F H R T S
 - L P * F L S S S * N H S G D D F I V Q A
 7141 - CTAGACTTGACAATTTTAGGTTCTGGCCGCTGAGTGGGTTTTGGCATATATGTTGTTTACA - 7200
 - L D L T I L G L A A E W V L A Y M L F T
 - * T * Q F * V W P L S G F W H I C C S Q
 - R L D N F R S G R * V G F G I Y V V H K
 7201 - AAATCTTTTATTATTAGGTTCTTTCAGCTATAATGCAGGTGTTCTTTGGCTATTTTGCT - 7260
 - K F F Y L L G L S A I M Q V F F G Y F A
 - N S F I Y * V F Q L * C R C S L A I L L
 - I L L F I R S F S Y N A G V L W L F C *
 7261 - AGTCATTTTCATCAGCAATTTGCTCATGTGGTTTATCATTAGTATTGTACAAATGGCA - 7320
 - S H F I S N S W L M W F I S I V Q M A
 - V I S S A I L G S C G L S L V L Y K W H
 - S F H Q Q F L A H V V Y H * Y C T N G T
 7321 - CCCGTTTCTGCAATGGTTAGGATGTACATCTTCTTTGCTTCTTCTACTACATATGGAAG - 7380
 - P V S A M V R M Y I F F A S F Y Y I W K
 - P F L Q W L G C T S S L L L S T T Y G R
 - R F C N G * D V H L L C F F L L H M E E
 7381 - AGCTATGTTTCATATCATGGATGGTTGCACCTCTTCGACTTGCATGATGTGCTATAAGCGC - 7440
 - S Y V H I M D G C T S S T C M M C Y K R
 - A M F I S W M V A P L R L A * C A I S A
 - L C S Y H G W L H L F D L H D V L * A Q
 7441 - AATCGTGCCACACGCGTTGAGTGTACAATTGTTAATGGCATGAAGAGATCTTTCTAT - 7500
 - N R A T R V E C T T I V N G M K R S F Y
 - I V P H A L S V Q L L L M A * R D L S M
 - S C H T R * V Y N Y C * W H E E I F L C
 7501 - GTCTATGCAAATGGAGCCGTTGCTTCTGCAAGACTCACAATTGGAATTGTCTCAATTGT - 7560
 - V Y A N G G R G F C K T H N W N C L N C
 - S M Q M E A V A S A R L T I G I V S I V
 - L C K W R P W L L Q D S Q L E L S Q L *

FIG. 11 Con't

7561 - GACACATTTTGCCTGGTAGTACATTCATTAGTGATGAAGTTGCTCGTGATTGTCCTC - 7620
 - D T F C T G S T F I S D E V A R D L S L
 - T H F A L V V H S L V M K L L V I C H S
 - H I L H W * Y I H * * S C S * F V T P
 7621 - CAGTTAAAAGACCAATCAACCCTACTGACCAGTCATCGTATATTGTTGATAGTGTGCT - 7680
 - Q F K R P I N P T D Q S S Y I V D S V A
 - S L K D Q S T L L T S H R I L L I V L L
 - V * K T N Q P Y * P V I V Y C * * C C C
 7681 - GTGAAAAATGGCGCGCTTACCTCTACTTTGACAAGGCTGGTCAAAAGACCTATGAGAGA - 7740
 - V K N G A L H L Y F D K A G Q K T Y E R
 - * K M A R F T S T L T R L V K R P M R D
 - E K W R A S P L L * Q G W S K D L * E T
 7741 - CATCGCTCTCCCATTTTGTCAATTGACAAATTGAGAGCTAACAACTAAAGGTTC - 7800
 - H P L S H F V N L D N L R A N N T K G S
 - I R S P I L S I * T I * E L T T L K V H
 - S A L P F C Q F R Q F E S * Q H * R F T
 7801 - CTGCCTATTAATGTCATAGTTTTGATGGCAAGTCCAAATGCGACGAGTCTGCTTCTAAG - 7860
 - L P I N V I V F D G K S K C D E S A S K
 - C L L M S * F L M A S P N A T S L L L S
 - A Y * C H S F * W Q V Q M R R V C F * V
 7861 - TCTGCTTCTGTACTACAGTCAGCTGATGTGCCAACCTATTCTGTTGCTTGACCAAGCT - 7920
 - S A S V Y Y S Q L M C Q P I L L L D Q A
 - L L L C T T V S * C A N L F C C L T K L
 - C F C V L Q S A D V P T Y S V A * P S S
 7921 - CTTGTATCAAACGTTGGAGATAGTACTGAAGTTCCGTTAAGATGTTTGTGCTTATGTC - 7980
 - L V S N V G D S T E V S V K M F D A Y V
 - L Y Q T L E I V L K F P L R C L M L M S
 - C I K R W R * Y * S F R * D V * C L C R
 7981 - GACACCTTTTCAGCAACTTTTGTCTATGGAAAACTTAAGGCAGTTGTTGCTACA - 8040
 - D T F S A T F S V P M E K L K A L V A T
 - T P F Q Q L L V F L W K N L R H L L L Q
 - H L F S N F * C S Y G K T * G T C C Y S
 8041 - GCTCACAGCGAGTTAGCAAAGGGTGTAGCTTTAGATGGTGTCTTTCTACATTCGTGTCA - 8100
 - A H S E L A K G V A L D G V L S T F V S
 - L T A S * Q R V * L * M V S F L H S C Q
 - S Q R V S K G C S F R W C P F Y I R V S
 8101 - GCTGCCGACAAGGTGTTGTTGATACCGATGTTGACACAAAGGATGTTATTGAATGTCTC - 8160
 - A A R Q G V V D T D V D T K D V I E C L
 - L P D K V L L I P M L T Q R M L L N V S
 - C P T R C C * Y R C * H K G C Y * M S Q
 8161 - AAACCTTACATCACTCTGACTTAGAAGTGACAGGTGACAGTTGTAACAATTCATGCTC - 8220
 - K L S H H S D L E V T G D S C N N F M L
 - N F H I T L T * K * Q V T V V T I S C S
 - T F T S L * L R S D R * Q L * Q F H A H
 8221 - ACCTATAATAAGGTTGAAAACATGACGCCAGAGATCTTGGCGCATGTATTGACTGTAAT - 8280
 - T Y N K V E N M T P R D L G A C I D C N
 - P I I R L K T * R P E I L A H V L T V M
 - L * * G * K H D A Q R S W R M Y * L * C
 8281 - GCAAGCATATCAATGCCCAAGTAGCAAAAAGTCACAATGTTTCACTCATCTGGAATGTA - 8340
 - A R H I N A Q V A K S H N V S L I W N V
 - Q G I S M P K * Q K V T M F H S S G M *
 - K A Y Q C P S S K K S Q C F T H L E C K
 8341 - AAAGACTACATGTCTTTATCTGAACAGCTGCGTAAACAATTCGTTACTGCTGCAAGAAG - 8400
 - K D Y M S L S E Q L R K Q I R T A A K K
 - K T T C L Y L N S C V N K F V L L P R R
 - R L H V F I * T A A * T N S Y C C Q E E

FIG. 11 Con't

8401 - AACAAACATACCTTTTACTACTAACTTGTGCTACAACACTAGACAGGTTGTCAATGTCATAACT - 8460
 - N N I P F T L T C A T T R Q V V N V I T
 - T T Y L L H * L V L Q L D R L S M S * L
 - Q H T F Y T N L C Y N * T G C Q C H N Y
 8461 - ACTAAAATCTCACTCAAGGGTGGTAAGATTGTTAGTACTTGTTTTAACTTATGCTTAAG - 8520
 - T K I S L K G G K I V S T C F K L M L K
 - L K S H S R V V R L L V L V L N L C L R
 - * N L T Q G W * D C * Y L F * T Y A * G
 8521 - GCCACATTATTGTGCGTTCTTGCTGCATTGGTTTGTATATCGTTATGCCAGTACATACA - 8580
 - A T L L C V L A A L V C Y I V M P V H T
 - P H Y C A F L L H W F V I S L C Q Y I H
 - H I I V R S C C I G L L Y R Y A S T Y I
 8581 - TTGTCAATCCATGATGGTTACACAAATGAAATCATTGGTTACAAAGCCATTGAGGATGGT - 8640
 - L S I H D G Y T N E I I G Y K A I Q D G
 - C Q S M M V T Q M K S L V T K P F R M V
 - V N P * W L H K * N H W L Q S H S G W C
 8641 - GTCACCTGACATCATTCTACTGATGATTGTTTTGCAAATAAACATGCTGTTTTGAC - 8700
 - V T R D I I S T D D C F A N K H A G F D
 - S L V T S F L L M I V L Q I N M L V L T
 - H S * H H F Y * * L F C K * T C W F * R
 8701 - GCATGGTTTTAGCCAGCGTGGTGGTTACATAAAAAATGACAAAAGCTGCCCTGTAGTAGCT - 8760
 - A W F S Q R G G S Y K N D K S C P V V A
 - H G L A S V V V H T K M T K A A L * * L
 - M V * P A W W F I Q K * Q K L P C S S C
 8761 - GCTATCATTACAAGAGAGATTGGTTTCATAGTGCCTGGCTTACCGGGTACTGTGCTGAGA - 8820
 - A I I T R E I G F I V P G L P G T V L R
 - L S L Q E R L V S * C L A Y R V L C * E
 - Y H Y K R D W F H S A W L T G Y C A E S
 8821 - GCAATCAATGGTGACTTCTTGCAFTTTCTACCTCGTGTTTTTAGTGCTGTTGGCAACATT - 8880
 - A I N G D F L H F L P R V F S A V G N I
 - Q S M V T S C I F Y L V F L V L L A T F
 - N Q W * L L A F S T S C F * C C W Q H L
 8881 - TGCTACACACCTTCCAAACTCATTGAGTATAGTATGTTTTGCTACCTCTGCTTGGCTTCTT - 8940
 - C Y T P S K L I E Y S D F A T S A C V L
 - A T H L P N S L S I V I L L P L L A F L
 - L H T F Q T H * V * * F C Y L C L R S C
 8941 - GCTGCTGAGTGACAATTTTAAGGATGCTATGGGCAAACCTGTCCATATTGTTATGAC - 9000
 - A A E C T I F K D A M G K P V P Y C Y D
 - L L S V Q F L R M L W A N L C H I V M T
 - C * V Y N F * G C Y G Q T C A I L L * H
 9001 - ACTAATTTGCTAGAGGGTCTATTTCTATAGTGAGCTTCGTCCAGACACTCGTTATGTG - 9060
 - T N L L E G S I S Y S E L R P D T R Y V
 - L I C * R V L F L I V S F V Q T L V M C
 - * F A R G F Y F L * * A S S R H S L C A
 9061 - CTTATGGATGGTTCCATCATAACAGTTTCTTAACACTTACCTGGAGGGTCTGTTAGAGTA - 9120
 - L M D G S I I Q F P N T Y L E G S V R V
 - L W M V P S Y S F L T L T W R V L L E *
 - Y G W F H H T V S * H L P G G F C * S S
 9121 - GTAACAACCTTTGATGCTGAGTACTGTAGACATGGTACATGCCAAAGGTGAGAAGTAGGT - 9180
 - V T T F D A E Y C R H G T C E R S E V G
 - * Q L L M L S T V D M V H A K G Q K * V
 - N N F * C * V L * T W Y M R K V R S R Y
 9181 - ATTTGCCTATCTACCAGTGGTAGATGGGTTCTTAATAATGAGCATTACAGAGCTCTATCA - 9240
 - I C L S T S G R W V L N N E H Y R A L S
 - F A Y L P V V D G F L I M S I T E L Y Q
 - L P I Y Q W * M G S * * * A L Q S S I R

FIG. 11 Con't

9241 - GGAGTTTCTGTGGTGTGATGCGATGAATCTCATAGCTAACATCTTTACTCCTCTTGTG - 9300
 - G V F C G V D A M N L I A N I F T P L V
 - E F S V V L M R * I S * L T S L L L L C
 - S F L W C * C D E S H S * H L Y S S C A
 9301 - CAACCTGTGGGTGCTTTAGATGTGTCTGCTTCAGTAGTGGCTGGTGGTATTATGCCATA - 9360
 - Q P V G A L D V S A S V V A G G I I A I
 - N L W V L * M C L L Q * W L V V L L P Y
 - T C G C F R C V C F S S G W W Y Y C H I
 9361 - TTGGTACTTGTGCTGCCTACTACTTTATGAAATTCAGACGTGTTTTGGTGACTACAAC - 9420
 - L V T C A A Y Y F M K F R R V F G E Y N
 - W * D L V L P T T L * N S D V F L V S T T
 - C L L C L L L Y E I Q T C F W * V Q P
 9421 - CATGTTGTTGCTGCTAATGCACTTTTGTGTTTGTGCTTTCATACTCTGTCTGGTA - 9480
 - H V V A A N A L L F L M S F T I L C L V
 - M L L L L M H F C F * C L S L Y S V W Y
 - C C C C * C T F V F D V F H Y T L S G T
 9481 - CCAGCTTACAGCTTCTGCCGGGAGTCTACTCAGTCTTTTACTTGTACTTGACATTCTAT - 9540
 - P A Y S F L P G V Y S V F Y L Y L T F Y
 - Q L T A F C R E S T Q S F T C T * H S I
 - S L Q L S A G S L L S L L L V L D I L F
 9541 - TTCACCAATGATGTTTCATCTTGGCTCACCTTCAATGGTTGCCATGTTTTCTCCTATT - 9600
 - F T N D V S F L A H L Q W F A M F S P I
 - S P M M F H S W L T F N G L P C F L L L
 - H Q * C F I L G S P S M V C H V F S Y C
 9601 - GTGCCTTTTTGGATAACAGCAATCTATGTATTCTGTATTCTCTGAAGCACTGCCATTGG - 9660
 - V P F W I T A I Y V F C I S L K H C H W
 - C L F G * Q Q S M Y S V F L * S T A I G
 - A F L D N S N L C I L Y F S E A L P L V
 9661 - TTCTTTAACTATCTTAGGAAAAGAGTCATGTTTAAATGGAGTTACATTTAGTACCTTC - 9720
 - F F N N Y L R K R V M F N G V T F S T F
 - S L T T I L G K E S C L M E L H L V P S
 - L * Q L S * E K S H V * W S Y I * Y L R
 9721 - GAGGAGCTGCTTTGTGTACCTTTTTGCTCAACAAGGAAATGTACCTAAAATTGCGTAGC - 9780
 - E E A A L C T F L L N K E M Y L K L R S
 - R R L L C V P F C S T R K C T * N C V A
 - G G C F V Y L F A Q Q G N V P K I A * R
 9781 - GAGACTGTGGCACTTACACAGTATAACAGGTATCTTGCTCTATATAACAAGTACAAG - 9840
 - E T L L P L T Q Y N R Y L A L Y N K Y K
 - R H C C H L H S I T G I L L Y I T S T S
 - D T V A T Y T V * Q V S C S I * Q V Q V
 9841 - TATTTCACTGGAGCCTTAGATACTACCAGCTATCGTGAAGCAGCTTGTGCCACTTAGCA - 9900
 - Y F S G A L D T T S Y R E A A C C H L A
 - I S V E P * I L P A I V K Q L A A T * Q
 - F Q W S L R Y Y Q L S * S S L L P L S K
 9901 - AAGGCTCTAAATGACTTTAGCAACTCAGGTGCTGATGTTCTCTACCAACCACCACAGACA - 9960
 - K A L N D F S N S G A D V L Y Q P P Q T
 - R L * M T L A T Q V L M F S T N H H R H
 - G S K * L * Q L R C * C S L P T T T D I
 9961 - TCAATCACTTCTGCTGTTCTGCAGAGTGGTTTTAGGAAAATGGCATTCCCGTCAGGCAAA - 10020
 - S I T S A V L Q S G F R K M A F P S G K
 - Q S L L L F C R V V L G K W H S R Q A K
 - N H F C C S A E W F * E N G I P V R Q S
 10021 - GTTGAAGGGTGCATGGTACAAGTAACCTGTGGAAGTACAAGTCTTAATGGATTGTGGTTG - 10080
 - V E G C M V Q V T C G T T T L N G L W L
 - L K G A W Y K * P V E L Q L L M D C G W
 - * R V H G T S N L W N Y N S * W I V V G

FIG. 11 Con't

10081 - GATGACACAGTATACTGTCCAAGACATGTCATTTGCACAGCAGAAGACATGCTTAATCCT - 10140
 - D D T V Y C P R H V I C T A E D M L N P
 - M T Q Y T V Q D M S F A Q Q K T C L I L
 - * H S I L S K T C H L H S R R H A * S *
 10141 - AACTATGAAGATCTGCTCATTCGCAAATCCAACCATAGCTTCTTGTTCAGGCTGGCAAT - 10200
 - N Y E D L L I R K S N H S F L V Q A G N
 - T M K I C S F A N P T I A F L F R L A M
 - L * R S A H S Q I Q P * L S C S G W Q C
 10201 - GTTCAACTCGTGTATTGGCCATTCTATGCAAATGTCTGCTTAGGCTTAAAGTTGAT - 10260
 - V Q L R V I G H S M Q N C L L R L K V D
 - F N F V L L A I L C K I V C L G L K L I
 - S T S C Y W P F Y A K L S A * A * S * Y
 10261 - ACTTCTAACCCCTAAGACACCCAAGTATAAATTTGTCCGTATCCAACCTGGTCAAACATT - 10320
 - T S N P K T P K Y K F V R I Q P G Q T F
 - L L T L R H P S I N L S V S N L V K H F
 - F * P * D T Q V * I C P Y P T W S N I F
 10321 - TCAGTCTAGCATGCTACAATGGTTCACCATCTGGTGTATATCAGTGTGCCATGAGACCT - 10380
 - S V L A C Y N G S P S G V Y Q C A M R P
 - Q F * H A T M V H H L V F I S V P * D L
 - S S S M L Q W F T I W C L S V C H E T *
 10381 - AATCATACCATTAAAGTTCTTCCCTAATGGATCATGTGGTAGTGTGGTTTTAACATT - 10440
 - N H T I K G S F L N G S C G S V G F N I
 - I I P L K V L S L M D H V V V L V L T L
 - S Y H * R F F P * W I M W * C W F * H *
 10441 - GATTATGATTGCGTGTCTTCTGCTATATGCATCATATGGAGCTTCCAACAGGAGTACAC - 10500
 - D Y D C V S F C Y M H H M E L P T G V H
 - I M I A C L S A I C I I W S F Q Q E Y T
 - L * L R V F L L Y A S Y G A S N R S T R
 10501 - GCTGGTACTGACTTAGAAGGTAAATPCTATGGTCCATTTGTTGACAGACAAACTGCACAG - 10560
 - A G T D L E G K F Y G P F V D R Q T A Q
 - L V L T * K V N S M V H L L T D K L H R
 - W Y * L R R * I L W S I C * Q T N C T G
 10561 - GCTGCAGGTACAGACACAACCATAACATTAAATGTTTTGGCATGGCTGTATGCTGCTGTT - 10620
 - A A G T D T T I T L N V L A W L Y A A V
 - L Q V Q T Q P * H * M F W H G C M L L L
 - C R Y R H N H N I K C F G M A V C C C Y
 10621 - ATCAATGGTATAGGTGGTTTCTTAATAGATTCCACCTACTTTGAATGACTTTAACCTT - 10680
 - I N G D R W F L N R F T T T L N D F N L
 - S M V I G G F L I D S P L L * M T L T L
 - Q W * * V V S * * I H H Y F E * L * P C
 10681 - GTGGCAATGAAGTACAACCTATGAACCTTTGACACAAGATCATGTTGACATATTGGGACCT - 10740
 - V A M K Y N Y E P L T Q D H V D I L G P
 - W Q * S T T M N L * H K I M L T Y W D L
 - G N E V Q L * T F D T R S C * H I G T S
 10741 - CTTTCTGCTCAAACAGGAATTGCCGTCTTAGATATGTGTGCTGCTTTGAAAGAGCTGCTG - 10800
 - L S A Q T G I A V L D M C A A L K E L L
 - F L L K Q E L P S * I C V L L * K S C C
 - F C S N R N C R L R Y V C C F E R A A A
 10801 - CAGAATGGTATGAATGGTCTACTATCCTTGGTAGCACTATTTTAGAAGATGAGTTTACA - 10860
 - Q N G M N G R T I L G S T I L E D E F T
 - R M V * M V V L S L V A L F * K M S L H
 - E W Y E W S Y Y P W * H Y F R R * V Y T
 10861 - CCATTTGATGTTGTTAGACAATGCTCTGGTGTACCTTCCAAGGTAAGTTCAAGAAAATT - 10920
 - P F D V V R Q C S G V T F Q G K F K K I
 - H L M L L D N A L V L P S K V S S R K L
 - I * C C * T M L W C Y L P R * V Q E N C

FIG. 11 Con't

10921 - GTTAAGGGCACTCATCATTGGATGCTTTTAACTTCTTGACATCACTATTGATCTTGTT - 10980
 - V K G T H H W M L L T F L T S L L I L V
 - L R A L I I G C F * L S * H H Y * F L F
 - * G H S S L D A F N F L D I T I D S C S
 10981 - CAAAGTACACAGTGGTCACTGTTTTCTTTGTTTACGAGAATGCTTTCTTGCCATTTACT - 11040
 - Q S T Q W S L F F F V Y E N A F L P F T
 - K V H S G H C F S L F T R M L S C H L L
 - K Y T V V T V F L C L R E C F L A I Y S
 11041 - CTTGGTATATGGCAATTGCTGCATGTGCTATGCTGCTTGTAAAGCATAAGCACGCATTC - 11100
 - L G I M A I A A C A M L L V K H K H A F
 - L V L W Q L L H V L C C L L S I S T H S
 - W Y Y G N C C M C Y A A C * A * A R I L
 11101 - TTGTGCTTGTCTTCTGTTACCTTCTTGTGCAACAGTTGCTTACTTTAATATGGTCTACATG - 11160
 - L C L F L L P S L A T V A Y F N M V Y M
 - C A C F C Y L L L Q Q L L T L I W S T C
 - V L V S V T F S C N S C L L * Y G L H A
 11161 - CCTGCTAGCTGGGTGATGCGTATCATGACATGGCTTGAATTGGCTGACACTAGCTTGTCT - 11220
 - P A S W V M R I M T W L E L A D T S L S
 - L L A G * C V S * H G L N W L T L A C L
 - C * L G D A Y H D M A * I G * H * L V W
 11221 - GGTTATAGGCTTAAGGATTGTGTTATGTATGCTTACGCTTTAGTTTTGCTTATTCTCATG - 11280
 - G Y R L K D C V M Y A S A L V L L I L M
 - V I G L R I V L C M L Q L * F C L F S *
 - L * A * G L C Y V C F S F S F A Y S H D
 11281 - ACAGCTCGCACTGTTTATGATGATGCTGCTAGACGTGTTGGACACTGATGAATGTCATT - 11340
 - T A R T V Y D D A A R R V W T L M N V I
 - Q L A L F M M M L L D V F G H * * M S L
 - S S H C L * * C C * T C L D T D E C H Y
 11341 - ACACTTGTAAAGTCTACTATGGTAATGCTTTAGATCAAGCTATTCCATGTGGGCC - 11400
 - T L V Y K V Y G N A L D Q A I S M W A
 - H L F T K S T M V M L * I K L F P C G P
 - T C L Q S L L W * C F R S S Y F H V G L
 11401 - TTAGTTATTTCTGTAACTCTAACTATTCTGGTGTGTTACGACTATCATGTTTTAGCT - 11460
 - L V I S V T S N Y S G V V T T I M F L A
 - * L F L * P L T I L V S L R L S C F * L
 - S Y F C N L * L F W C R Y D Y H V F S *
 11461 - AGAGCTATAGTGTGTTGTGTTGAGTATTACCCATTGTTATTTACTGGCAACACC - 11520
 - R A I V F V C V E Y Y P L L F I T G N T
 - E L * C L C V L S I T H C Y L L L A T P
 - S Y S V C V C * V L P I V I Y Y W Q H L
 11521 - TTACAGTGTATCATGCTTGTGTTTATTGTTTCTTAGGCTATTGTTGCTGCTGCTACTTTGGC - 11580
 - L Q C I M L V Y C F L G Y C C C C Y F G
 - Y S V S C L F I V S * A I V A A A T L A
 - T V Y H A C L L F L R L L L L L L L W P
 11581 - CTTTTCTGTTTACTCAACCGTTACTTCAGGCTTACTCTGGTGTGTTATGACTACTTGGTC - 11640
 - L F C L L N R Y F R L T L G V Y D Y L V
 - F S V Y S T V T S G L L L V F M T T W S
 - F L F T Q P L L Q A Y S W C L * L L G L
 11641 - TCTACACAAGAATTTAGGTATATGAACTCCAGGGGCTTTTGCCTCCTAAGAGTAGTATT - 11700
 - S T Q E F R Y M N S Q G L L P P K S S I
 - L H K N L G I * T P R G F C L L R V V L
 - Y T R I * V Y E L P G A F A S * E * Y *
 11701 - GATGCTTCAAGCTTAACATTAAGTTGTTGGGTATTGGAGGTAAACCATGTATCAAGGTT - 11760
 - D A F K L N I K L L G I G G K P C I K V
 - M L S S L T L S C W V L E V N H V S R L
 - C F Q A * H * V V G Y W R * T M Y Q G C

FIG. 11 Con't

11761 - GCTACTGTACAGTCTAAAATGTCTGACGTAAAGTGCACATCTGTGGTACTGCTCTCGGTT - 11820
 - A T V Q S K M S D V K C T S V V L L S V
 - L L Y S L K C L T * S A H L W Y C S R F
 - Y C T V * N V * R K V H I C G T A L G S
 11821 - CTTCAACAACTTAGAGTAGAGTCATCTTCTAAATTGTGGGCACAATGTGTACAACCTCCAC - 11880
 - L Q Q L R V E S S S K L W A Q C V Q L H
 - F N N L E * S H L L N C G H N V Y N S T
 - S T T * S R V I F * I V G T M C T T P Q
 11881 - AATGATATTCTTCTTGCAAAAGACACAACCTGAAGCTTTCGAGAAGATGGTTTCTCTTTTG - 11940
 - N D I L L A K D T T E A F E K M V S L L
 - M I F F L Q K T Q L K L S R R W F L F C
 - * Y S S C K R H N * S F R E D G F S F V
 11941 - TCTGTTTGTATCCATGCAGGGTGTGTAGACATTAATAGGTTGTGCGAGGAAATGCTC - 12000
 - S V L L S M Q G A V D I N R L C E E M L
 - L F C Y P C R V L * T L I G C A R K C S
 - C F A I H A G C C R H * * V V R G N A R
 12001 - GATAACCGTGTACTCTTCAGGCTATTGCTTCAGAATTTAGTTCITTTACCATCATATGCC - 12060
 - D N R A T L Q A I A S E F S S L P S Y A
 - I T V L L F R L L L Q N L V L Y H H M P
 - * P C Y S S G Y C F R I * F F T I I C R
 12061 - GCTTATGCCACTGCCAGGAGGCCTATGAGCAGGCTGTAGCTAATGGTGATTCTGAAGTC - 12120
 - A Y A T A Q E A Y E Q A V A N G D S E V
 - L M P L P R R P M S R L * L M V I L K S
 - L C H C P G G L * A G C S * W * F * S R
 12121 - GTTCTCAAAAAGTTAAAGAAATCTTTGAATGTGGCTAAATCTGAGTTTGACCGTGATGCT - 12180
 - V L K K L K K S L N V A K S E F D R D A
 - F S K S * R N L * M W L N L S L T V M L
 - S Q K V K E I F E C G * I * V * P * C C
 12181 - GCCATGCAACGCAAGTTGAAAAGATGGCAGATCAGGCTATGACCCAAATGTACAAACAG - 12240
 - A M Q R K L E K M A D Q A M T Q M Y K Q
 - P C N A S W K R W Q I R L * P K C T N R
 - H A T Q V G K D G R S G Y D P N V Q T G
 12241 - GCAAGATCTGAGGACAAGAGGGCAAAAGTAACTAGTGCTATGCAACAATGCTCTTCACT - 12300
 - A R S E D K R A K V T S A M Q T M L F T
 - Q D L R T R G Q K * L V L C K Q C S S L
 - K I * G Q E G K S N * C Y A N N A L H Y
 12301 - ATGCTTAGGAAGCTTGATAATGATGCACCTTAAACAATTATCAACAATGCGCGTGATGGT - 12360
 - M L R K L D N D A L N N I I N N A R D G
 - C L G S L I M M H L T T L S T M R V M V
 - A * E A * * * C T * Q H Y Q Q C A * W L
 12361 - TGTGTTCCACTCAACATCATACCATGACTACAGCAGCCAACTCATGGTTGTGTCCCT - 12420
 - C V P L N I I P L T T A A K L M V V V P
 - V F H S T S Y H * L Q Q P N S W L L S L
 - C S T Q H H T I D Y S S Q T H G C C P *
 12421 - GATTATGGTACCTACAAGAACACTTGTGATGGTAACACCTTTACATATGCATCTGCACTC - 12480
 - D Y G T Y K N T C D G N T F T Y A S A L
 - I M V P T R T L V M V T P L H M H L H S
 - L W Y L Q E H L * W * H L Y I C I C T L
 12481 - TGGGAAATCCAGCAAGTTGTTGATGCGGATAGCAAGATTGTTCAACTTAGTGAAATTAAC - 12540
 - W E I Q Q V V D A D S K I V Q L S E I N
 - G K S S K L L M R I A R L F N L V K L T
 - G N P A S C * C G * Q D C S T * * N * H
 12541 - ATGGACAATCACCAAAATTTGGCTTGGCCTTATTGTTACAGCTCTAAGAGCCAACCTCA - 12600
 - M D N L A W P L I V T A L R A N S
 - W T I H Q I W L G L L L L Q L * E P T Q
 - G Q F T K F G L A S Y C Y S S K S Q L S

FIG. 11 Con't

12601 - GCTGTTAAACTACAGAATAATGAACTGAGTCCAGTAGCACTACGACAGATGTCCTGTGCG - 12660
 - A V K L Q N N E L S P V A L R Q M S C A
 - L L N Y R I M N * V Q * H Y D R C P V R
 - C * T T E * * T E S S S T T T D V L C G

12661 - GCTGGTACCACACAAAACAGCTTGTACTGATGACAATGCACTTGCCTACTATAACAATTG - 12720
 - A G T T Q T A C T D D N A L A Y Y N N S
 - L V P H K Q L V L M T M H L P T I T I R
 - W Y H T N S L Y * * Q C T C L L * Q F E

12721 - AAGGGAGGTAGGTTTGTGCTGGCATTACTATCAGACCACCAAGATCTCAAATGGGCTAGA - 12780
 - K G G R F V L A L L S D H Q D L K W A R
 - R E V G L C W H Y Y Q T T K I S N G L D
 - G R * V C A G I T I R P P R S Q M G * I

12781 - TTCCTAAGAGTGTGGTACAGGTACAATTTACACAGAAGTGAACCACTTGTAGGTTT - 12840
 - F P K S D G T G T I Y T E L E P P C R F
 - S L R V M V Q V Q F T Q N W N H L V G L
 - P * E * W Y R Y N L H R T G T T L * V C

12841 - GTTACAGACACACAAAAGGGCTAAAGTGAATACTTGTACTTCATCAAAGGCTTAAAC - 12900
 - V T D T P K G P K V K Y L Y F I K G L N
 - L Q T H Q K G L K * N T C T S S K A * T
 - Y R T H T K R A * S E I L V L H Q R L K Q

12901 - AACCTAAATAGAGGTATGGTCTGGGAGTTTGTAGTCTACAGTACGTCTTCAGGCTGGA - 12960
 - N L N R G M V L G S L A A T V R L Q A G
 - T * I E V W C W A V * L L Q Y V F R L E
 - P K * R Y G A G Q F S C Y S T S S G W K

12961 - AATGCTACAGAAGTACCTGCCAATTCACCTGTGCTTTTCCTTCTGTGCTTTTGCAGTAGAC - 13020
 - N A T E V P A N S T V L S F C A F A V D
 - M L Q K Y L P I Q L C F P S V L L Q * T
 - C Y R S T C Q F N C A F L L C F C S R P

13021 - CCTGCTAAAGCATATAAGGATTACCTAGCAAGTGGAGGACAACCAATCACCAACTGTGTG - 13080
 - P A K A Y K D Y L A S G G Q P I T N C V
 - L L K H I R I T * Q V E D N Q S P T V *
 - C * S I * G L P S K W R T T N H Q L C E

13081 - AAGATGTTGTGTACACACTGGTACAGGACAGGCAATTACTGTAACACCAGAAGCTAAC - 13140
 - K M L C T H T G T G Q A I T V T P E A N
 - R C C V H T L V Q D R Q L L * H Q K L T
 - D V V Y T H W Y R T G N Y C N T R S * H

13141 - ATGGACCAAGAGTCCTTTGGTGGTGTCTCATGTTGTCTGTATTGTAGATGCCACATTGAC - 13200
 - M D Q E S F G G A S C C L Y C R C H I D
 - W T K S P L V V L H V V C I V D A T L T
 - G P R V L W W C F M L S V L * M P H * P

13201 - CATCCAAATCCTAAAGGATTCTGTGACTTGAAGGTAAGTACGTCCAATACCTACCACT - 13260
 - H P N P K G F C D L K G K Y V Q I P T T
 - I Q I L K D S V T * K V S T S K Y L P L
 - S K S * R I L * L E R * V R P N T Y H L

13261 - TGTGCTAATGACCCAGTGGGTTTACACTTAGAAACACAGTCTGTACCGTCTGCGGAATG - 13320
 - C A N D P V G F T L R N T V C T V C G M
 - V L M T Q W V L H L E T Q S V P S A E C
 - C * * P S G F Y T * K H S L Y R L R N V

13321 - TGGAAAGGTTATGGCTGTAGTGTGACCAACTCCGCGAACCCCTTGATGCAGTCTGCGGAT - 13380
 - W K G Y G C S C D Q L R E P L M Q S A D
 - G K V M A V V V T N S A N P * C S L R M
 - E R L W L * L * P T P R T L D A V C G C

13381 - GCATCAACGTTTTTAAACGGGTTTGGCGGTGAAGTGCAGCCCGTCTTACACCGTGCGGCA - 13440
 - A S T F L N G F A V * V Q P V L H R A A
 - H Q R F * T G L R C K C S P S Y T V R H
 - I N V F K R V C G V S A A R L T P C G T

FIG. 11 Con't

13441 - CAGGCACTAGTACTGATGTCGCTACAGGGCTTTTGATATTTACAACGAAAAAGTGCTG - 13500
 - Q A L V L M S S T G L L I F T T K K V L
 - R H * Y * C R L Q G F * Y L Q R K K C W
 - G T S T D V V Y R A F D I Y N E K S A G

13501 - GTTTGGCAAAGTTCCTAAAACTAATTGCTGTCGCTCCAGGAGAAGGATGAGGAAGGCA - 13560
 - V L Q S S * K L I A V A S R R R M R K A
 - F C K V P K N * L L S L P G E G * G R Q
 - F A K F L K T N C C R F Q E K D E E G N

13561 - ATTTATTAGACTCTTACTTTGTAGTTAAGAGGCATACTATGTCTAACTACCAACATGAAG - 13620
 - I Y * T L T L * L R G I L C L T T N M K
 - F I R L L L C S * E A Y Y V * L P T * R
 - L L D S Y F V V K R H T M S N Y Q H E E

13621 - AGACTATTATACTTGGTTAAAGATTGTCCAGCGGTTGCTGTCCATGACTTTTTCAAGT - 13680
 - R L F I T W L K I V Q R L L S M T F S S
 - D Y L * L G * R L S S G C C P * L F Q V
 - T I Y N L V K D C P A V A V H D F F K F

13681 - TTAGAGTAGATGGTGACATGGTACCACATATATCACGTCAGCGTCTAACTAAATACACAA - 13740
 - L E * M V T W Y H I Y H V S V * L N T Q
 - * S R W * H G T T Y I T S A S N * I H N
 - R V D G D M V P H I S R Q R L T K Y T M

13741 - TGGCTGATTTAGTCTATGCTCTACGTCATTTGATGAGGGTAATTGTGATACATTAAG - 13800
 - W L I * S M L Y V I L M R V I V I H * K
 - G * F S L C S T S F * * G * L * Y I K R
 - A D L V Y A L R H F D E G N C D T L K E

13801 - AAATACTCGTCACATACAATTGCTGTGATGATTATTTCAATAAGAAGGATTGGTATG - 13860
 - K Y S S H T I A V M M I I S I R R I G M
 - N T R H I Q L L * * * L F Q * E G L V *
 - I L V T Y N C C D D D Y F N K K D W Y D

13861 - ACTTCGTAGAGAATCCTGACATCTTACGCGTATATGCTAACTTAGGTGAGCGTGTACGCC - 13920
 - T S * R I L T S Y A Y M L T * V S V Y A
 - L R R E S * H L T R I C * L R * A C T P
 - F V E N P D I L R V Y A N L G E R V R Q

13921 - AATCATTATTAAGACTGTACAATTCTGCGATGCTATGCGTGATGCAGGCATTGTAGGCG - 13980
 - N H Y * R L Y N S A M L C V M Q A L * A
 - I I I K D C T I L R C Y A * C R H C R R
 - S L L K T V Q F C D A M R D A G I V G V

13981 - TACTGACATTAGATAATCAGGATCTTAATGGAACTGGTACGATTTCCGGTATTTCGTAC - 14040
 - Y * H * I I R I L M G T G T I S V I S Y
 - T D I R * S G S * W E L V R F R * F R T
 - L T L D N Q D L N G N W Y D F G D F V Q

14041 - AAGTAGCACCAGGCTGCGGAGTTCCTATTGTGGATTATATTACTCATTGCTGATGCCCA - 14100
 - K * H Q A A E F L L W I H I T H C * C P
 - S S T R L R S S Y C G F I L L I A D A H
 - V A P G C G V P I V D S Y Y S L L M P I

14101 - TCCTCACTTTGACTAGGCATTGGCTGCTGAGTCCCATATGGATGCTGATCTCGCAAAAC - 14160
 - S S L * L G H W L L S P I W M L I S Q N
 - P H F D * G I G C * V P Y G C * S R K T
 - L T L T R A L A A E S H M D A D L A K P

14161 - CACTTATTAAGTGGGATTTGCTGAAATATGATTTTACGGAAGAGAGACTTTGTCTCTTCG - 14220
 - H L L S G I C * N M I L R K R D F V S S
 - T Y * V G F A E I * F Y G R E T L S L R
 - L I K W D L L K Y D F T E E R L C L F D

14221 - ACCGTTATTTAAATATTGGGACCAGACATACCATCCCAATTGTATTAAGTGTGGATG - 14280
 - T V I L N I G T R H T I P I V L T V W M
 - P L F * I L G P D I P S Q L Y * L F G *
 - R Y F K Y W D Q T Y H P N C I N C L D D

FIG. 11 Con't

14281 - ATAGGTGTATCCTTCATTGTGCAAACCTTAATGTGTTATTTTCTACTGTGTTCCACCTA - 14340
 - I G V S F I V Q T L M C Y F L L C F H L
 - * V Y P S L C K L * C V I F Y C V S T Y
 - R C I L H C A N F N V L F S T V F P P T

14341 - CAAGTTTTGGACCACTAGTAAGAAAAATATTTGTAGATGGTGTTCCTTTTGTGTTTCAA - 14400
 - Q V L D H * * E K Y L * M V F L L L F Q
 - K F W T T S K K N I C R W C S F C C F N
 - S F G P L V R K I F V D G V P F V V S T

14401 - CTGGATACCATTTTCGTGAGTTAGGAGTCGTACATAATCAGGATGTAAACTTACATAGCT - 14460
 - L D T I F V S * E S Y I I R M * T Y I A
 - W I P F S * V R S R T * S G C K L T * L
 - G Y H F R E L G V V H N Q D V N L H S S

14461 - CGCGTCTCAGTTTCAAGGAACTTTGTAGTATGCTGCTGATCCAGCTATGCATGCAGCTT - 14520
 - R V S V S R N F * C M L L I Q L C M Q L
 - A S Q F Q G T F S V C C * S S Y A C S F
 - R L S F K E L L V Y A A D P A M H A A S

14521 - CTGGCAATTTATTGCTAGATAAACGCACTACATGCTTTTTCAGTAGCTGCACTAACAAACA - 14580
 - L A I Y C * I N A L H A F Q * L H * Q T
 - W Q F I A R * T H Y M L F S S C T N K Q
 - G N L L L D K R T T C F S V A A L T N N

14581 - ATGTTGCTTTTCAAACGTCAAAACCCGGTAATTTAATAAAGACTTTTATGACTTTGCTG - 14640
 - M L L F K L S N P V I L I K T F M T L L
 - C C F S N C Q T R * F * * R L L * L C C
 - V A F Q T V K P G N F N K D F Y D F A V

14641 - TGTCTAAAGGTTTCTTTAAGGAAGGAAGTTCTGTTGAACTAAAACACTTCTTCTTTGCTC - 14700
 - C L K V S L R K E V L L N * N T S S L L
 - V * R F L * G R K F C * T K T L L L C S
 - S K G F F K E G S S V E L K H F F F A Q

14701 - AGGATGGCAACGCTATCAGTGATTATGACTATTATCGTTATAATCTGCCAACAAATGT - 14760
 - R M A T L L S V I M T I I V I I C Q C
 - G W Q R C Y Q * L * L L S L * S A N N V
 - D G N A A I S D Y D Y Y R Y N L P T M C

14761 - GTGATATCAGACAACCTCTATTCGTAGTTGAAGTTGTTGATAAATACTTTGATTGTTACG - 14820
 - V I S D N S Y S * L K L L I N T L I V T
 - * Y Q T T P I R S * S C * * I L * L L R
 - D G I Q L L F V V E V V D K Y F D C Y D

14821 - ATGGTGGCTGTATTAATGCCAACCAAGTAATCGTTAACAATCTGGATAAATCAGCTGGTT - 14880
 - M V A V L M P T K * S L T I W I N Q L V
 - W W L Y * C Q P S N R * Q S G * I S W F
 - G G C I N A N Q V I V N N L D K S A G F

14881 - TCCCATTTAATAAATGGGGTAAGGCTAGACTTTATATGACTCAATGAGTTATGAGGATC - 14940
 - S H L I N G V R L D F I M T Q * V M R I
 - P I * * M G * G * T L L * L N E L * G S
 - P F N K W G K A R L Y Y D S M S Y E D Q

14941 - AAGATGCACCTTTTCGCGTATACTAAGCGTAATGTCATCCCTACTATAACTCAAATGAATC - 15000
 - K M H F S R I L S V M S S L L * L K * I
 - R C T F R V Y * A * C H P Y Y N S N E S
 - D A L F A Y T K R N V I P T I T Q M N L

15001 - TTAAGTATGCCATTAGTGCAAAGAATAGAGCTCGCACCGTAGCTGGTGTCTCTATCTGTA - 15060
 - L S M P L V Q R I E L A P * L V S L S V
 - * V C H * C K E * S S H R S W C L Y L *
 - K Y A I S A K N R A R T V A G V S I C S

15061 - GTRACTATGACAAATAGACAGTTTCATCAGAAATTATTGAAGTCAATAGCCGCACTAGAG - 15120
 - V L * Q I D S F I R N Y * S Q * P P L E
 - Y Y D K * T V S S E I I E V N S R H * R
 - T M T N R Q F H Q K L L K S I A A T R G

FIG. 11 Con't

15121 - GAGCTACTGTGGTAATTGGAACAAGCAAGTTTTACGGTGGCTGGCATAATATGTTAAAAA - 15180
 - E L L W * L E Q A S F T V A G I I C * K
 - S Y C G N W N K Q V L R W L A * Y V K N
 - A T V V I G T S K F Y G G W H N M L K T
 15181 - CTGTTTACAGTGATGTAGAACTCCACACCTTATGGGTTGGGATTATCCAAAATGTGACA - 15240
 - L F T V M * K L H T L W V G I I Q N V T
 - C L Q * C R N S T P Y G L G L S K M * Q
 - V Y S D V E T P H L M G W D Y P K C D R
 15241 - GAGCCATGCCTAACATGCTTAGGATAATGGCCTCTCTTGTCTTCTGCTCGCAAACATAACA - 15300
 - E P C L T C L G * W P L L F L L A N I T
 - S H A * H A * D N G L S C S C S Q T * H
 - A M P N M L R I M A S L V L A R K H N T
 15301 - CTTGCTGTAACCTTATCACACCGTTTCTACAGGTTAGCTAACGAGTGTGCGCAAGTATTA - 15360
 - L A V T Y H T V S T G * L T S V R K Y *
 - L L * L I T P F L Q V S * R V C A S I K
 - C C N L S H R F Y R L A N E C A Q V L S
 15361 - GTGAGATGGTCATGTGTGGCGGCTCACTATATGTTAAACCAGGTGAACATCATCCGGTG - 15420
 - V R W S C V A A H Y M L N Q V E H H P V
 - * D G H V W R L T I C * T R W N I I R *
 - E M V M C G G S L Y V K P G G T S S G D
 15421 - ATGCTACAACCTGCTTATGCTAATAGTGTCTTTAACATTGTCAAGCTGTTACAGCCAATG - 15480
 - M L Q L L M L I V S L T F V K L L Q P M
 - C Y N C L C * * C L * H L S S C Y S Q C
 - A T T A Y A N S V F N I C Q A V T A N V
 15481 - TAAATGCACCTCTTTCAACTGATGGTAATAAGATAGCTGACAAGTATGTCCGCAACTAC - 15540
 - * M H F F Q L M V I R * L T S M S A I Y
 - K C T S F N * W * * D S * Q V C P Q S T
 - N A L L S T D G N K I A D K Y V R N L Q
 15541 - AACACAGGCTCTATGAGTGTCTCTATAGAAATAGGGATGTTGATCATGAATTCGTGGATG - 15600
 - N T G S M S V S I E I G M L I M N S W M
 - T Q A L * V S L * K * G C * S * I R G *
 - H R L Y E C L Y R N R D V D H E F V D E
 15601 - AGTTTTACGCTTACCTGCGTAAACATTTCTCCATGATGATTCTTTCTGATGATGCCGTTG - 15660
 - S F T L T C V N I S P * * F F L M M P L
 - V L R L P A * T F L H D D S F * * C R C
 - F Y A Y L R K H F S M M I L S D D A V V
 15661 - TGTGCTATAACAGTAACTATGCGGCTCAAGGTTTAGTAGCTAGCATTAAAGAACTTTAAGG - 15720
 - C A I T V T M R L K V * * L A L R T L R
 - V L * Q * L C G S R F S S * H * E L * G
 - C Y N S N Y A A Q G L V A S I K N F K A
 15721 - CAGTTCTTTTATTATCAAAATAATGTGTTTCATGTCTGAGGCAAAATGTTGGACTGAGACTG - 15780
 - Q F F I I K I M C S C L R Q N V G L R L
 - S S L L S K * C V H V * G K M L D * D *
 - V L Y Y Q N N V F M S E A K C W T E T D
 15781 - ACCTTACTAAAGGACCTCACGAATTTGCTCACAGCATAACAATGCTAGTTAAACAAGGAG - 15840
 - T L L K D L T N F A H S I Q C * L N K E
 - P Y * R T S R I L L T A Y N A S * T R R
 - L T K G P H E F C S Q H T M L V K Q G D
 15841 - ATGATTACGTGTACCTGCCTTACCCAGATCCATCAAGAATATTAGCGCAGGCTGTTTTG - 15900
 - M I T C T C L T Q I H Q E Y * A Q A V L
 - * L R V P A L P R S I K N I R R R L F C
 - D Y V Y L P Y P D P S R I L G A G C F V
 15901 - TCGATGATATTGTCAAAACAGATGGTACACTTATGATTGAAAGGTTTCGTGCTCACTGGCTA - 15960
 - S M I L S K Q M V H L * L K G S C H W L
 - R * Y C Q N R W Y T Y D * K V R V T G Y
 - D D I V K T D G T L M I E R F V S L A I

FIG. 11 Con't

15961 - TTGATGCTTACCCACTTACAAAACATCCTAATCAGGAGTATGCTGATGCTTTTCACTTGT - 16020
 - L M L T H L Q N I L I R S M L M S F T C
 - * C L P T Y K T S * S G V C * C L S L V
 - D A Y P L T K H P N Q E Y A D V F H L Y
 16021 - ATTTACAATACATTAGAAAAGTTACATGATGAGCTTACTGGCCACATGTTGGACATGTATT - 16080
 - I Y N T L E S Y M M S L L A T C W T C I
 - F T I H * K V T * * A Y W P H V G H V F
 - L Q Y I R K L H D E L T G H M L D M Y S
 16081 - CCGTAATGCTAACTAATGATAACACCTCACGGTACTGGGAACCTGAGTTTTATGAGGCTA - 16140
 - P * C * L M I T P H G T G N L S F M R L
 - R N A N * * * H L T V L G T * V L * G Y
 - V M L T N D N T S R Y W E P E F Y E A M
 16141 - TGTACACACATACAGTCTTGCAGGCTGTAGGTGTGTATTGTGCAATTCACAGA - 16200
 - C T H H I Q S C R L * V L V Y C A I H R
 - V H T T Y S L A G C R C L C I V Q F T D
 - Y T P H T V L Q A V G A C V L C N S Q T
 16201 - CTTCACTTCGTTGCGGTGCCTGTATTAGGAGACCATTCTATGTTGCAAGTGTGCTATG - 16260
 - L H F V A V P V L G D H S Y V A S A A M
 - F T S L R C L Y * E T I P M L Q V L L *
 - S L R C G A C I R R P F L C C K C C Y D
 16261 - ACCATGTCATTTCAACATCACACAAATTAGTGTGTCTGTTAATCCCTATGTTGCAATG - 16320
 - T M S F Q H H T N * C C L L I P M F A M
 - P C H F N I T Q I S V V C * S L C L Q C
 - H V I S T S H K L V L S V N P Y V C N A
 16321 - CCCAGGTTGTGATGTCACTGATGTGACACAACCTGTATCTAGGAGGTATGAGCTATTATT - 16380
 - P Q V V M S L M * H N C I * E V * A I I
 - P R L * C H * C D T T V S R R Y E L L L
 - P G C D V T D V T Q L Y L G G M S Y Y C
 16381 - GCAAGTCACATAAGCCTCCCATAGTTTTCCATTATGTGCTAATGGTCAGGTTTTGGTT - 16440
 - A S H I S L P L V F H Y V L M V R F L V
 - Q V T * A S H * F S I M C * W S G F W F
 - K S H K P P I S F P L C A N G Q V F G L
 16441 - TATACAAAAACATGTGTAGGCAGTGACAATGCTACTGACTTCAATGCGATAGCAACAT - 16500
 - Y T K T H V * A V T M S L T S M R * Q H
 - I Q K H M C R Q * Q C H * L Q C D S N M
 - Y K N T C V G S D N V T D F N A I A T C
 16501 - GTGATTGGACTAATGCTGGCGATTACATACTTGCCAACACTGTACTGAGAGACTCAAGC - 16560
 - V I G L M L A I T Y L P T L V L R D S S
 - * L D * C W R L H T C Q H L Y * E T Q A
 - D W T N A G D Y I L A N T C T E R L K L
 16561 - TTTTCGCAGCAGAAACGCTCAAAGCCACTGAGGAAACATTTAAGCTGCATATGGTATTG - 16620
 - F S Q Q K R S K P L R K H L S C H M V L
 - F R S R N A Q S H * G N I * A V I W Y C
 - F A A E T L K A T E E T F K L S Y G I A
 16621 - CCACTGTACGCGAAGTACTCTCTGACAGAGAATGCATCTTTCATGGGAGGTTGGAAAAC - 16680
 - P L Y A K Y S L T E N C I F H G R L E N
 - H C T R S T L * Q R I A S F M G G W K T
 - T V R E V L S D R E L H L S W E V G K P
 16681 - CTAGACCACCATTGAACAGAACTATGTCTTTACTGGTTACCGTGTAACTAAAAATAGTA - 16740
 - L D H H * T E T M S L L V T V * L K I V
 - * T T I E Q K L C L Y W L P C N * K * *
 - R P P L N R N Y V F T G Y R V T K N S K
 16741 - AAGTACAGATTGGAGAGTACACCTTTGAAAAAGGTGACTATGGTGATGCTGTTGTGTACA - 16800
 - K Y R L E S T P L K K V T M V M L L C T
 - S T D W R V H L * K R * L W * C C C V Q
 - V Q I G E Y T F E K G D Y G D A V V Y R

FIG. 11 Con't

16801 - GAGGTACTACGACATACAAGTTGAATGTTGGTGATTACTTTGTGTTGACATCTCACACTG - 16860
 - E V L R H T S * M L V I T L C * H L T L
 - R Y Y D I Q V E C W * L L C V D I S H C
 - G T T T Y K L N V G D Y F V L T S H T V
 16861 - TAATGCCACTTAGTGACCTACTCTAGTGCCACAAGAGCACTATGTGAGAATTACTGGCT - 16920
 - * C H L V H L L * C H K S T M * E L L A
 - N A T * C T Y S S A T R A L C E N Y W L
 - M P L S A P T L V P Q E H Y V R I T G L
 16921 - TGTACCCAACTCAACATCTCAGATGAGTTTCTAGCAATGTTGCAAATTATCAAAGG - 16980
 - C T Q H S T S Q M S F L A M L Q I I K R
 - V P N T Q H L R * V F * Q C C K L S K G
 - Y P T L N I S D E F S S N V A N Y Q K V
 16981 - TCGGCATGCAAAGTACTCTACTCCAAGGACCCTGGTACTGGTAAGAGTCATTTTG - 17040
 - S A C K S T L H S K D H L V L V R V I L
 - R H A K V L Y T P R T T W Y W * E S F C
 - G M Q K Y S T L Q G P P G T G K S H F A
 17041 - CCATCGGACTTGCTCTCTATTACCCATCTGCTCGCATAGTGTATACGGCATGCTCTCATG - 17100
 - P S D L L S I T H L L A * C I R H A L M
 - H R T C S L L P I C S H S V Y G M L S C
 - I G L A L Y Y P S A R I V Y T A C S H A
 17101 - CAGCTGTTGATGCCCTATGTGAAAAGGCATTAATAATTTGCCCATAGATAAATGTAGTA - 17160
 - Q L L M P Y V K R H * N I C P * I N V V
 - S C * C P M * K G I K I F A H R * M * *
 - A V D A L C E K A L K Y L P I D K C S R
 17161 - GAATCATACCTGCGCGTGCGCGTAGAGTGTGATAAATCAAAGTGAATTCAACAC - 17220
 - E S Y L R V R A * S V L I N S K * I Q H
 - N H T C A C A R R V F * * I Q S E F N T
 - I I P A R A R V E C F D K F K V N S T L
 17221 - TAGAACAGTATGTTTTCTGCACTGTAAATGCATTGCCAGAAACAAGTCTGACATTGTAG - 17280
 - * N S M F S A L * M H C Q K Q L L T L *
 - R T V C F L H C K C I A R N N C * H C S
 - E Q Y V F C T V N A L P E T T A D I V V
 17281 - TCTTTGATGAAATCTCTATGGCTACTAATTATGACTTGAGTGTGTCAATGCTAGACTTC - 17340
 - S L M K S L W L L I M T * V L S M L D F
 - L * * N L Y G Y * L * L E C C Q C * T S
 - F D E I S M A T N Y D L S V V N A R L R
 17341 - GTGCAAAACTACGTCTATATTGGCGATCCTGCTCAATTACCAGCCCCCGCACATTGC - 17400
 - V Q N T T S I L A I L L N Y Q P P A H C
 - C K T L R L Y W R S C S I T S P P H I A
 - A K H Y V Y I G D P A Q L P A P R T L L
 17401 - TGAATAAAGGCACACTAGAACCAGAATATTTAATTCAGTGTGCAGACTTATGAAAACAA - 17460
 - * L K A H * N Q N I L I Q C A D L * K Q
 - D * R H T R T R I F * F S V Q T Y E N N
 - T K G T L E P E Y F N S V C R L M K T I
 17461 - TAGGTCCAGACATGTTCTTGAAGTGTGCGCGTTGCTGCTGAAATGTTGACACTG - 17520
 - * V Q T C S L E L V A V V L L K L L T L
 - R S R H V P W N L S P L S C * N C * H C
 - G P D M F L G T C R R C P A E I V D T V
 17521 - TGAGTGCCTTAGTTTATGACAATAAGCTAAAAGCACACAAGGATAAGTCAGCTCAATGCT - 17580
 - * V L * F M T I S * K H T R I S Q L N A
 - E C F S L * Q * A K S T Q G * V S S M L
 - S A L V Y D N K L K A H K D K S A Q C F
 17581 - TCAAATGTTCTACAAGGTGTTATTACACATGATGTTTCATCTGCAATCAACAGACCTC - 17640
 - S K C S T K V L L H M M F H L Q S T D L
 - Q N V L Q R C Y Y T * C F I C N Q Q T S
 - K M F Y K G V I T H D V S S A I N R P Q

FIG. 11 Con't

17641 - AAATAGCGTGTGAAGAGAATTTCTTACACGCAATCCTGCTTGGAGAAAAGCTGTTTTTA - 17700
 - K * A L * E N F L H A I L L G E K L F L
 - N R R C K R I S Y T Q S C L E K S C F Y
 - I G V V R E F L T R N P A W R K A V F I
 17701 - TCTCACCTTATAATTCACAGAACGCTGTAGCTTCAAAAATCTTAGGATTGCCTACGCAGA - 17760
 - S H L I I H R T L * L Q K S * D C L R R
 - L T L * F T E R C S F K N L R I A Y A D
 - S P Y N S Q N A V A S K I L G L P T Q T
 17761 - CTGTTGATTCATCACAGGTTCTGAATATGACTATGTCATATTCACACAACTACTGAAA - 17820
 - L L I H H R V L N M T M S Y S H K L L K
 - C * F I T G F * I * L C H I H T N Y * N
 - V D S S Q G S E Y D Y V I F T Q T T E T
 17821 - CAGCACTCTGTAAATGTCAACCGCTTCAATGTGGCTATCACAAGGGCAAAAATTGGCA - 17880
 - Q H T L V M S T A S M W L S Q G Q K L A
 - S T L L * C Q P L Q C G Y H K G K N W H
 - A H S C N V N R F N V A I T R A K I G I
 17881 - TTTTGTGCATAATGTCTGATAGAGATCTTTATGACAACTGCAATTTACAAGTCTAGAAA - 17940
 - F C A * C L I E I F M T N C N L Q V * K
 - F V H N V * * R S L * Q T A I Y K S R N
 - L C I M S D R D L Y D K L Q F T S L E I
 17941 - TACCAGTCGCAATGTGGCTACATTACAAGCAGAAAATGTAAGTGGACTTTTTAAGGACT - 18000
 - Y H V A M W L H Y K Q K M * L D F L R T
 - T T S Q C G Y I T S R K C N W T F * G L
 - P R R N V A T L Q A E N V T G L F K D C
 18001 - GTAGTAAGATCATTACTGGTCTTTCATCCTACACAGGCACCTACACACCTCAGCGTTGATA - 18060
 - V V R S L L V F I L H R H L H T S A L I
 - * * D H Y W S S S Y T G T Y T P Q R * Y
 - S K I I T G L H P T Q A P T H L S V D I
 18061 - TAAAATTCAAGACTGAAGGATTATGTGTTGACATACCAGGCATACCAAAGGACATGACCT - 18120
 - * N S R L K D Y V L T Y Q A Y Q R T * P
 - K I Q D * R I M C * H T R H T K G H D L
 - K F K T E G L C V D I P G I P K D M T Y
 18121 - ACCGTAGACTCATCTCTATGATGGGTTTCAAAATGAATTACCAAGTCAATGGTTACCCTA - 18180
 - T V D S S L * W V S K * I T K S M V T L
 - P * T H L Y D G F Q N E L P S Q W L P *
 - R R L I S M M G F K M N Y Q V N G Y P N
 18181 - ATATGTTTATCACCCGGAAGAAGCTATTTCGTCACGTTTCGTCGCGTGGATTGGCTTTGATG - 18240
 - I C L S P A K K L F V T F V R G L A L M
 - Y V Y H P R R S Y S S R S C V D W L * C
 - M F I T R E E A I R H V R A W I G F D V
 18241 - TAGAGGGCTGTCATGCAACTAGAGATGCTGTGGGTAACCTACCTCTCCAGCTAGGAT - 18300
 - * R A V M Q L E M L W V L T Y L S S * D
 - R G L S C N * R C C G Y * P T S P A R I
 - E G C H A T R D A V G T N L P L Q L G F
 18301 - TTTCTACAGGTGTTAACTTAGTAGCTGTACCGACTGGTTATGTTGACACTGAAAATAACA - 18360
 - F L Q V L T * * L Y R L V M L T L K I T
 - F Y R C * L S S C T D W L C * H * K * H
 - S T G V N L V A V P T G Y V D T E N N T
 18361 - CAGAATTCACCAGGTTAATGCAAAACCTCCAGGTGACCAGTTTAAACATCTTATAC - 18420
 - Q N S P E L M Q N L H Q V T S L N I L Y
 - R I H Q S * C K T S T R * P V * T S Y T
 - E F T R V N A K P P P G D Q F K H L I P
 18421 - CACTCATGTATAAAGGCTTGCCCTGGAATGTAGTGCCTATTAAGATAGTACAAATGCTCA - 18480
 - H S C I K A C P G M * C V L R * Y K C S
 - T H V * R L A L E C S A Y * D S T N A Q
 - L M Y K G L P W N V V R I K I V Q M L S

FIG. 11 Con't

18481 - GTGATACACTGAAAGGATTGTGCAGACAGAGTCGTGTTTCGTCCTTTGGGCGCATGGCTTTG - 18540
 - V I H * K D C Q T E S C S S F G R M A L
 - * Y T E R I V R Q S R V R P L G A W L *
 - D T L K G L S D R V V F V L W A H G F E
 18541 - AGCTTACATCAATGAAGTACTTTGTCAAGATTGGACCTGAAAGAACGTGTGTCTGTGTG - 18600
 - S L H Q * S T L S R L D L K E R V V C V
 - A Y I N E V L C Q D W T * K N V L S V *
 - L T S M K Y F V K I G P E R T C C L C D
 18601 - ACAAACGTGCAACTTGCTTTTCTACTTCATCAGATACTTATGCCTGCTGGAATCATTCTG - 18660
 - T N V Q L A F L L H Q I L M P A G I I L
 - Q T C N L L F Y F I R Y L C L L E S F C
 - K R A T C F S T S S D T Y A C W N H S V
 18661 - TGGGTTTTGACTATGTCTATAACCCATTTATGATTGATGTTTCAGCAGTGGGGCTTTACGG - 18720
 - W V L T M S I T H L * L M F S S G A L R
 - G F * L C L * P I Y D * C S A V G L Y G
 - G F D Y V Y N P F M I D V Q Q W G F T G
 18721 - GTAACCTTCAGAGTAACCATGACCAACATTGCCAGGTACATGGAAATGCACATGTGGCTA - 18780
 - V T F R V T M T N I A R Y M E M H M W L
 - * P S E * P * P T L P G T W K C T C G *
 - N L Q S N H D Q H C Q V H G N A H V A S
 18781 - GTTGTGATGCTATCATGACTAGATGTTTAGCAGTCCATGAGTGCTTTGTTAAGCGCGTGTG - 18840
 - V V M L S * L D V * Q S M S A L L S A L
 - L * C Y H D * M F S S P * V L C * A R *
 - C D A I M T R C L A V H E C F V K R V D
 18841 - ATTGTCTGTTGAATACCCTATTATAGGAGATGAAGTGAAGGGTTAATTCTGCTTGCAGAA - 18900
 - I G L L N T L L * E M N * G L I L L A E
 - L V C * I P Y Y R R * T E G * F C L Q K
 - W S V E Y P I I G D E L R V N S A C R K
 18901 - AAGTACAACACATGGTTGTGAAGTCTGCATTGCTTGCTGATAAGTTTCCAGTTCTTCATG - 18960
 - K Y N T W L * S L H C L L I S F Q F F M
 - S T T H G C E V C I A C * * V S S S S *
 - V Q H M V V K S A L L A D K F P V L H D
 18961 - ACATTGGAAATCCAAGCTATCAAGTGTGTGCCTCAGGCTGAAGTAGAATGGAAGTTCT - 19020
 - T L E I Q R L S S V C L R L K * N G S S
 - H W K S K G Y Q V C A S G * S R M E V L
 - I G N P K A I K C V P Q A E V E W K F Y
 19021 - ACGATGCTCAGCCATGTAGTGACAAAGCTTACAAAATAGAGGAACCTTCTATTCTTATG - 19080
 - T M L S H V V T K L T K * R N S S I L M
 - R C S A M * * Q S L Q N R G T L L F L C
 - D A Q P C S D K A Y K I E E L F Y S Y A
 19081 - CTACACATCACGATAAATCACTGATGGTGTGTTGTTGTTTGGGAATTGTAACGTTGATC - 19140
 - L H I T I N S L M V F V C F G I V T L I
 - Y T S R * I H * W C L F V L E L * R * S
 - T H H D K F T D G V C L F W N C N V D R
 19141 - GTTACCCAGCCAATGCAATTGTGTGTAGTTTGACACAAGAGTCTTGTCAAACCTGAACT - 19200
 - V T Q P M Q L C V G L T Q E S C Q T * T
 - L P S Q C N C V * V * H K S L V K L E L
 - Y P A N A I V C R F D T R V L S N L N L
 19201 - TACCAGGCTGTGATGGTGGTAGTTTGTATGTGAATAAGCATGCATTCCACACTCCAGCTT - 19260
 - Y Q A V M V V V C M * I S M H S T L Q L
 - T R L * W W * F V C E * A C I P H S S F
 - P G C D G G S L Y V N K H A F H T P A F
 19261 - TCGATAAAAGTGCAATTTACTAATTTAAAGCAATTGCCTTTCTTTTACTATTCTGATAGTC - 19320
 - S I K V H L L I * S N C L S F T I L I V
 - R * K C I Y * F K A I A F L L L F * * S
 - D K S A F T N L K Q L P F F Y Y S D S P

FIG. 11 Con't

19321 - CTTGTGAGTCTCATGGCAAACAAGTAGTGTGGATATTGATTATGTTCCACTCAAATCTG - 19380
 - L V S L M A N K * C R I L I M F H S N L
 - L * V S W Q T S S V G Y * L C S T Q I C
 - C E S H G K Q V V S D I D Y V P L K S A
 19381 - CTACGTGATTACACGATGCAATTTAGGTGGTGCTGTTGCAGACACCATGCAAATGAGT - 19440
 - L R V L H D A I * V V L F A D T M Q M S
 - Y V Y Y T M Q F R W C C L Q T P C K * V
 - T C I T R C N L G G A V C R H H A N E Y
 19441 - ACCGACAGTACTTGGATGCATATAATATGATGATTTCTGCTGGATTAGCCTATGATTT - 19500
 - T D S T W M H I I * * F L L D L A Y G F
 - P T V L G C I * Y D D F C W I * P M D L
 - R Q Y L D A Y N M M I S A G F S L W I Y
 19501 - ACAAACAATTTGATACTTATAACCTGTGGAATACATTTACCAGGTTACAGAGTTTAGAAA - 19560
 - T N N L I L I T C G I H L P G Y R V * K
 - Q T I * Y L * P V E Y I Y Q V T E F R K
 - K Q F D T Y N L W N T F T R L Q S L E N
 19561 - ATGTGGCTTATAATGTTGTTAATAAAGGACACTTTGATGGACACGCCGGCGAAGCACCTG - 19620
 - M W L I M L L I K D T L M D T P A K H L
 - C G L * C C * * R T L * W T R R R S T C
 - V A Y N V V N K G H F D G H A G E A P V
 19621 - TTTCCATCATTAAATAATGCTGTTTACACAAAGGTAGATGGTATTGATGTGGAGATCTTTG - 19680
 - F P S L I M L F T Q R * M V L M W R S L
 - F H H * * C C L H K G R W Y * C G D L *
 - S I I N A V Y T K V D G I D V E I F E
 19681 - AAAATAAGACAACACTTCCTGTTAATGTTGCATTTGAGCTTTGGGCTAAGCGTAACATTA - 19740
 - K I R Q H F L L M L H L S F G L S V T L
 - K * D N T S C * C C I * A L G * A * H *
 - N K T T L P V N V A F E L W A K R N I K
 19741 - AACCAGTGCCAGAGATTAAGATACTCAATAATTTGGGTGTTGATATCGCTGCTAATACTG - 19800
 - N Q C Q R L R Y S I I W V L I S L L I L
 - T S A R D * D T Q * F G C * Y R C * Y C
 - P V P E I K I L N N L G V D I A A N T V
 19801 - TAATCTGGGACTACAAAGAGAAGCCCCAGCACATGTATCTACAATAGGTGCTGCACAA - 19860
 - * S G T T K E K P Q H M Y L Q * V S A Q
 - N L G L Q K R S P S T C I Y N R C L H N
 - I W D Y K R E A P A H V S T I G V C T M
 19861 - TGACTGACATTGCCAAGAACCTACTGAGAGTGCTTGTCTTCACTACTGTCTTGTGTTG - 19920
 - * L T L P R N L L R V L V L H L L S C L
 - D * H C Q E T Y * E C L F F T Y C L V *
 - T D I A K K P T E S A C S S L T V L F D
 19921 - ATGGTAGAGTGAAGGACAGGTAGACCTTTTGTAGAAACGCCGTAATGGTGTTTTAATAA - 19980
 - M V E W K D R * T F L E T P V M V F * *
 - W * S G R T G R P F * K R P * W C F N N
 - G R V E G Q V D L F R N A R N G V L I T
 19981 - CAGAAGGTTCAAGTCAAAGGTCTAACACCTTCAAAGGACCAGCACAGCTAGCGTCAATG - 20040
 - Q K V Q S K V * H L Q R D Q H K L A S M
 - R R F S Q R S N T F K G T S T S * R Q W
 - E G S V K G L T P S K G P A Q A S V N G
 20041 - GAGTCACATTAATGGAGAATCAGTAAAAACACAGTTTAACTACTTTAAGAAAGTAGAGC - 20100
 - E S H * L E N Q * K H S L T T L R K * T
 - S H I N W R I S K N T V * L L * E S R R
 - V T L I G E S V K T Q F N Y F K K V D G
 20101 - GCATTATCAACAGTTGCCTGAAACCTACTTTACTCAGAGCAGAGACTTAGAGGATTTA - 20160
 - A L F N S C L K P T L L R A E T * R I L
 - H Y S T V A * N L L Y S E Q R L R G F *
 - I I Q Q L P E T Y F T Q S R D L E D F K

FIG. 11 Con't

20161 - AGCCAGATCACAAATGGAACTGACTTTCTCGAGCTCGCTATGGATGAATTCATACAGC - 20220
 - S P D H K W K L T F S S S L W M N S Y S
 - A Q I T N G N * L S R A R Y G * I H T A
 - P R S Q M E T D F L E L A M D E F I Q R
 20221 - GATATAAGCTCGAGGGCTATGCCTTCGAACACATCGTTTATGGAGATTCAGTCATGGAC - 20280
 - D I S S R A M P S N T S F M E I S V M D
 - I * A R G L C L R T H R L W R F Q S W T
 - Y K L E G Y A F E H I V Y G D F S H G Q
 20281 - AACTTGGCGGTCTTCATTTAATGATAGGCTTAGCCAAGCGCTCACAAAGATTCACCACTTA - 20340
 - N L A V F I * * * A * P S A H K I H H L
 - T W R S S F N D R L S Q A L T R F T T *
 - L G G L H L M I G L A K R S Q D S P L K
 20341 - AATTAGAGGATTTTATCCCTATGGACAGCACAGTGA AAAATTACTTCATAACAGATGCGC - 20400
 - N * R I L S L W T A Q * K I T S * Q M R
 - I R G F Y P Y G Q H S E K L L H N R C A
 - L E D F I P M D S T V K N Y F I T D A Q
 20401 - AAACAGGTTTCATCAAAATGTGTGTCTGTGATTGATCTTTACTTGATGACTTTGTGCG - 20460
 - K Q V H Q N V C V L * L I F Y L M T L S
 - N R F I K M C V F C D * S F T * * L C R
 - T G S S K C V C S V I D L L L D D F V E
 20461 - AGATAATAAAGTCACAAGATTTGTCAGTGATTTCAAAAGTGGTCAAGTTACAATTGACT - 20520
 - R * * S H K I C Q * F Q K W S R L Q L T
 - D N K V T R F V S D F K S G Q G Y N * L
 - I I K S Q D L S V I S K V V K V T I D Y
 20521 - ATGCTGAAATTTCAATTCATGCTTTGGTGTAAAGGATGGACATGTTGAAACCTTCTACCAA - 20580
 - M L K F H S C F G V R M D M L K P S T Q
 - C * N F I H A L V * G W T C * N L L P K
 - A E I S F M L W C K D G H V E T F Y P K
 20581 - AACTACAAGCAAGTCAAGCGTGGCAACCAGGTGTGCGATGCCTAACTTGTACAAGATGC - 20640
 - N Y K Q V K R G N Q V L R C L T C T R C
 - T T S K S S V A T R C C D A * L V Q D A
 - L Q A S Q A W Q P G V A M P N L Y K M Q
 20641 - AAAGAATGCTTCTTGA AAAAGTGTGACCTTCAGAATTATGGTGA AAAATGCTGTATACCAA - 20700
 - K E C F L K S V T F R I M V K M L L Y Q
 - K N A S * K V * P S E L W * K C C Y T K
 - R M L L E K C D L Q N Y G E N A V I P K
 20701 - AAGGAATAATGATGAATGTCGAAAGTATACTCAACTGTGCAACTTAAATACACTTA - 20760
 - K E * * * M S Q S I L N C V N T * I H L
 - R N N D E C R K V Y S T V S I L K Y T Y
 - G I M N V A K Y T Q L C Q Y L N T L T
 20761 - CTTTAGCTGTACCCTACAACATGAGAGTTATTCACTTTGGTGTGGCTCTGATAAAGGAG - 20820
 - L * L Y P T T * E L F T L V L A L I K E
 - F S C T L Q H E S Y S L W C W L * * R S
 - L A V P Y N M R V I H F G A G S D K G V
 20821 - TTGCACCAGGTACAGCTGTGCTCAGACAATGGTTGCCAACTGGCACACTACTTGTGCGATT - 20880
 - L H Q V Q L C S D N G C Q L A H Y L S I
 - C T R Y S C A Q T M V A N W H T T C R F
 - A P G T A V L R Q W L P T G T L L V D S
 20881 - CAGATCTTAATGACTTCGCTCCGACGAGATTCTACTTTAATTGGAGACTGTGCAACAG - 20940
 - Q I L M T S S P T Q I L L * L E T V Q Q
 - R S * * L R L R R R F Y F N W R L C N S
 - D L N D F V S D A D S T L I G D C A T V
 20941 - TACATACGGCTAATAAATGGGACCTTATTATTAGCGATATGTATGACCTTAGGACCAAAC - 21000
 - Y I R L I N G T L L L A I C M T L G P N
 - T Y G * * M G P Y Y * R Y V * P * D Q T
 - H T A N K W D L I I S D M Y D P R T K H

FIG. 11 Con't

21001 - ATGTGACAAAAGAGAATGACTCTAAAGAAGGGTTTTTCACTTATCTGTGTGGATTATATAA - 21060
 - M * Q K R M T L K K G F S L I C V D L *
 - C D K R E * L * R R V F H L S V W I Y K
 - V T K E N D S K E G F F T Y L C G F I K

21061 - AGCAAAACTAGCCCTGGGTGTTCTATAGCTGTAAAGATAACAGAGCATTCTTGGGAATG - 21120
 - S K N * P W V V L * L * R * Q S I L G M
 - A K T S P G W F Y S C K D N R A F L E C
 - Q K L A L G G S I A V K I T E H S W N A

21121 - CTGACCTTTACAAGCTTATGGGCCATTTCTCATGGTGGACAGCTTTTGTACAAATGTAA - 21180
 - L T F T S L W A I S H G G Q L L L Q M *
 - * P L Q A Y G P F L M V D S F C Y K C K
 - D L Y K L M G H F S W W T A F V T N V N

21181 - ATGCATCATCGGAAGCATTTTAATTGGGGCTAACTATCTTGGCAAGCCGAAGAAC - 21240
 - M H H H R K H F * L G L T I L A S R R N
 - C I I I G S I F N W G * L S W Q A E G T
 - A S S S E A F L I G A N Y L G K P K E Q

21241 - AAATTGATGGCTATACCATGCATGCTAACTACATTTTCTGGAGGAACAAATCCTATCC - 21300
 - K L M A I P C M L T T F S G G T Q I L S
 - N * W L Y H A C * L H F L E E H K S Y P
 - I D G Y T M H A N Y I F W R N T N P I Q

21301 - AGTTGTCTTCCTATTCCTACTCTTTGACATGAGCAAATTCCTCTTAAATTAAGAGGAACTG - 21360
 - S C L P I H S L T * A N F L L N * E E L
 - V V F L F T L * H E Q I S S * I K R N C
 - L F S S Y S L F D M S K F P L K L R G T A

21361 - CTGTAATGTCTCTTAAGGAGAATCAATCAATGATATGATTATTCTCTTCTGGAAAAAG - 21420
 - L * C L L R R I K S M I * F I L F W K K
 - C N V S * G E S N Q * Y D L F S S G K R
 - V M S L K E N Q I N D M I Y S L L E K G

21421 - GTAGGCTTATCATTAGAGAAAACAACAGAGTTGTGGTTTCAAGTGATATTCCTGTAAACA - 21480
 - V G L S L E K T T E L W F Q V I F L L T
 - * A Y H * R K Q Q S C G F K * Y S C * Q
 - R L I I R E N N R V V V S S D I L V N N

21481 - ACTAAACGAACATGTTTATTTCTTATTATTCTTACTCTCACTAGTGGTAGTGACCTTG - 21540
 - T K R T C L F S Y Y F L L S L V V V T L
 - L N E H V Y F L I I S Y S H * W * * P *
 - * T N M F I F L L F L T L T S G S D L D

21541 - ACCGGTGCACCACTTTTGATGATGTTCAAGCTCCTAATTACACTCAACATACTTCATCTA - 21600
 - T G A P L L M M F K L L I T L N I L H L
 - P V H H F * * C S S S * L H S T Y F I Y
 - R C T T F D D V Q A P N Y T Q H T S S M

21601 - TGAGGGGGTTTACTATCCTGATGAAATTTTATAGATCAGACACTCTTATTTAACTCAGG - 21660
 - * G G F T I L M K F L D Q T L F I * L R
 - E G G L L S * * N F * I R H S L F N S G
 - R G V Y Y P D E I F R S D T L Y L T Q D

21661 - ATTTATTTCTCCATTTTATTCTAATGTTACAGGGTTTCATACTATTAATCATACGTTTG - 21720
 - I Y F F H F I L M L Q G F I L L I I R L
 - F I S S I L F * C Y R V S Y Y * S Y V W
 - L F L P F Y S N V T G F H T I N H T F G

21721 - GCAACCTGTACATACCTTTTAAGGATGGTATTATTGCTGCCACAGAGAAATCAAATG - 21780
 - A T L S Y L L R M V F I L L P Q R N Q M
 - Q P C H T F * G W Y L F C C H R E I K C
 - N P V I P F K D G I Y F A A T E K S N V

21781 - TTGTCCGTGGTGGGTTTTGGTCTACCATGAACAACAAGTCACAGTCGGTGATTATTA - 21840
 - L S V V G F L V L P * T T S H S R * L L
 - C P W L G F W F Y H E Q Q V T V G D Y Y
 - V R G W V F G S T M N N K S Q S V I I I

FIG. 11 Con't

21841 - TTAACAATTCTACTAATGTTGTTATACGAGCATGTAACTTTGAATTGTGTGACAACCCTT - 21900
 - L T I L L M L L Y E H V T L N C V T T L
 - * Q F Y * C C Y T S M * L * I V * Q P F
 - N N S T N V V I R A C N F E L C D N P F

21901 - TCTTTGCTGTTTCTAAACCCATGGGTACACAGACATACTATGATATTCGATAATGCAT - 21960
 - S L L F L N P W V H R H I L * Y S I M H
 - L C C F * T H G Y T D T Y Y D I R * C I
 - F A V S K P M G T Q T H T M I F D N A F

21961 - TTAATTGCACTTTTCGAGTACATATCTGATGCCTTTTCGCTTGATGTTTCAGAAAAGTCAG - 22020
 - L I A L S S T Y L M P F R L M F Q K S Q
 - * L H F R V H I * C L F A * C F R K V R
 - N C T F E Y I S D A F S L D V S E K S G

22021 - GTAATTTTAAACACTTACGAGAGTTTGTGTTTAAAAATAAGATGGGTTTCTCTATGTTT - 22080
 - V I L N T Y E S L C L K I K M G F S M F
 - * F * T L T R V C V * K * R W V S L C L
 - N F K H L R E F V F K N K D G F L Y V Y

22081 - ATAAGGGCTATCAACCTATAGATGTAGTTCGTGATCTACCTTCTGGTTTTAACACTTTGA - 22140
 - I R A I N L * M * F V I Y L L V L T L *
 - * G L S T Y R C S S * S T F W F * H F E
 - K G Y Q P I D V V R D L P S G F N T L K

22141 - AACCTATTTTTAAGTTGCCTCTTGGTATTAACATTACAAATTTTAGAGCCATTCTTACAG - 22200
 - N L F L S C L L V L T L Q I L E P F L Q
 - T Y F * V A S W Y * H Y K F * S H S Y S
 - P I F K L P L G I N I T N F R A I L T A

22201 - CCTTTTCACCTGCTCAAGACATTTGGGGCAGTCAGCTGCAGCCTATTTTGTGGCTATT - 22260
 - P F H L L K T F G A R Q L Q P I L L A I
 - L F T C S R H L G H V S C S L F C W L F
 - F S P A Q D I W G T S A A A Y F V G Y L

22261 - TAAAGCCAACTACATTTATGCTCAAGTATGATGAAAATGGTACAATCACAGATGCTGTG - 22320
 - * S Q L H L C S S M M K M V Q S Q M L L
 - K A N Y I Y A Q V * * K W Y N H R C C *
 - K P T T F M L K Y D E N G T I T D A V D

22321 - ATTGTTCTCAAATCCACTTGCTGAACCTCAAATGCTCTGTTAAGAGCTTTGAGATTGACA - 22380
 - I V L K I H L L N S N A L L R A L R L T
 - L F S K S T C * T Q M L C * E L * D * Q
 - C S Q N P L A E L K C S V K S F E I D K

22381 - AAGGAATTTACCAGACCTCTAATTTACAGGTTGTCCCTCAGGAGATGTTGTGAGATTCC - 22440
 - K E F T R P L I S G L F P Q E M L * D S
 - R N L P D L * F Q G C S L R R C C E I P
 - G I Y Q T S N F R V V P S G D V V R F P

22441 - CTAATATTACAACTTGTGTCTTTTGGAGAGGTTTTTAATGCTACTAAATTCCTTCTG - 22500
 - L I L Q T C V L L E R F L M L L N S L L
 - * Y Y K L V S F W R G F * C Y * I P F C
 - N I T N L C P F G E V F N A T K F P S V

22501 - TCTATGCATGGGAGAGAAAAAATTTCTAATTTGTTGCTGATTACTCTGTGCTCTACA - 22560
 - S M H G R E K K F L I V L L I T L C S T
 - L C M G E K K N F * L C C * L L C A L Q
 - Y A W E R K K I S N C V A D Y S V L Y N

22561 - ACTCAACATTTTTTCAACCTTAAAGTGTATGGCGTTTCTGCCACTAAGTTGAATGATC - 22620
 - T Q H F F Q P L S A M A F L P L S * M I
 - L N I F F N L * V L W R F C H * V E * S
 - S T F F S T F K C Y G V S A T K L N D L

22621 - TTTGCTTCCCAATGCTATGCAGATTTTGTAGTCAAGGGAGATGATGTAAGACAAA - 22680
 - F A S P M S M Q I L L * S R E M M * D K
 - L L L Q C L C R F F C S Q G R * C K T N
 - C F S N V Y A D S F V V K G D D V R Q I

FIG. 11 Con't

22681 - TAGCGCCAGGACAACTGGTGTATTGCTGATTATAATTATAAAATTGCCAGATGATTCA - 22740
 - * R Q D K L V L L L I I I I N C Q M I S
 - S A R T N W C Y C * L * L * I A R * F H
 - A P G Q T G V I A D Y N Y K L P D D F M
 22741 - TGGGTTGTGTCCTTGCTTGGAAATACTAGGAACATTGATGCTACTTCAACTGGTAATTATA - 22800
 - W V V S L L G I L G T L M L L Q L V I I
 - G L C P C L E Y * E H * C Y F N W * L *
 - G C V L A W N T R N I D A T S T G N Y N
 22801 - ATTATAAATATAGGTATCTTAGACATGGCAAGCTTAGGCCCTTTGAGAGAGACATATCTA - 22860
 - I I N I G I L D M A S L G P L R E T Y L
 - L * I * V S * T W Q A * A L * E R H I *
 - Y K Y R Y L R H G K L R P F E R D I S N
 22861 - ATGTGCCTTTCTCCCCTGATGGCAAACCTGCACCCACCTGCTCTTAATTGTTATTGGC - 22920
 - M C L S P L M A N L A P H L L L I V I G
 - C A F L P * W Q T L H P T C S * L L L A
 - V P F S P D G K P C T P P A L N C Y W P
 22921 - CATTAAATGATTATGGTTTTTACACCACTACTGGCATTGGCTACCAACCTTACAGAGTTG - 22980
 - H * M I M V F T P L L A L A T N L T E L
 - I K * L W F L H Y W H W L P T L Q S C
 - L N D Y G F Y T T T G I G Y Q P Y R V V
 22981 - TAGTACTTTCTTTTGAACCTTTAAATGCACCGGCCCGTTTGTGGACAAAATTATCCA - 23040
 - * Y F L L N F * M H R P R F V D Q N Y P
 - S T F F * T F K C T G H G L W T K I I H
 - V L S F E L L N A P A T V C G P K L S T
 23041 - CTGACCTTATAAGAACCAGTGTGTCAATTTTAATTTAATGGACTCACTGGTACTGGTG - 23100
 - L T L L R T S V S I L I L M D S L V L V
 - * P Y * E P V C Q F * F * W T H W Y W C
 - D L I K N Q C V N F N F N G L T G T G V
 23101 - TGTTAACTCCTTCTTCAAAGAGATTTCAACCATTTCAACAATTTGGCCGTGATGTTTCTG - 23160
 - C * L L L Q R D F N H F N N L A V M F L
 - V N S F F K E I S T I S T I W P * C F *
 - L T P S S K R F Q P F Q Q F G R D V S D
 23161 - ATTTCACTGATTCGGTTCGAGATCCTAAAACATCTGAAATATTAGACATTTACCTTGCT - 23220
 - I S L I P F E I L K H L K Y * T F H L A
 - F H * F R S R S * N I * N I R H F T L L
 - F T D S V R D P K T S E I L D I S P C S
 23221 - CTTTTGGGGGTGAAGTGAATTACACCTGGAACAAATGCTTCATCTGAAGTTGCTGTTC - 23280
 - L L G V * V * L H L E Q M L H L K L L F
 - F W G C K C N Y T W N K C F I * S C C S
 - F G G V S V I T P G T N A S S E V A V L
 23281 - TATATCAAGATGTTAACTGCACCTGATGTTTCTACAGCAATTCATGCAGATCAACTCACAC - 23340
 - Y I K M L T A L M F L Q Q F M Q I N S H
 - I S R C * L H * C F Y S N S C R S T H T
 - Y Q D V N C T D V S T A I H A D Q L T P
 23341 - CAGCTTGGCGCATATATTCTACTGGAAACAATGTATTCCAGACTCAAGCAGGCTGTCTTA - 23400
 - Q L G A Y I L L E T M Y S R L K Q A V L
 - S L A H I F Y W K Q C I P D S S R L S Y
 - A W R I Y S T G N N V F Q T Q A G C L I
 23401 - TAGGAGCTGAGCATGTCGACACTTCTTATGAGTGGACATTCCATTGGAGCTGGCATT - 23460
 - * E L S M S T L L M S A T F L L E L A F
 - R S * A C R H F L * V R H S Y W S W H L
 - G A E H V D T S Y E C D I P I G A G I C
 23461 - GTGCTAGTTACCATACAGTTTCTTTATTACGTAGTACTAGCCAAAATCTATTGTGGCTT - 23520
 - V L V T I Q F L Y Y V V L A K N L L W L
 - C * L P Y S F F I T * Y * P K I Y C G L
 - A S Y H T V S L L R S T S Q K S I V A Y

FIG. 11 Con't

23521 - ATACTATGTCTTTAGGTGCTGATAGTTCAATTGCTTACTCTAATAACACCATTGCTATAC - 23580
 - I L C L * V L I V Q L L T L I T P L L Y
 - Y Y V F R C * * F N C L L * * H H C Y T
 - T M S L G A D S S I A Y S N N T I A I P
 23581 - CTACTAACTTTTCAATTAGCATTACTACAGAAGTAATGCCTGTTTCTATGGCTAAAACCT - 23640
 - L L T F Q L A L L Q K * C L F L W L K P
 - Y * L F N * H Y Y R S N A C F Y G * N L
 - T N F S I S I T T E V M P V S M A K T S
 23641 - CCGTAGATTGTAATATGTACATCTGCGGAGATTCTACTGAATGTGCTAATTGCTTCTCC - 23700
 - P * I V I C T S A E I L L N V L I C F S
 - R R L * Y V H L R R F Y * M C * F A S P
 - V D C N M Y I C G D S T E C A N L L L Q
 23701 - AATATGGTAGCTTTTGACACAATAATCGTGCACTCTCAGGTATTGCTGCTGAACAGG - 23760
 - N M V A F A H N * I V H S Q V L L L N R
 - I W * L L H T T K S C T L R Y C C * T G
 - Y G S F C T Q L N R A L S G I A A E Q D
 23761 - ATCGCAACACACGTGAAGTGTTCGCTCAAGTCAAACAAATGTACAAAACCCCAACTTGA - 23820
 - I A T H V K C S L K S N K C T K P Q L *
 - S Q H T * S V R S S Q T N V Q N P N F E
 - R N T R E V F A Q V K Q M Y K T P T L K
 23821 - AATATTTTGGTGGTTTTAATTTTTCACAATATTACCTGACCCTCTAAAGCCAATAAGA - 23880
 - N I L V V L I F H K Y Y L T L * S Q L R
 - I F W W F * F F T N I T * P S K A N * E
 - Y F G G F N F S Q I L P D P L K P T K R
 23881 - GGTCTTTTATTGAGGACTTGCTCTTTAATAAGGTGACACTCGCTGATGCTGGCTTCATGA - 23940
 - G L L L R T C S L I R * H S L M L A S *
 - V F Y * G L A L * * G D T R * C W L H E
 - S F I E D L L F N K V T L A D A G F M K
 23941 - AGCAATATGGCGAATGCCTAGGTGATATTAATGCTAGAGATCTCATTGTGCGCAGAAGT - 24000
 - S N M A N A * V I L M L E I S F V R R S
 - A I W R M P R * Y * C * R S H L C A E V
 - Q Y G E C L G D I N A R D L I C A Q K F
 24001 - TCAATGGACTTACAGTGTGCCACCTCTGCTCACTGATGATGATTGCTGCCTCACTG - 24060
 - S M D L Q C C H L C S L M I * L L P T L
 - Q W T Y S V A T S A H * * Y D C C L H C
 - N G L T V L P P L L T D D M I A A Y T A
 24061 - CTGCTCTAGTTAGTGGTACTGCCACTGCTGGATGGACATTTGGTGTGGCGCTGCTCTTC - 24120
 - L L * L V V L P L L D G H L V L A L L F
 - C S S * W Y C H C W M D I W C W R C S S
 - A L V S G T A T A G W T F G A G A A L Q
 24121 - AAATACCTTTTGTATGCAAATGGCATATAGGTTCAATGGCATTGGAGTTACCCAAAATG - 24180
 - K Y L L L C K W H I G S M A L E L P K M
 - N T F C Y A N G I * V Q W H W S Y P K C
 - I P F A M Q M A Y R F N G I G V T Q N V
 24181 - TTCTCTATGAGAACCAAAAACAAATCGCCAACCAATTTAACAAGCGGATTAGTCAAATTC - 24240
 - F S M R T K N K S P T N L T R R L V K F
 - S L * E P K T N R Q P I * Q G D * S N S
 - L Y E N Q K Q I A N Q F N K A I S Q I Q
 24241 - AAGAATCACTTACAACAACATCACTGCATTGGGCAAGCTGCAAGACGTTGTTAACAGA - 24300
 - K N H L Q Q H Q L H W A S C K T L L T R
 - R I T Y N N I N C I G Q A A R R C * P E
 - E S L T T T S T A L G K L Q D V V N Q N
 24301 - ATGCTCAAGCATTAAACACACTTGTAAACAACTTAGCTCTAATTTTGGTGAATTTCAA - 24360
 - M L K H * T H L L N N L A L I L V Q F Q
 - C S S I K H T C * T T * L * F W C N F K
 - A Q A L N T L V K Q L S S N F G A I S S

FIG. 11 Con't

24361 - GTGTGCTAAATGATATCCTTTTCGCGACTTGATAAAGTCGAGCGGAGGTACAAATTGACA - 24420
 - V C * M I S F R D L I K S R R R R Y K L T
 - C A K * Y P F A T * * S R G G G T N * Q
 - V L N D I L S R L D K V E A E V Q I D R

24421 - GGTTAATTACAGGCAGACTTCAAAGCCTTCAAACCTATGTAACACAACAATAATCAGGG - 24480
 - G * L Q A D F K A F K P M * H N N * S G
 - V N Y R Q T S K P S N L C N T T T N Q G
 - L I T G R L Q S L Q T Y V T Q Q L I R A

24481 - CTGCTGAAATCAGGGCTTCTGCTAATCTTGCTGCTACTAAAATGTCTGAGTGTGTTCTTG - 24540
 - L L K S G L L L I L L L L K C L S V F L
 - C * N Q G F C * S C C Y * N V * V C S W
 - A E I R A S A N L A A T K M S E C V L G

24541 - GACAATCAAAAAGAGTTGACTTTTGTGGAAAGGGCTACCACCTTATGTCTTCCCACAAG - 24600
 - D N Q K E L T F V E R A T T L C P S H K
 - T I K K S * L L W K G L P P Y V L P T S
 - Q S K R V D F C G K G Y H L M S F P Q A

24601 - CAGCCCCGATGGTGTGTTCTTCTACATGTACGTATGTGCCATCCCAGGAGAGGAAGT - 24660
 - Q P R M V L S S Y M S R M C H P R R G T
 - S P A W C C L P T C H V C A I P G E E L
 - A P H G V V F L H V T Y V P S Q E R N F

24661 - TCACCACAGCGCCAGCAATTTGTGATGAAGGCAAGCATACTTCCCTCGTGAAGGTGTTT - 24720
 - S P Q R Q Q F V M K A K H T S L V K V F
 - H H S A S N L S * R Q S I L P S * R C F
 - T T A P A I C H E G K A Y F P R E G V F

24721 - TTGTGTTTAAATGGCACTTCTTGGTTTATTACACAGGAACTTCTTTTCTCCACAAATAA - 24780
 - L C L M A L L G L L H R G T S F L H K *
 - C V * W H F L V Y Y T E E L L F S T N N
 - V F N G T S W F I T Q R N F F S P Q I I

24781 - TTACTACAGACAATACATTTGCTCTCAGGAAATTGTGATGTCGTTATTGGCATCATTAACA - 24840
 - L L Q T I H L S Q E I V M S L L A S L T
 - Y Y R Q Y I C L R K L * C R Y W H H * Q
 - T T D N T F V S G N C D V V I G I I N N

24841 - ACACAGTTTATGATCCTCTGCAACCTGAGCTTGACTCATTCAAGAAGAGCTGGACAAGT - 24900
 - T Q F M I L C N L S L T H S K K S W T S
 - H S L * S S A T * A * L I Q R R A G Q V
 - T V Y D P L Q P E L D S F K E E L D K Y

24901 - ACTTCAAAAATCATACATCACCAGATGTTGATCTTGGCGACATTCAGGCATTAACGCCTT - 24960
 - T S K I I H H Q M L I L A T F Q A L T L
 - L Q K S Y I T R C * S W R H F R H * R F
 - F K N H T S P D V D L G D I S G I N A S

24961 - CTGTCGTC AACATTCAAAAAGAAATTGACCGCTCAATGAGGTCGCTAAAAATTTAAATG - 25020
 - L S S T F K K K L T A S M R S L K I * M
 - C R Q H S K R N * P P Q * G R * K F K *
 - V V N I Q K E I D R L N E V A K N L N E

25021 - AATCACTCATTGACCTTCAAGAATTGGGAAAATATGAGCAATATATTAATGGCCTTGGT - 25080
 - N H S L T F K N W E N M S N I L N G L G
 - I T H * P S R I G K I * A I Y * M A L V
 - S L I D L Q E L G K Y E Q Y I K W P W Y

25081 - ATGTTTGGCTCGGCTTCAATGCTGACTAATGGCCATCGTCATGGTTACAATCTTGCTTT - 25140
 - M F G S A S L L D * L P S S W L Q S C F
 - C L A R L H C W T N C H R H G Y N L A L
 - V W L G F I A G L I A I V M V T I L L C

25141 - GTTGCATGACTAGTTGTTGAGTTGCCTCAAGGGTGCATGCTCTGTGGTTCTTGCTGCA - 25200
 - V A * L V V A V A S R V H A L V V L A A
 - L H D * L L Q L P Q G C M L L W F L L Q
 - C M T S C C S C L K G A C S C G S C C K

FIG. 11 Con't

25201 - AGTTTGATGAGGATGACTCTGAGCCAGTTCTCAAGGGTGTCAAATTACATTACACATAAA - 25260
 - S L M R M T L S Q F S R V S N Y I T H K
 - V * * G * L * A S S Q G C Q I T L H I N
 - F D E D D S E P V L K G V K L H Y T * T

25261 - CGAACTTATGGATTTGTTTATGAGATTTTTTACTCTTGGATCAATTACTGCACAGCCAGT - 25320
 - R T Y G F V Y E I F Y S W I N Y C T A S
 - E L M D L F M R F F T L G S I T A Q P V
 - N L W I C L * D F L L L D Q L L H S Q *

25321 - AAAAATTGACAATGCTTCTCCTGCAAGTACTGTTTCATGCTACAGCAACGATACCGCTACA - 25380
 - K N * Q C F S C K Y C S C Y S N D T A T
 - K I D N A S P A S T V H A T A T I P L Q
 - K L T M L L L Q V L F M L Q Q R Y R Y K

25381 - AGCCTCACTCCCTTTCCGGATGGCTTGTATTGGCGTTGCATTCTTGCTGTTTTTCAGAG - 25440
 - S L T P F R M A C Y W R C I S C C F S E
 - A S L P F G W L V I G V A F L A V F Q S
 - P H S L S D G L L L A L H F L L F F R A

25441 - CGCTACAAAATAATTGGCTCAATAAAAGATGGCAGCTAGCCCTTTATAAGGGCTTCCA - 25500
 - R Y Q N N C A Q * K M A A S P L * G L P
 - A T K I I A L N K R W Q L A L Y K G F Q
 - L P K * L R S I K D G S * P F I R A S S

25501 - GTTCATTTGCAATTTACTGCTGCTATTTGTTACCATCTATTCACATCTTTTGCTTGTCGC - 25560
 - V H L Q F T A A I C Y H L F T S F A C R
 - F I C N L L L L F V T I Y S H L L L V A
 - S F A I Y C C Y L L P S I H I F C L S L

25561 - TGCAGGTAAGGAGGCGCAATTTTTGTACCTCTATGCCTTGATATATTTTCTACAATGCAT - 25620
 - C R * G G A I F V P L C L D I F S T M H
 - A G K E A Q F L Y L Y A L I Y F L Q C I
 - Q V R R R N F C T S M P * Y I F Y N A S

25621 - CAACGCATGTAGAATTATTATGAGATGTTGGCTTTGTTGGAAGTGCAAATCCAAGAACCC - 25680
 - Q R M * N Y Y E M L A L L E V Q I Q E P
 - N A C R I I M R C W L C W K C K S K N P
 - T H V E L L * D V G F V G S A N P R T H

25681 - ATTACTTTATGATGCCAACTACTTTGTTTTGCTGGCACACATAACTATGACTACTGTAT - 25740
 - I T L * C Q L L C L L A H T * L * L L Y
 - L L Y D A N Y F V C W H T H N Y D Y C I
 - Y F M M P T T L F A G T H I T M T T V Y

25741 - ACCATATAACAGTGTACAGATAACAATTGTCGTTACTGAAGTGACGGCATTTCACACC - 25800
 - T I * Q C H R Y N C R Y * R * R H F N T
 - P Y N S V T D T I V V T E G D G I S T P
 - H I T V S Q I Q L S L L K V T A F Q H Q

25801 - AAAACTCAAAGAAGACTACCAAATGGTGGTTATTCTGAGGATAGGCACTCAGGTGTTAA - 25860
 - K T Q R R L P N W W L F * G * A L R C *
 - K L K E D Y Q I G G Y S E D R H S G V K
 - N S K K T T K L V V I L R I G T Q V L K

25861 - AGACTATGTCGTTGTACATGGCTATTTACCGAAGTTTACTACCAGCTTGAGTCTACACA - 25920
 - R L C R C T W L F H R S L L P A * V Y T
 - D Y V V V H G Y F T E V Y Y Q L E S T Q
 - T M S L Y M A I S P K F T T S L S L H K

25921 - AATTACTACAGACACTGGTATTGAAAATGCTACATTCTTCATCTTTTACAAGCTTGTTAA - 25980
 - N Y Y R H W Y * K C Y I L H L * Q A C *
 - I T T D T G I E N A T F F I F N K L V K
 - L L Q T L V L K M L H S S S L T S L L K

25981 - AGACCCACCGAATGTGCAAATACACAATCGACGGCTCTTCAGGAGTTGCTAATCCAGC - 26040
 - R P T E C A N T H N R R L F R S C * S S
 - D P P N V Q I H T I D G S S G V A N P A
 - T H R M C K Y T Q S T A L Q E L L I Q Q

FIG. 11 Con't

26041 - AATGGATCCAATTTATGATGAGCCGACGACGACTACTAGCGTGCCTTTGTAAGCACAAGA - 26100
 - N G S N L * * A D D D Y * R A F V S T R
 - M D P I Y D E P T T T T S V P L * A Q E
 - W I Q F M M S R R R L L A C L C K H K K
 26101 - AAGTGAGTACGAACCTATGTACTCATTTCGTTTCGGGAAGAACAGGTACGTTAATAGTTAA - 26160
 - K * V R T Y V L I R F G R N R Y V N S *
 - S E Y E L M Y S F V S E E T G T L I V N
 - V S T N L C T H S F R K K Q V R * * L I
 26161 - TAGCGTACTTCTTTTCTTGCTTTTCGTTTCTTGCTAGTCACACTAGCCATCCTAC - 26220
 - * R T S F S C F R G I L A S H T S H P Y
 - S V L L F L A F V V F L L V T L A I L T
 - A Y F F F L L S W Y S C * S H * P S L L
 26221 - TGGCTTCGATTGTGTGCGTACTGCTGCAATATTGTTAACGTGAGTTAGTAAAACCAAC - 26280
 - C A S I V C V L L Q Y C * R E F S K T N
 - A L R L C A Y C C N I V N V S L V K P T
 - R F D C V R T A A I L L T * V * * N Q R
 26281 - GGTTCGCTACTCGCGTGTAAATACTGAACTCTTCTGAAGGAGTTCCTGATCTTCT - 26340
 - G L R L L A C * K S E L F * R S S * S S
 - V Y V Y S R V K N L N S S E G V P D L L
 - F T S T R V L K I * T L L K E F L I F W
 26341 - GGTCTAAACGAACCTAATATTATTCTGTTTGAAGTAAACATTGCTTATCATG - 26400
 - G L N E L T I I I I L F G T L T L L I M
 - V * T N * L L L L F C L E L * H C L S W
 - S K R T N Y Y Y Y S V W N F N I A Y H G
 26401 - GCAGACAACGGTACTATTACCGTTGAGGAGCTTAAACAACCTCTGGAACAATGGAACCTA - 26460
 - A D N G T I T V E E L K Q L L E Q W N L
 - Q T T V L L P L R S L N N S W N N G T *
 - R Q R Y Y Y R * G A * T T P G T M E P S
 26461 - GTAATAGGTTTCTTATTCTAGCCTGGATTATGTTACTACAATTTGCCTATTCTAATCGG - 26520
 - V I G F L F L A W I M L L Q F A Y S N R
 - * * V S Y S * P G L C Y Y N L P I L I G
 - N R F P I P S L D Y V T T I C L F * S E
 26521 - AACAGGTTTTTGTACATAATAAAGCTGTTTTCTCTGGCTCTTGTGGCCAGTAACACTT - 26580
 - N R F L Y I I K L V F L W L L W P V T L
 - T G F C T * * S L F S S G S C G Q * H L
 - Q V F V H N K A C F P L A L V A S N T C
 26581 - GCTTGTGTTGCTGCTGTTGCTACAGAATTAATGGGTGACTGGCGGGATTGCGATT - 26640
 - A C F V L A V V Y R I N W V T G G I A I
 - L V L C L L L S T E L I G * L A G L R L
 - L F C A C C C L Q N * L G D W R D C D C
 26641 - GCAATGGCTTGTATTGTAGGCTTGATGTGGCTTAGCTACTTCGTTGCTTCCTCAGGCTG - 26700
 - A M A C I V G L M W L S Y F V A S F R L
 - Q W L V L * A * C G L A T S L L P S G C
 - N G L Y C R L D V A * L L R C F L Q A V
 26701 - TTTGCTCGTACCCGCTCAATGTGGTCATTCAACCCAGAAACAACATTCTTCTCAATGTG - 26760
 - F A R T R S M W S F N P E T N I L L N V
 - L L V P A Q C G H S T Q K Q T F F S M C
 - C S Y P L N V V I Q P R N K H S S Q C A
 26761 - CCTCTCCGGGGACAATTTGACCAGACCGCTCATGAAAGTGAACCTGTCATTGGTGCT - 26820
 - P L R G T I V T R P L M E S E L V I G A
 - L S G G Q L * P D R S W K V N L S L V L
 - S P G D N C D Q T A H G K * T C H W C C
 26821 - GTGATCATTTCGTTGCTGCACTTGCGAATGGCCGACACTCCCTAGGGCGCTGTGACATTAAG - 26880
 - V I I R G H L R M A G H S L G R C D I K
 - * S F V V T C E W P D T P * G A V T L R
 - D H S W S L A N G R T L P R A L * H * G

FIG. 11 Con't

26881 - GACCTGCCAAAAGAGATCACTGTGGCTACATCACGAACGCTTTCTTATTACAAATTAGGA - 26940
 - D L P K E I T V A T S R T L S Y Y K L G
 - T C Q K R S L W L H H E R F L I T N * E
 - P A K R D H C G Y I T N A F L L Q I R S
 26941 - GCGTCGCAGCGTGTAGGCACTGATTCAGGTTTTGCTGCATACAACCGCTACCGTATTGGA - 27000
 - A S Q R V G T D S G F A A Y N R Y R I G
 - R R S V * A L I Q V L L H T T A T V L E
 - V A A C R H * F R F C C I Q P L P Y W K
 27001 - AACTATAAATTAATAACAGACCACGCCGTTAGCAACGACAATATTGCTTTGCTAGTACAG - 27060
 - N Y K L N T D H A G S N D N I A L L V Q
 - T I N * I Q T T P V A T T I L L C * Y S
 - L * I K Y R P R R * Q R Q Y C F A S T V
 27061 - TAAGTGACAACAGATGTTTCATCTTGTGACTTCCAGGTTACAATAGCAGAGATATTGAT - 27120
 - * V T T D V S S C * L P G Y N S R D I D
 - K * Q Q M F H L V D F Q V T I A E I L I
 - S D N R C F I L L T S R L Q * Q R Y * L
 27121 - TATCATATGAGGACTTTTCAGGATTGCTATTTGGAATCTTGACGTTATAATAAGTTCAAT - 27180
 - Y H Y E D F Q D C Y L E S * R Y N K F N
 - I I M R T F R I A I W N L D V I I S S I
 - S L * G L S G L L F G I L T L * * V Q *
 27181 - AGTGAGACAATTATTTAAGCCTCTAAGTAAGAAGATTATTCGGAGTTAGATGATGAAGA - 27240
 - S E T I I * A S N * E E L F G V R * * R
 - V R Q L F K P L T K K N Y S E L D D E E
 - * D N Y L S L * L R R I I R S * M M K N
 27241 - ACCTATGGAGTTAGATTATCCATAAAACGAACATGAAAATTATTCTCTCTGACATTGA - 27300
 - T Y G V R L S I K R T * K L F S S * H *
 - P M E L D Y P * N E H E N Y S L P D I D
 - L W S * I I H K T N M K I I L F L T L I
 27301 - TTGTATTTACATCTTGCGAGCTATATCACTATCAGGAGTGTGTTAGAGGTACGACTGTAC - 27360
 - L Y L H L A S Y I T I R S V L E V R L Y
 - C I Y I L R A I S L S G V C * R Y D C T
 - V F T S C E L Y H Y Q E C V R G T T V L
 27361 - TACTAAAAGAACCTTGCCCATCAGGAACATACGAGGGCAATTCACCATTTCACCCCTTG - 27420
 - Y * K N L A H Q E H T R A I H H F T L L
 - T K R T L P I R N I R G Q F T I S P S C
 - L K E P C P S G T Y E G N S P F H P L A
 27421 - CTGACAATAAATTTGCACTAAGTTCAGTACACACTTTGCTTTTGTGCTGCTGACG - 27480
 - L T I N L H * L A L A H T L L L L V L T
 - * Q * I C T N L H * H T L C F C L C * R
 - D N K F A L T C T S T H F A F A C A D G
 27481 - GTACTCGACATACCTATCAGCTGCGTGAAGATCAGTTTCACCAAAACTTTTCATCAGAC - 27540
 - V L D I P I S C V Q D Q F H Q N F S S D
 - Y S T Y L S A A C K I S F T K T F H Q T
 - T R H T Y Q L R A R S V S P K L F I R Q
 27541 - AAGAGGAGGTTCAACAAGAGCTCTACTCGCCACTTTTCTCATTGTTGCTGCTCTAGTAT - 27600
 - K R R F N K S S T R H F F S L L L L * Y
 - R G G S T R A L L A T F S H C C C S S I
 - E E V Q Q E L Y S P L F L I V A A L V F
 27601 - TTTTAATACTTTGCTTCACCATTAAGAGAAAGACAGAATGAATGAGCTCACTTTAATGA - 27660
 - F * Y F A S P L R E R Q N E * A H F N *
 - F N T L L H H * E K D R M N E L T L I D
 - L I L C F T I K R K T E * M S S L * L T
 27661 - CTTCTATTTGTGCTTTTGTAGCCTTTCTGCTATTCTGTTTAAATAATGCTTATTATATT - 27720
 - L L F V L F S L S A I P C F N N A Y Y I
 - F Y L C F L A F L L F L V L I M L I I F
 - S I C A F * P F C Y S L F * * C L L Y F

FIG. 11 Con't

27721 - TTGGTTTTCACTCGAAATCCAGGATCTAGAAGAACCTTGTACCAAAGTCTAAACGAACAT - 27780
 - L V F T R N P G S R R T L Y Q S L N E H
 - W F S L E I Q D L E E P C T K V * T N M
 - G F H S K S R I * K N L V P K S K R T *
 27781 - GAAACTTCTCATTGTTTTGACTTGTATTTCTCTATGCAGTTGCATATGCACTGTAGTACA - 27840
 - E T S H C F D L Y F S M Q L H M H C S T
 - K L L I V L T C I S L C S C I C T V V Q
 - N F S L F * L V F L Y A V A Y A L * Y S
 27841 - GCGCTGTGCATCTAATAACCTCATGTGCTTGAAGATCCTTGTAAAGGTACAACACTAGGG - 27900
 - A L C I * * T S C A * R S L * G T T L G
 - R C A S N K P H V L E D P C K V Q H * G
 - A V H L I N L M C L K I L V R Y N T R G
 27901 - GTAATACTTATAGCACTGCTTGGCTTGTGCTCTAGGAAAGGTTTTACCTTTTCATAGAT - 27960
 - V I L I A L L G F V L * E R F Y L F I D
 - * Y L * H C L A L C S R K G F T F S * M
 - N T Y S T A W L C A L G K V L P F H R W
 27961 - GGCACACTATGGTTCAAACATGCACACCTAATGTTACTATCAACTGTCAAGATCCAGCTG - 28020
 - G T L W F K H A H L M L L S T V K I Q L
 - A H Y G S N M H T * C Y Y Q L S R S S W
 - H T M V Q T C T P N V T I N C Q D P A G
 28021 - GTGGTGCCTTATAGCTAGGTGTTGGTACCTTCATGAAGGTCACCAAACCTGCTGCATTTA - 28080
 - V V R L * L G V G T F M K V T K L L H L
 - W C A Y S * V L V P S * R S P N C C I *
 - G A L I A R C W Y L H E G H Q T A A F R
 28081 - GAGACGTACTTGTGTTTTAAATAAACGAACAAATTAATGTCTGATAATGGACCCCAA - 28140
 - E T Y L L F * I N E Q I K M S D N G P Q
 - R R T C C F K * T N K L K C L I M D P N
 - D V L V V L N K R T N * N V * * W T P I
 28141 - TCAAACCAACGTAGTGCCCCCGCATTACATTTGGTGGACCCACAGATTCAACTGACAAT - 28200
 - S N Q R S A P R I T F G G P T D S T D N
 - Q T N V V P P A L H L V D P Q I Q L T I
 - K P T * C P P H Y I W W T H R F N * Q *
 28201 - AACCGAATGGAGGACGCAATGGGGCAAGGCCAAAACAGCGCCGACCCCAAGGTTTACCC - 28260
 - N Q N G G R N G A R P K Q R R P Q G L P
 - T R M E D A M G Q G Q N S A D P K V Y P
 - P E W R T Q W G K A K T A P T P R F T Q
 28261 - AATAATACTGCGTCTGGTTCACAGCTCTCACTCAGCATGGCAAGGAGGAACTTAGATTC - 28320
 - N N T A S W F T A L T Q H G K E E L R F
 - I I L R L G S Q L S L S M A R R N L D S
 - * Y C V L V H S S H S A W Q G G T * I P
 28321 - CCTCGAGGCCAGGGCGTTCCAATCAACACCAATAGTGGTCCAGATGACCAAATGGCTAC - 28380
 - P R G Q G V P I N T N S G P D D Q I G Y
 - L E A R A F Q S T P I V V Q M T K L A T
 - S R P G R S N Q H Q * W S R * P N W L L
 28381 - TACCGAAGAGCTACCCGACGAGTTCGTGGTGGTGACGGCAAATGAAGAGCTCAGCCCC - 28440
 - Y R R A T R R V R G G D G K M K E L S P
 - T E E L P D E F V V V T A K * K S S A P
 - P K S Y P T S S W W * R Q N E R A Q P Q
 28441 - AGATGGTACTTCTATTACCTAGGAAGTGGCCAGAAAGCTTCACTTCCCTACGGCGCTAAC - 28500
 - R W Y F Y Y L G T G P E A S L P Y G A N
 - D G T S I T * E L A Q K L H F P T A L T
 - M V L L L P R N W P R S F T S L R R * Q
 28501 - AAAGAAGGCATCGTATGGGTTGCAACTGAGGGAGCCTTGAATACACCCAAAGACCACATT - 28560
 - K E G I V W V A T E G A L N T P K D H I
 - K K A S Y G L Q L R E P * I H P K T T L
 - R R H R M G C N * G S L E Y T Q R P H W

FIG. 11 Con't

28561 - GGCACCCGCAATCCTAATAACAATGCTGCCACCGTGTACAACCTTCTCAAGGAACAACA - 28620
 - G T R N P N N N A A T V L Q L P Q G T T
 - A P A I L I T M L P P C Y N F L K E Q H
 - H P Q S * * Q C C H R A T T S S R N N I
 28621 - TTGCCAAAAGGCTTCTACGCAGAGGGAAGCAGAGGCGGCAGTCAAGCCTTCTCTCGCTCC - 28680
 - L P K G F Y A E G S R G G S Q A S S R S
 - C Q K A S T Q R E A E A A V K P L L A P
 - A K R L L R R G K Q R R Q S S L F S L L
 28681 - TCATCACGTAGTCGGGTAATCAAGAAATCAACTCTGGCAGCAGTAGGGGAAATCT - 28740
 - S S R S R G N S R N S T P G S S R G N S
 - H H V V A V I Q E I Q L L A A V G E I L
 - I T * S R * F K K F N S W Q Q * G K F S
 28741 - CCTGCTCGAATGGCTAGCGGAGGTGGTGAACCTGCCCTCGCGCTATTGCTGCTAGACAGA - 28800
 - P A R M A S G G G E T A L A L L L L D R
 - L L E W L A E V V K L P S R Y C C * T D
 - C S N G * R R W * N C P R A I A A R Q I
 28801 - TTGAACCAGCTTGAGAGCAAAGTTTCTGGTAAAGGCCAACAAACAAGGCCAACTGTC - 28860
 - L N Q L E S K V S G K G Q Q Q Q G Q T V
 - * T S L R A K F L V K A N N N K A K L S
 - E P A * E Q S F W * R P T T T R P N C H
 28861 - ACTAAGAAATCTGCTGCTGAGGCATCTAAAAGCCTCGCCAAAACGTACTGCCACAAAA - 28920
 - T K K S A A E A S K K P R Q K R T A T K
 - L R N L L L R H L K S L A K N V L P Q N
 - * E I C C * G I * K A S P K T Y C H K T
 28921 - CAGTACAACGCTCAAGCATTGGGAGACGTGGTCCAGAACAACCCCAAGGAAATTC - 28980
 - Q Y N V T Q A F G R R G P E Q T Q G N F
 - S T T S L K H L G D V V Q N K P K E I S
 - V Q R H S S I W E T W S R T N P R K F R
 28981 - GGGACCAAGACCTAATCAGACAAGGAACCTGATTACAACATTGGCCGCAAATTGCACAA - 29040
 - G D Q D L I R Q G T D Y K H W P Q I A Q
 - G T K T * S D K E L I T N I G R K L H N
 - G P R P N Q T R N * L Q T L A A N C T I
 29041 - TTTGCTCAAAGTGCCTCTGCATTCTTTGGAATGTCACGCATTGGCATGGAAGTCACACCT - 29100
 - F A P S A S A F F G M S R I G M E V T P
 - L L Q V P L H S L E C H A L A W K S H L
 - C S K C L C I L W N V T H W H G S H T F
 29101 - TCGGGAACATGGCTGACTTATCATGGGCCATTAAATTGGATGACAAGATCCACAATTC - 29160
 - S G T W L T Y H G A I K L D D K D P Q F
 - R E H G * L I M E P L N W M T K I H N S
 - G N M A D L S W S H * I G * Q R S T I Q
 29161 - AAAGACAACGTCATACTGCTGAACAAGCACATTGACGCATACAAAACATTCCCACCAACA - 29220
 - K D N V I L L N K H I D A Y K T F P P T
 - K T T S Y C * T S T L T H T K H S H Q Q
 - R Q R H T A E Q A H * R I Q N I P T N R
 29221 - GAGCCTAAAAGGACAAAAGAAAAGACTGATGAAGCTCAGCCTTGGCCGAGAGACAA - 29280
 - E P K K D K K K K T D E A Q P L P Q R Q
 - S L K R T K R K R L M K L S L C R R D K
 - A * K G Q K E K D * * S S A F A A E T K
 29281 - AAGAAGCAGCCCACTGTGACTCTTCTCTCGGGCTGACATGGATGATTTCTCCAGACAA - 29340
 - K K Q P T V T L L P A A D M D D F S R Q
 - R S S P L * L F F L R L T W M I S P D N
 - E A A H C D S S S C G * H G * F L Q T T
 29341 - CTTCAAATTCATGAGTGGAGCTTCTGCTGATTCAACTCAGGCATAAACTCATGATG - 29400
 - L Q N S M S G A S A D S T Q A * T L M M
 - F K I P * V E L L L I Q L R H K H S * *
 - S K F H E W S F C * F N S G I N T H D D

FIG. 11 Con't

29401 - ACCACACAAGGCAGATGGGCTATGTAAACGTTTTTCGCAATTCGTTTACGATACATAGTC - 29460
 - T T Q G R W A M * T F S Q F R L R Y I V
 - P H K A D G L C K R F R N S V Y D T * S
 - H T R Q M G Y V N V F A I P F T I H S L
 29461 - TACTCTTGTGCAGAAATGAATTCGTAACAAACAGCACAGTAGGTTTAGTTAACTTTA - 29520
 - Y S C A E * I L V T K Q H K * V * L T L
 - T L V Q N E F S * L N S T S R F S * L *
 - L L C R M N S R N * T A Q V G L V N F N
 29521 - ATCTCACATAGCAATCTTTAATCAATGTGTAACATTAGGGAGGACTTGAAAGAGCCACCA - 29580
 - I S H S N L * S M C N I R E D L K E P P
 - S H I A I F N Q C V T L G R T * K S H H
 - L T * Q S L I N V * H * G G L E R A T T
 29581 - CATTTTCATCGAGGCCACGCGGAGTACGATCGAGGGTACAGTGAATAATGCTAGGGAGAG - 29640
 - H F H R G H A E Y D R G Y S E * C * G E
 - I F I E A T R S T I E G T V N N A R E S
 - F S S R P R G V R S R V Q * I M L G R A
 29641 - CTGCCTATATGGAAGAGCCCTAATGTGTAATAATTTTAGTAGTGCTATCCCCATGTG - 29700
 - L P I W K S P N V * N * F * * C Y P H V
 - C L Y G R A L M C K I N F S S A I P M *
 - A Y M E E P * C V K L I L V V L S P C D
 29701 - ATTTAATAGCTTCTTAGGAGAATGACAAAAAAAAAAAAAAAAA - 29742
 - I L I A S * E N D K K K K K X
 - F * * L L R R M T K K K K X
 - F N S F L G E * Q K K K K X

FIG. 11 Con't

1 - TTTTTTTTTTTTTTGTGATTCTCCTAAGAAGCTATTAATAACACATGGGGATAGCACTA - 60
 - F F F F F V I L L R S Y * N H M G I A L
 - F F F F L S F S * E A I K I T W G * H Y
 - F F F F C H S P K K L L K S H G D S T T
 61 - CTAAATTAATTTTACACATTAGGGCTCTTCCATATAGGCAGCTCTCCCTAGCATTATTC - 120
 - L K L I L H I R A L P Y R Q L S L A L F
 - * N * F Y T L G L F H I G S S P * H Y S
 - K I N F T H * G S S I * A A L P S I I H
 121 - ACTGTACCCTCGATCGTACTCCGCGTGGCCTCGATGAAAATGTGGTGGCTCTTTCAAGTC - 180
 - T V P S I V L R V A S M K M W W L F Q V
 - L Y P R S Y S A W P R * K C G G S F K S
 - C T L D R T P R G L D E N V V A L S S P
 181 - CTCCTAATGTTACACATTGATTAAGATTGCTATGTGAGATTAAAGTAACTAAACCTA - 240
 - L P N V T H * L K I A M * D * S * L N L
 - S L M L H I D * R L L C E I K V N * T Y
 - P * C Y T L I K D C Y V R L K L T K P T
 241 - CTTGTGCTGTTTGTAGTTACGAGAATTCATTCTGCACAAGAGTAGACTATGTATCGTAAACG - 300
 - L V L F S Y E N S F C T R V D Y V S * T
 - L C C L V T R I H S A Q E * T M Y R K R
 - C A V * L R E F I L H K S R L C I V N G
 301 - GAATTGCGAAAACGTTTACATAGCCCATCTGCCTGTGTGGTCATCATGAGTGTATATGC - 360
 - E L R K R L H S P S A L C G H H E C L C
 - N C E N V Y I A H L P C V V I M S V Y A
 - I A K T F T * P I C L V W S S * V F M P
 361 - CTGAGTTGAATCAGCAGAAGCTCCACTCATGGAATTTGAAGTTGTCTGGAGAAATCATC - 420
 - L S * I S R S S T H G I L K L S G E I I
 - * V E S A E A P L M E F * S C L E K S S
 - E L N Q Q K L H S W N F E V V W R N H P
 421 - CATGTCAGCCGAGGAAGAGTACAGTGGGCTGCTTCTTTGTCTCTGCGGCAAAGG - 480
 - H V S R R R K K S H S G L L L L S L R Q R
 - M S A A G R R V T V G C F F C L C G K G
 - C Q P Q E E E S Q W A A S F V S A A K A
 481 - CTGAGCTTCATCAGTCTTTTTCTTTTTGTCTTTTTAGGCTCTGTTGGTGGGAATGTTTT - 540
 - L S F I S L F L F V L F R L C W W E C F
 - * A S S V F F F L S F L G S V G G N V L
 - E L H Q S F S F C P F * A L L V G M F C
 541 - GTATGCGTCAATGTGCTTGTTCAGCAGTATGACGTGTCTTTGAATTGTGATCTTTGTC - 600
 - V C V N V L V Q Q Y D V V F E L W I F V
 - Y A S M C L F S S M T L S L N C G S L S
 - M R Q C A C S A V * R C L * I V D L C H
 601 - ATCCAATTTAATGGCTCCATGATAAGTCAGCCATGTTCCCGAAGGTGTGACTTCCATGCC - 660
 - I Q F N G S M I S Q P C S R R C D F H A
 - S N L M A P * * V S H V P E G V T S M P
 - P I * W L H D K S A M F P K V * L P C Q
 661 - AATGCGTGACATTCCAAAGAATGCAGAGGCACTTGAGCAAATTGTGCAATTTGCGGCCA - 720
 - N A * H S K E C R G T W S K L C N L R P
 - M R D I P K N A E A L G A N C A I C G Q
 - C V T F Q R M Q R H L E Q I V Q F A A N
 721 - ATGTTTGAATCAGTTCCTTGTCTGATTAGGTCTTGGTCCCCGAAATTCCTTGGGTTTG - 780
 - M F V I S S L S D * V L V P E I S L G L
 - C L * S V P C L I R S W S P K F P W V C
 - V C N Q F L V * L G L G P R N F L G F V
 781 - TTCTGGACCAGTCTCCCAAATGCTTGTGAGTGTACTGTTTGTGGCAGTACGTTT - 840
 - F W T T S P K C L S D V V L F C G S T F
 - S G P R L P N A * V T L Y C F V A V R F
 - L D H V S Q M L E * R C T V L W Q Y V F

FIG. 12

841 - TTGGCGAGGCTTTTGTAGATGCCTCAGCAGCAGATTCTTAGTGACAGTTGGCCTTGTG - 900
 - L A R L F R C L S S R F L S D S L A L L
 - W R G F L D A S A A D F L V T V W P C C
 - G E A F * M P Q Q Q I S * * Q F G L V V
 901 - TTGTTGGCCTTTACCAGAACTTGTCTCTCAAGCTGGTTCAATCTGTCTAGCAGCAATAG - 960
 - L L A F T R N F A L K L V Q S V * Q Q *
 - C W P L P E T L L S S W F N L S S S N S
 - V G L Y Q K L C S Q A G S I C L A A I A
 961 - CGCGAGGGCAGTTTACCACCTCCGCTAGCCATTCGAGCAGGAGAATTTCCCTACTGCT - 1020
 - R E G S F T T S A S H S S R R I S P T A
 - A R A V S P P P L A I R A G E F P L L L
 - R G Q F H H L R * P F E Q E N F P Y C C
 1021 - GCCAGGAGTTGAATTTCTTGAATTACCGCGACTACGTGATGAGGAGCGAGAAGAGGCTTG - 1080
 - A R S * I S * I T A T T * * G A R R G L
 - P G V E F L E L P R L R D E E R E A *
 - Q E L N F L N Y R D Y V M R S E K R L D
 1081 - ACTGCCGCTCTGCTTCCCTCTGCGTAGAAGCCTTTTGGCAATGTTGTTCCCTTGAGGAAG - 1140
 - T A A S A S L C V E A F W Q C C S L R K
 - L P P L L P S A * K P F G N V V P * G S
 - C R L C F P L R R S L L A M L F L E E V
 1141 - TTGTAGCACGGTGGCAGCATTGTTATTAGGATTGCGGGTCCAATGTGGTCTTTGGGTGT - 1200
 - L * H G G S I V I R I A G A N V V F G C
 - C S T V A A L L L G L R V P M W S L G V
 - V A R W Q H C Y * D C G C Q C G L W V Y
 1201 - ATCAAGGCTCCCTCAGTTGCAACCCATACGATGCCTTCTTTGTTAGCGCCGTAGGGAAG - 1260
 - I Q G S L S C N P Y D A F F V S A V G K
 - F K A P S V A T H T M P S L L A P * G S
 - S R L P Q L Q P I R C L L C * R R R E V
 1261 - TGAAGCTTCTGGCCAGTTCCCTAGGTAATAGAAGTACCATCTGGGGCTGAGCTCTTTCAT - 1320
 - * S F W A S S * V I E V P S G A E L F H
 - E A S G P V P R * * K Y H L G L S S F I
 - K L L G Q F L G N R S T I W G * A L S F
 1321 - TTTGCCGTACCACCACGAACCTCGTCGGGTAGCTCTTCGGTAGTAGCCAATTTGGTCATC - 1380
 - F A V T T T N S S G S S S V V A N L V I
 - L P S P P R T R R V A L R * * P I W S S
 - C R H H H E L V G * L F G S S Q F G H L
 1381 - TGGACCACTATTGGTGTGATTGGAACGCCCTGGCCTCGAGGGAATCTAAGTTCCTCCTT - 1440
 - W T T I G V D W N A L A S R E S K F L L
 - G P L L V L I G T P W P R G N L S S S L
 - D H Y W C * L E R P G L E G I * V P P C
 1441 - GCCATGCTGAGTGAGAGCTGTGAACCAAGACGAGTATTATTGGGTAAACCTTGGGGTCG - 1500
 - A M L S E S C E P R R S I I G * T L G S
 - P C * V R A V N Q D A V L L G K P W G R
 - H A E * E L * T K T Q Y Y W V N L G V G
 1501 - GCGCTGTTTTGGCCTTGCCTTCCATTCTGGTTATTGTGAGTTGAATCTGT - 1560
 - A L F W P C P I A S S I L V I V S * I C
 - R C F G L A P L R P P F W L L S V E S V
 - A V L A L P H C V L H S G Y C Q L N L W
 1561 - GGGTCCACAAATGTAATGCGGGGGCACTACGTTGGTTTGGATTGGGGTCCATTATCAGA - 1620
 - G S T K C N A G G T T L V * L G S I I R
 - G P P N V M R G A L R W F D W G P L S D
 - V H Q M * C G G H Y V G L I G V H Y Q T
 1621 - CATTTAATTTGTTGTTTATTTAAACAACAAGTACGTCTCTAAATGCAGCAGTTTGGT - 1680
 - H F N L F V Y L K Q Q V R L * M Q Q F G
 - I L I C S F I * N N K Y V S K C S S L V
 - F * F V R L F K T T S T S L N A A V W *

FIG. 12 Con't

1681 - GACCTTCATGAAGGTACCAACACCTAGCTATAAGCGCACACCAGCTGGATCTTGACAGT - 1740
 - D L H E G T N T * L * A H H Q L D L D S
 - T F M K V P T P S Y K R T T S W I L T V
 - P S * R Y Q H L A I S A P P A G S * Q L
 1741 - TGATAGTAACATTAGGTGTCATGTTTGAACCATAGTGTGCCATCTATGAAAAGGTAATA - 1800
 - * * * H * V C M F E P * C A I Y E K V K
 - D S N I R C A C L N H S V P S M K R * N
 - I V T L G V H V * T I V C H L * K G K T
 1801 - CCTTTCCTAGAGCACAAAGCCAAGCAGTGTCTATAAGTATTACCCCTAGTGTGTACCTTA - 1860
 - P F L E H K A K Q C Y K Y Y P * C C T L
 - L S * S T K P S A I S I T P S V V P Y
 - F P R A Q S Q A V L * V L P L V L Y L T
 1861 - CAAGGATCTTCAAGCACATGAGGTTTATTAGATGCACAGCGCTGTACTACAGTGCATATG - 1920
 - Q G S S S T * G L L D A Q R C T T V H M
 - K D L Q A H E V Y * M H S A V L Q C I C
 - R I F K H M R F I R C T A L Y Y S A Y A
 1921 - CAACTGCATAGAGAAATACAAGTCAAACAATGAGAAGTTTCATGTTTCGTTTAGACTTTG - 1980
 - Q L H R E I Q V K T M R S F M F V * T L
 - N C I E K Y K S Q * E V S C S F R L W
 - T A * R N T S Q N N E K F H V R L D F G
 1981 - GTACAAGGTTCTTCTAGATCCTGGATTCGAGTGAAAACCAAATATAATAAGCATTATT - 2040
 - V Q G S S R S W I S S E N Q N I I S I I
 - Y K V L L D P G F R V K T K I * * A L L
 - T R F F * I L D F E * K P K Y N K H Y *
 2041 - AAAACAAGGAATAGCAGAAAGGCTAAAAAGCACAAATAGAAGTCAATTAAGTGAGCTCA - 2100
 - K T R N S R K A K K H K * K S I K V S S
 - K Q G I A E R L K S T N R S Q L K * A H
 - N K E * Q K G * K A Q I E V N * S E L I
 2101 - TTCATTCTGTCTTTCTCTTAATGGTGAAGCAAAGTATTAATAACTAGAGCAGCAACAA - 2160
 - F I L S F S * W * S K V L K I L E Q Q Q
 - S F C L S L N G E A K Y * K Y * S S N N
 - H S A V F L L M V K Q S I K N T R A A T T M
 2161 - TGAGAAAAAGTGGCGAGTAGAGCTCTGTGTAACCTCCTCTGTCTGATGAAAAGTTTTG - 2220
 - * E K V A S R A L V E P P L V * * K V L
 - E K K W R V E L L L N L L L S D E K F W
 - R K S G E * S S C * T S S C L M K S F G
 2221 - GTGAACTGATCTGCACGCAGCTGATAGGTATGTCGAGTACCGTCAGCACAAAGCAAAG - 2280
 - V K L I L H A A D R Y V E Y R Q H K Q K
 - * N * S C T Q L I G M S S T V S T S K S
 - E T D L A R S * * V C R V P S A Q A K A
 2281 - CAAAGTGTGTGCTAGTGAAGTTAGTCAAATTTATTGTCAGCAAGAGGGTGAAATGGTG - 2340
 - Q S V C * C K L V Q I Y C Q Q E G E M V
 - K V C A S A S * C K F I V S K R V K W *
 - K C V L V Q V S A N L L S A R G * N G E
 2341 - AATTGCCCTCGTATGTTCCCTGATGGGCAAGGTTCTTTTAGTAGTACAGTCGTACCTCTAA - 2400
 - N C P R M F L M G K V L L V V Q S Y L *
 - I A L V C S * W A R F F * * Y S R T S N
 - L P S Y V P D G Q G S F S S T V V P L T
 2401 - CAACTCCTGATAGTATAGTCTCGCAAGATGTAATAACAATCAATGTCAGGAAGAGAA - 2460
 - H T P D S D I A R K M * I Q S M S G R E
 - T L L I V I * L A R C K Y N Q C Q E E N
 - H S * * * Y S S Q D V N T I N V R K R I
 2461 - TAATTTTCATGTTGTTTTATGGATAATCTAACCCATAGGTTCTTCATCATCTAACTCC - 2520
 - * F S C S F Y G * S N S I G S S S S N S
 - N F H V R F M D N L T P * V L H H L T P
 - I F M F V L W I I * L H R F F I I * L R

FIG. 12 Con't

2521 - GAATAATTCCTCTTAGTTAGAGGCTTAAATAATTGTCTCACTATTGAACTTATTATAACG - 2580
 - E * F F L V R G L N N C L T I E L I I T
 - N N S S * L E A * I I V S L L N L L * R
 - I I L L S * R L K * L S H Y * T Y Y N V
 2581 - TCAAGATTCCAAATAGCAATCCTGAAAGTCCTCATAATGATAATCAATATCTCTGCTATT - 2640
 - S R F Q I A I L K V L I M I I N I S A I
 - Q D S K * Q S * K S S * * * S I S L L L
 - K I P N S N P E S P H N D N Q Y L C Y C
 2641 - GTAACCTGGAAGTCAACAAGATGAAACATCTGTTGTCCTACTGTACTAGCAAAGCAAT - 2700
 - V T W K S T R * N I C C H L L Y * Q S N
 - * P G S Q Q D E T S V V T Y C T S K A I
 - N L E V N K M K H L L S L T V L A K Q Y
 2701 - ATTGTCGTTGCTACCGCGTGGTCTGTATTATTAATTATAGTTTCCAATACGGTAGCGGTT - 2760
 - I V V A T G V V C I * F I V S N T V A V
 - L S L L P A W S V F N L * F P I R * R L
 - C R C Y R R G L Y L I Y S F Q Y G S G C
 2761 - GTATGCAGCAAAACCTGAATCAGTGCCTACAGCCTGCGACGCTCCTAATTTGTAATAAGA - 2820
 - V C S K T * I S A Y T L R R S * F V I R
 - Y A A K P E S V P T R C D A P N L * * E
 - M Q Q N L N Q C L H A A T L L I C N K K
 2821 - AAGCGTTCGTGATGTAGCCACAGTGATCTCTTTTGGCAGGTCCTTAATGTCACAGCGCCC - 2880
 - K R S * C S H S D L F W Q V L N V T A P
 - S V R D V A T V I S F G R S L M S Q R P
 - A F V M * P Q * S L L A G P * C H S A L
 2881 - TAGGGAGTGTCCGGCCATTCCGAAGTGACCACGAATGATCAGCACCAATGACAAGTTC - 2940
 - * G V S G H S Q V T T N D H S T N D K F
 - R E C P A I R K * P R M I T A P M T S S
 - G S V R P F A S D H E * S Q H Q * Q V H
 2941 - ACTTTCCATGAGCGGTCTGGTCACAATTGTCCCCGGAGAGGCACATTGAGAAGAATGTT - 3000
 - T F H E R S G H N C P P E R H I E K N V
 - L S M S G L V T I V P R R G T L R R M F
 - F P * A V W S Q L S P G E A H * E E C L
 3001 - TGTTTCTGGGTTGAATGACCACATTGAGCGGTACGAGCAACAGCCTGAAGGAAGCAAC - 3060
 - C F W V E * P H * A G T S K Q P E G S N
 - V S G L N D H I E R V R A N S L K E A T
 - F L G * M T T L S G Y E Q T A * R K Q R
 3061 - GAAGTAGCTAAGCCACATCAAGCCTACAATACAAGCATTGCAATCGCAATCCC GCCAGT - 3120
 - E V A K P H Q A Y N T S H C N R N P A S
 - K * L S H I K P T I Q A I A I A I P P V
 - S S * A T S S L Q Y K P L Q S Q S R Q S
 3121 - CACCAATTAATTCTGTAGACAACAGCACAACAAGCAAGTGTACTGGCCACAA - 3180
 - H P I N S V D N S K H K T S K C Y W P Q
 - T Q L I L * T T A S T K Q A S V T G H K
 - P N * F C R Q Q Q A Q N K Q V L L A T R
 3181 - GAGCCAGAGGAAAACAAGCTTTATTATGTACAAAACCTGTTCCGATTAGAATAGGCAAA - 3240
 - E P E E N K L Y Y V Q K P V P I R I G K
 - S Q R K T S F I M Y K N L F R L E * A N
 - A R G K Q A L L C T K T C S D * N R Q I
 3241 - TTGTAGTAACATAATCCAGGCTAGGAATAGGAAACCTATTACTAGGTTCCATTGTCCAG - 3300
 - L * * H N P G * E * E T Y Y * V P L F Q
 - C S N I I Q A R N R K P I T R F H C S R
 - V V T * S R L G I G N L L L G S I V P G
 3301 - GAGTTGTTTAAAGCTCCTCAACGGTAATAGTACCGTTGCTGCCATGATAAGCAATGTAA - 3360
 - E L F K L L N G N S T V V C H D K Q C *
 - S C L S S S T V I V P L S A M I S N V K
 - V V * A P Q R * * Y R C L P * * A M L K

FIG. 12 Con't

3361 - AGTTCCAAACAGAATAATAATAATAGTTAGTTCGTTTAGACCAGAAGATCAGGAACTCCT - 3420
 - S S K Q N N N N S * F V * T R R S G T P
 - V P N R I I I I V S S F R P E D Q E L L
 - F Q T E * * * * L V R L D Q K I R N S F
 3421 - TCAGAAGAGTTCAGATTTTAAACACGCGAGTAGACGTAACCGTTGGTTTTACTAAACTC - 3480
 - S E E F R F L T R E * T * T V G F T K L
 - Q K S S D F * H A S R R R K P L V L L N S
 - R R V Q I F N T R V D V N R W F Y * T H
 3481 - ACGTTAACAATATTGCAGCAGTACGCACACAATCGAAGCGCAGTAAGGATGGCTAGTGTG - 3540
 - T L T I L Q Q Y A H N R S A V R M A S V
 - R * Q Y C S S T H T I E A Q * G W L V *
 - V N N I A A V R T Q S K R S K D G * C D
 3541 - ACTAGCAAGAATACCACGAAAGCAAGAAAAGAGTACGCTATTAAC TATTAACGTACCT - 3600
 - T S K N T T K A R K R S T L L T I N V P
 - L A R I P R K Q E K E V R Y * L L T Y L
 - * Q E Y H E S K K K Y A I N Y * R T C
 3601 - GTTCTTCCGAAACGAATGAGTACATAAGTTCGFACTCACTTTCTTGTGCTTACAAAGGC - 3660
 - V S S E T N E Y I S S Y S L S C A Y K G
 - F L P K R M S T * V R T H F L V L T K A
 - F F R N E * V H K F V L T F L C L Q R H
 3661 - ACGCTAGTAGTCGTCGCTCATATAAATGGATCCATTGCTGGATTAGCAACTCCT - 3720
 - T L V V V V G S S * I G S I A G L A T P
 - R * * S S S A H H K L D P L L D * Q L L
 - A S S R R L I I N W I H C W I S N *
 3721 - GAAGAGCCGTCGATTGTGTGATTTGCACATTCGGTGGGCTTTAACAAGCTGTAAAG - 3780
 - E E P S I V C I C T F G G S L T S L L K
 - K S R R L C V F A H S V G L * Q A C * R
 - R A V D C V Y L H I R W V F N K L V K D
 3781 - ATGAAGAATGTAGCATTTTCAATACAGTGTCTGTAGTAATTTGTGTAGACTCAAGCTGG - 3840
 - M K N V A F S I P V S V V I C V D S S W
 - * R E * H F Q Y Q C L * * F V * T Q A G
 - E E C S I F N T S V C S N L C R L K L V
 3841 - TAGTAACTTCGGTGAAATAGCCATGTACAACGACATAGTCTTTAACACCTGAGTGCCTA - 3900
 - * * T S V K * P C T T T * S L T P E C L
 - S K L R * N S H V Q R H S L * H L S A Y
 - V N F G E I A M Y N D I V F N T * V P I
 3901 - TCCTCAGAATAACCACCAATTTGGTAGTCTTCTTTGAGTTTGGTGTGAAATGCCGTCA - 3960
 - S S E * P P I W * S S L S F G V E M P S
 - P Q N N H Q F G S L L * V L V L K C R H
 - L R I T T N L V V F F E F W C * N A V T
 3961 - CCTTCAGTAACGACAATTGTATCTGTGACACTGTTATATGGTATACAGTAGTCATAGTTA - 4020
 - P S V T T I V S V T L L Y G I Q * S * L
 - L Q * R Q L Y L * H C Y M V Y S S H S Y
 - F S N D N C I C D T V I W Y T V V I V M
 4021 - TGTGTGTGCCAGCAAACAAGTAGTTGGCATCATAAAGTAATGGGTTCTTGGATTGCAC - 4080
 - C V C Q Q T K * L A S * S N G F L D L H
 - V C A S K Q S S W H H K V M G S W I C T
 - C V P A N K V V G I I K * W V L G F A L
 4081 - TTCCAACAAGCCAACATCTCATAATAATTCTACATGCGTTGATGCATTGTAGAAAATAT - 4140
 - F Q Q S Q H L I I I L H A L M H C R K Y
 - S N K A N I S * * F Y M R * C I V E N I
 - P T K P T S H N N S T C V D A L * K I Y
 4141 - ATCAAGGCATAGAGGTACAAAATTCGCCTCCTTACCTGCAGCGACAAGCAAAGATGT - 4200
 - I K A * R Y K N C A S L P A A T S K R C
 - S R H R G T K I A P P Y L Q R Q A K D V
 - Q G I E V Q K L R L L T C S D K Q K M *

FIG. 12 Con't

4201 - GAATAGATGGTAACAAATAGCAGCAGTAAATTGCAAATGAACTGGAAGCCCTTATAAAGG - 4260
 - E * M V T N S S S K L Q M N W K P L * R
 - N R W * Q I A A V N C K * T G S P Y K G
 - I D G N K * Q Q * I A N E L E A L I K G
 4261 - GCTAGCTGCCATCTTTTATTGAGCGCAATTATTTTGGTAGCGCTCTGAAAAACAGCAAGA - 4320
 - A S C H L L L S A I I L V A L * K T A R
 - L A A I F Y * A Q L F W * R S E K Q Q E
 - * L P S F I E R N Y F G S A L K N S K K
 4321 - AATGCAACGCCAATAACAAGCCATCCGAAAGGGAGTGAGGCTTGTAGCGGTATCGTTGCT - 4380
 - N A T P I T S H P K G S E A C S G I V A
 - M Q R Q * Q A I R K G V R L V A V S L L
 - C N A N N K P S E R E * G L * R Y R C C
 4381 - GTAGCATGAACAGTACTTGCAGGAGAAGCATTGTCAATTTTTACTGGCTGTGCAGTAATT - 4440
 - V A * T V L A G E A L S I F T G C A V I
 - * H E Q Y L Q E K H C Q F L L A V Q * L
 - S M N S T C R R S I V N F Y W L C S N *
 4441 - GATCCAAGAGTAAAAATCTCATAAACAAATCCATAAGTTCGTTTATGTGTAATGTAATT - 4500
 - D P R V K N L I N K S I S S F M C N V I
 - I Q E * K I S * T N P * V R L C V M * F
 - S K S K K S H K Q I H K F V Y V * C N L
 4501 - TGACACCCTTGAGAACTGGCTCAGAGTCATCTCATCAAAGTTCGAGCAAGAACCACAAG - 4560
 - * H P * E L A Q S H P H Q T C S K N H K
 - D T L E N W L R V I L I K L A A R T T R
 - T P L R T G S E S S S S N L Q Q E P Q E
 4561 - AGCATGACCCCTTGAGGCAACTGCAACAAC TAGTCATGCAACAAAGCAAGATTGTAACCA - 4620
 - S M H P * G N C N N * S C N K A R L * P
 - A C T L E A T A T T S H A T K Q D C N H
 - H A P L R Q L Q Q L V M Q Q S K I V T M
 4621 - TGACGATGGCAATTAGTCCAGCAATGAAGCCGAGCCAAACATACCAAGGCCATTTAATAT - 4680
 - * R W Q L V Q Q * S R A K H T K A I * Y
 - D D G N * S S N E A E P N I P R P F N I
 - T M A I S P A M K P S Q T Y Q G H L I Y
 4681 - ATTGCTCATATTTCCCAATCTTGAAGGTCAATGAGTGATTCAATTTAAATTTTAGCGA - 4740
 - I A H I F P I L E G Q * V I H L N F * R
 - L L I F S Q F L K V N E * F I * I F S D
 - C S Y F P N S * R S M S D S F K F L A T
 4741 - CCTCATTGAGGCGGTCAATTTCTTTTGAATGTTGACGACAGAAGCGTTAATGCCTGAAA - 4800
 - P H * G G Q F L F E C * R Q K R * C L K
 - L I E A V N F F L N V D D R S V N A * N
 - S L R R S I S F * M L T T E A L M P E M
 4801 - TGTCGCCAAGATCAACATCTGGTGATGATTTTTGAAGTACTTGTCCAGCTCTTCTT - 4860
 - C R Q D Q H L V M Y D F * S T C P A L L
 - V A K I N I W * C M I F E V L V Q L F F
 - S P R S T S G D V * F L K Y L S S S S L
 4861 - TGAATGAGTCAAGCTCAGGTTGCAGAGGATCATAAAGTGTGTTAATGATGCCAATAA - 4920
 - * M S Q A Q V A E D H K L C C * * C Q *
 - E * V K L R L Q R I I N C V V N D A N N
 - N E S S S G C R G S * T V L L M M P I T
 4921 - CGACATCACAAATTCCTGAGACAAATGTATTGTCTGTAGTAATTATTTGTGGAGAAAAGA - 4980
 - R H H N F L R Q M Y C L * * L F V E K R
 - D I T I S * D K C I V C S N Y L W R K E
 - T S Q F P E T N V L S V V I I C G E K K
 4981 - AGTTCCTCTGTGTAATAAACCAAGAAGTGCCATTAACACAAAAACACCTTCACGAGGGA - 5040
 - S S L V * * T K K C H * T Q K H L H E G
 - V P L C N K P R S A I K H K N T F T R E
 - F L C V I N Q E V P L N T K T P S R G K

FIG. 12 Con't

5041 - AGTATGCTTTGCCTTCATGACAAATTGCTGGCGCTGGTGAAGTTCTCTCCTGGGATG - 5100
 - S M L C L H D K L L A L W * S S S P G M
 - V C F A F M T N C W R C G E V P L L G W
 - Y A L P S * Q I A G A V V K F L S W D G
 5101 - GCACATACGTGACATGTAGGAAGACAACACCATGCGGGGCTGCTTGTGGGAAGGACATAA - 5160
 - A H T * H V G R Q H H A G L L V G R T *
 - H I R D M * E D N T M R G C L W E G H K
 - T Y V T C R K T T P C G A A C G K D I R
 5161 - GGTGGTAGCCCTTTCCACAAAAGTCAACTCTTTTTGATTGTCCAAGAACACACTCAGACA - 5220
 - G G S P F H K S Q L F L I V Q E H T Q T
 - V V A L S T K V N S F * L S K N T L R H
 - W * P F P Q K S T L F D C P R T H S D I
 5221 - TTTTAGTAGCAGCAAGATTAGCAGAAGCCCTGATTTAGCAGCCCTGATTAGTTGTTGTG - 5280
 - F * * Q Q D * Q K P * F Q Q P * L V V V
 - F S S S K I S R S P D F S S P D * L L C
 - L V A A R L A E A L I S A A L I S C C V
 5281 - TTACATAGGTTGAAGGCTTTGAAGTCTGCCTGTAATTAACCTGTCAATTTGTACCTCCG - 5340
 - L H R F E G F E V C L * L T C Q F V P P
 - Y I G L K A L K S A C N * P V N L Y L R
 - T * V * R L * S L P V I N L S I C T S A
 5341 - CCTCGACTTTATCAAGTCGCGAAAGGATATCATTAGCACACTTGAATTCACCAAAAT - 5400
 - P R L Y Q V A K G Y H L A H L K L H Q N
 - L D F I K S R E K D I I * H T * N C T K I
 - S T L S S R E R I S F S T L E I A P K L
 5401 - TAGACTAAGTTGTTTTAACAAGTGTGTTTAAATGCTTGAGCATTCTGGTTAACACAGTCTT - 5460
 - * S * V V * Q V C L M L E H S G * Q R L
 - R A K L F N K C V * C L S I L V N N V L
 - E L S C L T S V F N A * A F W L T T S C
 5461 - GCAGCTTGCCCAATGCAGTTGATGTTGTTGAAGTATTCTGAATTTGACTAATCGCCT - 5520
 - A A C P M Q L M L L * V I L E F D * S P
 - Q L A Q C S * C C C K * F L N L T N R L
 - S L P N A V D V V V S D S * I * L I A L
 5521 - TGTTAAATTTGGTTGGCGATTTGTTTTGGTTCTCATAGAGAACATTTGGGTAACCTCAA - 5580
 - C * I G W R F V F G S H R E H F G * L Q
 - V K L V G D L F L V L I E N I L G N S N
 - L N W L A I C F W F S * R T F W V T P M
 5581 - TGCCATTGAACCTATATGCCATTGCATAGCAAAAGGTATTTGAAGAGCAGCGCCAGCAG - 5640
 - C H * T Y M P F A * Q K V F E E Q R Q H
 - A I E P I C H L H S K R Y L K S S A S T
 - P L N L Y A I C I A K G I * R A A P A P
 5641 - CAAATGTCCATCCAGCAGTGGCAGTACCCTAAGTCCATTGAAGTCCATTGCGCACAAATGA - 5700
 - Q M S I Q Q W Q Y H * L E Q Q C R Q Q S
 - K C P S S S G S T T N * S S S V G S N H
 - N V H P A V A V P L T R A A V * A A I I
 5701 - TATCATCAGTGAGCAGAGGTGGCAACACTGTAAGTCCATTGAAGTCCATTGCGCACAAATGA - 5760
 - Y H Q * A E V A T L * V H * T S A H K *
 - I I S E Q R W Q H C K S I E L L R T N E
 - S S V S R G G N T V S P L N F C A Q M R
 5761 - GATCTTAGCATTAATATCACCTAGGCATTCGCCATATTGCTTCATGAAGCCAGCATCAG - 5820
 - D L * H * Y H L G I R H I A S * S Q H Q
 - I S S I N I T * A F A I L L H E A S I S
 - S L A L I S P R H S P Y C F M K P A S A
 5821 - CGAGTGCACCTTATTAAGAGCAAGTCCCTCAATAAAAGACCTCTTAGTTGGCTTTAGAG - 5880
 - R V S P Y * R A S P Q * K T S * L A L E
 - E C H L I K E Q V L N K R P L S W L * R
 - S V T L L K S K S S I K D L L V G F R G

FIG. 12 Con't

5881 - GGTCAGGTAATATTTGTGAAAAATTAACCACCAAATATTTCAAAGTTGGGTTTTGT - 5940
 - G Q V I F V K N * N H Q N I S K L G F C
 - V R * Y L * K I K T T K I F Q S W G F V
 - S G N I C E K L K P P K Y F K V G V L Y
 5941 - ACATTTGTTTACTTGAGCGAACACTTCACGTGTGTGCGATCCTGTTTCAGCAGCAATAC - 6000
 - T F V * L E R T L H V C C D P V Q Q Q Y
 - H L F D L S E H F T C V A I L F S S N T
 - I C L T * A N T S R V L R S C S A A I P
 6001 - CTGAGAGTGCACGATTTAGTTGTGTGCAAAAGCTACCATATTGGAGAAGCAAATTAGCAC - 6060
 - L R V H D L V V C K S Y H I G E A N * H
 - * E C T I * L C A K A T I L E K Q I S T
 - E S A R F S C V Q K L P Y W R S K L A H
 6061 - ATTCAGTAGAATCTCCGAGATGTACATATTACAATCTACGGAGTTTTAGCCATAGAAA - 6120
 - I Q * N L R R C T Y Y N L R R F * P * K
 - F S R I S A D V H I T I Y G G F S H R N
 - S V E S P Q M Y I L Q S T E V L A I E T
 6121 - CAGGCATTACTTCTGTAGTAATGCTAATGAAAAGTTAGTAGGTATAGCAATGGTGTAT - 6180
 - Q A L L L * * C * L K S * * V * Q W C Y
 - R H Y F C S N A N * K V S R Y S N G V I
 - G I T S V V M L I E K L V G I A M V L L
 6181 - TAGAGTAAGCAATGAACTATCAGCACCTAAAGACATAGTATAAGCCACAATAGATTTTT - 6240
 - * S K Q L N Y Q H L K T * Y K P Q * I F
 - R V S N * T I S T * R H S I S H N R F L
 - E * A I E L S A P K D I V * A T I D F W
 6241 - GGCTAGTACTACGTAATAAAGAACTGTATGGTAACTAGCACAAATGCCAGCTCCAATAG - 6300
 - G * Y T V I K R L Y G N * H K C Q L Q *
 - A S T T * * R N C M V T S T N A S S N R
 - L V L R N K E T V W * L A Q M P A P I G
 6301 - GAATGTCGCACTCATAAGAAGTGTGACATGCTCAGCTCCTATAAGACAGCCTGCTTGAG - 6360
 - E C R T H K K C R H A Q L L * D S L L E
 - N V A L I R S V D M L S S Y K T A C L S
 - M S H S * E V S T C S A P I R Q P A * V
 6361 - TCTGGAATACATTGTTCCAGTAGAATATATGCGCCAAGCTGGTGTGAGTTGATCTGCAT - 6420
 - S G I H C F Q * N I C A K L V * V D L H
 - L E Y I V S S R I Y A P S W C E L I C M
 - W N T L F P V E Y M R Q A G V S * S A *
 6421 - GAATTGCTGTAGAAACATCAGTGCAGTTAACATCTTGATATAGAACAGCAACTTCAGATG - 6480
 - E L L * K H Q C S * H L D I E Q Q L Q M
 - N C C R N I S A V N I L I * N S N F R *
 - I A V E T S V Q L T S * Y R T A T S D E
 6481 - AAGCATTGTTCCAGGTGTAATTACACTTACCCCCAAAAGAGCAAGGTGAAATGTCTA - 6540
 - K H L F Q V * L H L H P Q K S K V K C L
 - S I C S R C N Y T Y T P K R A R * N V *
 - A F V P G V I T L T P P K E Q G E M S N
 6541 - ATATTTTCAGATGTTTTAGGATCTCGAACGGAATCAGTGAAATCAGAAACATCACGGCCAA - 6600
 - I F Q M F * D L E R N Q * N Q K H H G Q
 - Y F R C F R I S N G I S E I R N I T A K
 - I S D V L G S R T E S V K S E T S R P N
 6601 - ATTGTTGAAATGGTTGAAATCTCTTTGAAGAAGGAGTTAACACACCAGTACCAGTGAGTC - 6660
 - I V E M V E I S L K K E L T H Q Y Q * V
 - L L K W L K S L * R R S * H T S T S E S
 - C * N G * N L F E E G V N T P V P V S P
 6661 - CATTAATAAATAAATTGACACACTGGTTCTTAATAAGGTCAGTGGATAATTTGGTCCAC - 6720
 - H * N * N * H T G S * * G Q W I I L V H
 - I K I K I D T L V L N K V S G * F W S T
 - L K L K L T H W F L I R S V D N F G P Q

FIG. 12 Con't

6721 - AAACCGTGGCCGGTGCATTTAAAAGTTCAAAGAAAGTACTACAACCTCTGTAAGGTTGGT - 6780
 - K P W P V H L K V Q K K V L Q L C K V G
 - N R G R C I * K F K R K Y Y N S V R L V
 - T V A G A F K S S K E S T T T L * G W *
 6781 - AGCCAATGCCAGTAGTGGTGTAAAAACCATAATCATTAAATGGCCAATAACAATTAAGAG - 6840
 - S Q C Q * W C K N H N H L M A N N N * E
 - A N A S S G V K T I I I * W P I T I K S
 - P M P V V V * K P * S F N G Q * Q L R A
 6841 - CAGGTGGGGTGAAGGTTTGCCATCAGGGGAGAAAGGCACATTAGATATGTCTCTCTCAA - 6900
 - Q V G C K V C H Q G R K A H * I C L S Q
 - R W G A R F A I R G E R H I R Y V S L K
 - G G V Q G L P S G E K G T L D M S L S K
 6901 - AGGCCTAAGCTTGCCATGTCTAAGATACCTATATTATAATTATAATTACCAGTTGAAG - 6960
 - R A * A C H V * D T Y I Y N Y N Y Q L K
 - G P K L A M S K I P I F I I I I T S * S
 - G L S L P C L R Y L Y L * L * L P V E V
 6961 - TAGCATCAATGTTCTTAGTTCCTAAGCAAGGACACAACCCATGAAATCATCTGGCAATT - 7020
 - * H Q C S * Y S K Q G H N P * N H L A I
 - S I N V P S I P S K D T T H E I I W Q F
 - A S M F L V F Q A R T Q P M K S S G N L
 7021 - TATAATTATAATCAGCAATAACACCAGTTTGTCTGCGCTATTTGTCTTACATCATCTC - 7080
 - Y N Y N Q Q * H Q F V L A L F V L H H L
 - I I I I S N N T P L S W R Y L S Y I I S
 - * L * S A I T P V C P G A I C L T S S P
 7081 - CCTTGACTACAAAAGAATCTGCATAGACATTGGAGAAGCAAAGATCATTCAACTTAGTGG - 7140
 - P * L Q K N L H R H W R S K D H S T * W
 - L D Y K R I C I D I G E A K I I Q L S G
 - L T T K E S A * T L E K Q R S F N L V A
 7141 - CAGAAACGCCATAGCACTTAAAGGTTGAAAAAATGTTGAGTTGTAGAGCACAGAGTAAT - 7200
 - Q K R H S T * R L K K M L S C R A Q S N
 - R N A I A L K G * K K C * V V E H R V I
 - E T P * H L K V E K N V E L * S T E * S
 7201 - CAGCAACACAATTAGAAATTTTTTCTCTCCCATGCATAGACAGAAGGGAATTTAGTAG - 7260
 - Q Q H N * K F F F S P M H R Q K G I * *
 - S N T I R N F F S L P C I D R R E F S S
 - A T Q L E I F F L S H A * T E G N L V A
 7261 - CATTAAAACTCTCCAAAAGGACACAAGTTTGTAAATATTAGGGAATCTCACACATCTC - 7320
 - H * K P L Q K D T S L * Y * G I S Q H L
 - I K N L S K R T Q V C N I R E S H N I S
 - L K T S P K G H K F V I L G N L T T S P
 7321 - CTGAGGGAACAACCCTGAAATTAGAGGTCTGGTAAATTCCTTTGTCAATCTCAAAGCTCT - 7380
 - L R E Q P * N * R S G K F L C Q S Q S S
 - * G N N P E I R G L V N S F V N L K A L
 - E G T T L K L E V W * I P L S I S K L L
 7381 - TAACAGAGCATTGAGTTCAGCAAGTGGATTTTGAACAATCAACAGCATCTGTGATTG - 7440
 - * Q S I * V Q Q V D F E N N Q Q H L * L
 - N R A F E F S K W I L R T I N S I C D C
 - T E H L S S A S G F * E Q S T A S V I V
 7441 - TACCATTTTCATCATACTTGAGCATAAATGTAGTTGGCTTTAAATAGCCAACAAAATAGG - 7500
 - Y H F H H T * A * M * L A L N S Q Q N R
 - T I F I I L E H K C S W L * I A N K I G
 - P F S S Y L S I N V V G F K * P T K * A
 7501 - CTGCAGCTGACGTGCCCAATGTCTTGAGCAGGTGAAAAGGCTGTAAGAATGGCTCTAA - 7560
 - L Q L T C P K C L E Q V K R L * E W L *
 - C S * R A P N V L S R * K G C K N G S K
 - A A D V P Q M S * A G E K A V R M A L K

FIG. 12 Con't

7561 - AATTGTAAATGTTAATACCAAGAGGCAACTTAAAAATAGGTTTCAAAGTGTTAAAACCAG - 7620
 - N L * C * Y Q E A T * K * V S K C * N Q
 - I C N V N T K R Q L K N R F Q S V K T R
 - F V M L I P R G N L K I G F K V L K P E
 7621 - AAGGTAGATCACGAACACTACATCTATAGGTTGATAGCCCTTATAAACATAGAGAAACCCAT - 7680
 - K V D H E L H L * V D S P Y K H R E T H
 - R * I T N Y I Y R L I A L I N I E K P I
 - G R S R T T S I G * * P L * T * R N P S
 7681 - CTTTATTTTTAAACACAAACTCTCGTAAGTGTTTAAAATTACCTGACTTTTCTGAAACAT - 7740
 - L Y F * T Q T L V S V * N Y L T F L K H
 - F I F K H K L S * V F K I T * L F * N I
 - L F L N T N S R K C L K L P D F S E T S
 7741 - CAAGCGAAAAGGCATCAGATATGTACTCGAAAGTGAATTAATGCATTATCGAATCA - 7800
 - Q A K R H Q I C T R K C N * M H Y R I S
 - K R K G I R Y V L E S A I K C I I E Y H
 - S E K A S D M Y S K V Q L N A L S N I I
 7801 - TAGTATGTGTCTGTGTACCCATGGGTTTAGAAACAGCAAAGAAAGGGTTGTCACACAATT - 7860
 - * Y V S V Y P W V * K Q Q R K G C H T I
 - S M C L C T H G F R N S K E R V V T Q F
 - V C V C V P M G L E T A K K G L S H N S
 7861 - CAAAGTTACATGCTCGTATAACAACATTAGTAGAATTGTTAATAATAATCACCGACTGTG - 7920
 - Q S Y M L V * Q H * * N C * * * S P T V
 - K V T C S Y N N I S R I V N N N H R L *
 - K L H A R I T T L V E L L I I I T D C D
 7921 - ACTTGTGTTCATGGTAGAACCAAAAACCAACCACGGACAACATTTGATTTCTCTGTGG - 7980
 - T C C S W * N Q K P N H G Q H L I S L W
 - L V V H G R T K N P T T D N I * F L C G
 - L L F M V E P K T Q P R T T F D F S V A
 7981 - CAGCAAAATAAATACCATCCTTAAAAGGTATGACAGGGTTGCCAAACGTATGATTAATAG - 8040
 - Q Q N K Y H P * K V * Q G C Q T Y D * *
 - S K I N T I L K R Y D R V A K R M I N S
 - A K * I P S L K G M T G L P N V * L I V
 8041 - TATGAAACCCGTGAACATTAGAATAAAATGGAAGAAATAAATCCTGAGTTAAATAAAGAG - 8100
 - Y E T L * H * N K M E E I N P E L N K E
 - M K P C N I R I K W K K * I L S * I K S
 - * N P V T L E * N G R N K S * V K * R V
 8101 - TGTCTGATCTAAAAATTTTCATCAGGATAGTAAACCCCTCATAGATGAAGTATGTTGAG - 8160
 - C L I * K F H Q D S K P P S * M K Y V E
 - V * S K N F I R I V N P P H R * S M L S
 - S D L K I S S G * * T P L I D E V C * V
 8161 - TGTAATTAGGAGCTTGAACATCAAAAAGTGGTGCACCGGTCAAGGTCACTACCACTAG - 8220
 - C N * E L E H H Q K W C T G Q G H Y H *
 - V I R S L N I I K S G A P V K V T T T S
 - * L G A * T S S K V V H R S R S L P L V
 8221 - TGAGAGTAAGAAATAATAAGAAAATAAACATGTTTCGTTTAGTTGTTAACAAGAATATCAC - 8280
 - * E * E I I R K * T C S F S C * Q E Y H
 - E S K K * * E N K H V R L V V N K N I T
 - R V R N N K K I N M F V * L L T R I S L
 8281 - TTGAAACCACAACCTCTGTTGTTTTCTCTAATGATAAGCCTACCTTTTCCAGAAGAGAAT - 8340
 - L K P Q L C C F L * * * A Y L F P E E N
 - * N H N S V V F S N D K P T F F Q K R I
 - E T T T L L F S L M I S L P F S R R E *
 8341 - AAATCATATCATTGATTTGATTCTCCTTAAGAGACATTACAGCAGTTCCTCTTAATTTAA - 8400
 - K S Y H * F D S P * E T L Q Q F L L I *
 - N H I I D L I L L K R H Y S S S S * F K
 - I I S L I * F S L R D I T A V P L N L R

FIG. 12 Con't

8401 - GAGGAAATTTGCTCATGTCAAAGAGTGAATAGGAAGACAACCTGGATAGGATTTGTGTTCC - 8460
 - E E I C S C Q R V N R K T T G * D L C S
 - R K F A H V K E * I G R Q L D R I C V P
 - G N L L M S K S E * E D N W I G F V F L
 8461 - TCCAGAAAATGTAGTTAGCATGCATGGTATAGCCATCAATTTGTTCCCTTCGGCTTGCCAA - 8520
 - S R K C S * H A W Y S H Q F V P S A C Q
 - P E N V V S M H G I A I N L F L R L A K
 - Q K M * L A C M V * P S I C S F G L P R
 8521 - GATAGTTAGCCCCAATTA AAAATGCTTCCGATGATGATGCATTTACATTTGTAACAAAAG - 8580
 - D S * P Q L K M L P M M M H L H L * Q K
 - I V S P N * K C F R * * C I Y I C N K S
 - * L A P I K N A S D D D A F T F V T K A
 8581 - CTGTCCACCATGAGAAATGGCCATAAGCTTGTAAGGTCAGCATTCCAAGAATGCTCTG - 8640
 - L S T M R N G P * A C K G Q H S K N A L
 - C P P * E M A H K L V K V S I P R M L C
 - V H H E K W P I S L * R S A F Q E C S V
 8641 - TTATCTTTACAGCTATAGAACCACCCAGGGCTAGTTTTGCTTTATAAATCCACACAGAT - 8700
 - L S L Q L * N H P G L V F A L * I H T D
 - Y L Y S Y R T T Q G * F L L Y K S T Q I
 - I F T A I E P P R A S F C F I N P H R *
 8701 - AAGTGAAAACCCCTTCTTTAGAGTCATTCTCTTTTGTACATGTTGGTCTAGGGTCAT - 8760
 - K * K T L L * S H S L L S H V W S * G H
 - S E K P F F R V I L F C H M F G P R V I
 - V K N P S L E S F S F V T C L V L G S Y
 8761 - ACATATCGCTAATAATAAGGTCCCATTTATTAGCCGTATGACTGTTGCACAGTCTCCAA - 8820
 - T Y R * * * G P I Y * P . Y V L L H S L Q
 - H I A N N K V P F I S R M Y C C T V S N
 - I S L I I R S H L L A V C T V A Q S P I
 8821 - TTAAAGTAGAATCTGCGTCGGAGACGAAGTCATTAAGATCTGAATCGACAAGTAGTGTGC - 8880
 - L K * N L R R R R R S H * D L N R Q V V C
 - * S R I C V G D E V I K I * I D K * C A
 - K V E S A S E T K S L R S E S T S S V P
 8881 - CAGTTGGCAACCATTGTCTGAGCACAGCTGTACCTGGTGCAACTCCTTTATCAGAGCCAG - 8940
 - Q L A T I V * A Q L Y L V Q L L Y Q S Q
 - S W Q P L S E H S C T W C N S F I R A S
 - V G N H C L S T A V P G A T P L S E P A
 8941 - CACCAAAGTGAATAACTCTCATGTTGTAGGGTACAGCTAAAGTAAGTGTATTAAAGTATT - 9000
 - H Q S E * L S C C R V Q L K * V Y L S I
 - T K V N N S H V V G Y S * S K C I * V L
 - P K * I T L M L * G T A K V S V F K Y *
 9001 - GACACAGTTGAGTATACTTTGCGACATTATCATTATTCCTTTTGGTATAACAGCATT - 9060
 - D T V E Y T L R H S S L F L L V * Q H F
 - T Q L S I L C D I H H Y S F W Y N S I F
 - H S * V Y F A T F I I I P F G I T A F S
 9061 - CACCATAATCTGAAGGTCACACTTTCAAGAAGCATTCTTTGCATCTTGTACAAGTTAG - 9120
 - H H N S E G H T F Q E A F F A S C T S *
 - T I I L K V T L F K K H S L H L V Q V R
 - P * F * R S H F S R S I L C I L Y K L G
 9121 - GCATCGCAACACCTGGTTGCCACGCTTGACTTGCTTTAGTTTTGGGTAGAAGGTTCAA - 9180
 - A S Q H L V A T L D L L V V L G R R F Q
 - H R N T W L P R L T C L * F W V E G F N
 - I A T P G C H A * L A C S F G * K V S T
 9181 - CATGTCCATCCTTACACCAAAGCATGAATGAAATTTTCAGCATAGTCAATTGTAACCTTGA - 9240
 - H V H P Y T K A * M K F Q H S Q L * P *
 - M S I L T P K H E * N F S I V N C N L D
 - C P S L H Q S M N E I S A * S I V T L T

FIG. 12 Con't

9241 - CCACTTTTGAATCACTGACAAATCTGTGACTTTATTATCTCGACAAAGTCATCAAGTA - 9300
 - P L L K S L T N L V T L L S R Q S H Q V
 - H F * N H * Q I L * L Y Y L D K V I K *
 - T F E I T D K S C D F I I S T K S S S K
 9301 - AAAGATCAATCACAGAACACACACATTTTGATGAACCTGTTTGCATCTGTTATGAAGT - 9360
 - K D Q S Q N T H I L M N L F A H L L * S
 - K I N H R T H T F * * T C L R I C Y E V
 - R S I T E H T H F D E P V C A S V M K *
 9361 - AATTTTTCCTGCTGCTCCATAGGGATAAAATCCTCTAATTTAAGTGGTGAATCTTGTG - 9420
 - N F S L C C P * G * N P L I * V V N L V
 - I F H C A V H R D K I L * F K W * I L *
 - F F T V L S I G I K S S N L S G E S C E
 9421 - AGCGCTTGGCTAAGCCTATCATTAAATGAAGACCGCAAGTTGTCCATGACTGAAATCTC - 9480
 - S A W L S L S L N E D R Q V V H D * N L
 - A L G * A Y H * M K T A K L S M T E I S
 - R L A K P I I K * R P P S C P * L K S P
 9481 - CATAAACGATGTGTTGCGAAGCATAGCCCTCGAGCTTATATCGCTGTATGAATTCATCCA - 9540
 - H K R C V R R H S P R A Y I A V * I H P
 - I N D V F E G I A L E L I S L Y E F I H
 - * T M C S K A * P S S L Y R C M N S S I
 9541 - TAGCGAGCTCGAGAAAGTCAGTTTCCATTTGTGATCTGGGCTTAAATCCTCTAAGTCTC - 9600
 - * R A R E S Q F P F V I W A * N P L S L
 - S E L E K V S F H L * S G L K I L * V S
 - A S S R K S V S I C D L G L K S S K S L
 9601 - TGCTCTGAGTAAAGTAGGTTTCAGGCAACTGTTGAATAATGCCGTCTACTTTCTTAAAGT - 9660
 - C S E * S R F Q A T V E * C R L L S * S
 - A L S K V G F R Q L L N N A V Y F L K V
 - L * V K * V S G N C * I M P S T F L K *
 9661 - AGTTAAACTGTTTTTACTGATTCTCCAATTAATGTGACTCCATTGACGCTAGCTTGTG - 9720
 - S * T V F L L I L Q L M * L H * R * L V
 - V K L C F Y * F S N * C D S I D A S L C
 - L N C V F T D S P I N V T P L T L A C A
 9721 - CTGGTCCCTTTGAAGGTGTTAGACCTTTGACTGAACCTTCTGTTATTAACACCATAC - 9780
 - L V P L K V L D L * L N L L L L K H H Y
 - W S L * R C * T F D * T F C Y * N T I T
 - G P F E G V R P L T E P S V I K T P L R
 9781 - GGGCGTTTCTAAAAAGGTCTACCTGCCTTCCACTCTACCATCAAACAAGACAGTAAGTG - 9840
 - G R F * K G L P V L P L Y H Q T R Q * V
 - G V S K K V Y L S F H S T I K Q D S K *
 - A F L K R S T C P S T L P S N K T V S E
 9841 - AAGAACAAGCACTCTCAGTAGGTTTCTGGCAATGTGAGTCTGTCAGACACCTATTG - 9900
 - K N K H S Q * V S W Q C Q S L C R H L L
 - R T S T L S R F L G N V S H C A D T Y C
 - E Q A L S V G F L A M S V I V Q T P I V
 9901 - TAGATACATGTGCTGGGCTTCTCTTTGTAGTCCAGATTACAGTATTAGCAGGATAT - 9960
 - * I H V L G L L F C S P R L Q Y * Q R Y
 - R Y M C W G F S F V V P D Y S I S S D I
 - D T C A G A S L L * S Q I T V L A A I S
 9961 - CAACACCCAAATTATTGAGTATCTTAATCTCTGGCACTGGTTTAAATGTTACGCTTAGCCC - 10020
 - Q H P N Y * V S * S L A L V * C Y A * P
 - N T Q I I E Y L N L W H W F N V T L S P
 - T P K L L S I L I S G T G L M L R L A Q
 10021 - AAAGCTCAAATGCAACATTAACAGGAAGTGTGTCTTATTTCAAAGATCTCCACATCAA - 10080
 - K A Q M Q H * Q E V L S Y F Q R S P H Q
 - K L K C N I N R K C C L I F K D L H I N
 - S S N A T L T G S V V L F S K I S T S I

FIG. 12 Con't

10081 - TACCATCTACCTTTGTGTAACAGCATTATTAATGATGGAAACAGGTGCTTCGCCGGCGT - 10140
 - Y H L P L C K Q H Y * * W K Q V L R R R
 - T I Y L C V N S I I N D G N R C F A G V
 - P S T F V * T A L L M M E T G A S P A C

10141 - GTCCATCAAAGTGCCTTTATTAACAACATTATAAGCCACATTTTCTAAACTCTGTAACC - 10200
 - V H Q S V L Y * Q H Y K P H F L N S V T
 - S I K V S F I N N I I S H I F * T L * P
 - P S K C P L L T T L * A T F S K L C N L

10201 - TGGTAAATGTATTCCACAGGTTATAAGTATCAAATGTTTGTAAATCCATAGGCTAAATC - 10260
 - W * M Y S T G Y K Y Q I V C K S I G * I
 - G K C I P Q V I S I K L F V N P * A K S
 - V N V F H R L * V S N C L * I H R L N P

10261 - CAGCAGAAATCATCATATTATATGCATCCAAGTACTGTCGGTACTCATTGTCATGGTGTGTC - 10320
 - Q Q K S S Y Y M H P S T V G T H L H G V
 - S R N H H I I C I Q V L S V L I C M V S
 - A E I I I L Y A S K Y C R Y S F A W C L

10321 - TGCAAACAGCACCACCTAAATTGCATCGTGTAAATACACGTAGCAGATTTGAGTGGAAACAT - 10380
 - C K Q H H L N C I V * Y T * Q I * V E H
 - A N S T T * I A S C N T R S R F E W N I
 - Q T A P P K L H R V I H V A D L S G T *

10381 - AATCAATATCCGACACTACTTGTGGCCATGAGACTACAAGGACTATCAGAATAGTAAA - 10440
 - N Q Y P T L L V C H E T H K D Y Q N S K
 - I N I R H Y L F A M R L T R T I R I V K
 - S I S D T T C L P * D S Q G L S E * * K

10441 - AGAAAGGCAATTGCTTTAAATTAGTAAATGCACCTTTTATCGAAAGCTGGAGTGTGGAATG - 10500
 - R K A I A L N * * M H F Y R K L E C G M
 - E R Q L L * I S K C T F I E S W S V E C
 - K G N C F K L V N A L L S K A G V W N A

10501 - CATGCTTATTCACATACAACTACCACCATCAGCCCTGGTAAGTTCAAGTTTGACAAGA - 10560
 - H A Y S H T N Y H H H S L V S S S L T R
 - M L I H I Q T T T I T A W * V Q V * Q D
 - C L F T Y K L P P S Q P G K F K F D K T

10561 - CTCTTGTGTCAAACCTACACACAATGCATTGGCTGGGTAACGATCAACGTTACAATTCC - 10620
 - L L C Q T Y T Q L H W L G N D Q R Y N S
 - S C V K P T H N C I G W V T I N V T I P
 - L V S N L H T I A L A G * R S T L Q F Q

10621 - AAAACAAACAAACACCATCAGTGAATTTATCGTGATGTGTAGCATAAGAATAGAAGAGTT - 10680
 - K T N K H H Q * I Y R D V * H K N R R V
 - K Q T N T I S E F I V M C S I R I E E F
 - N K Q T P S V N L S * C V A * E * K S S

10681 - CCTCTATTTTGTAAAGCTTTGTCACTACATGGCTGAGCATCGTAGAACTTCCATTCTACTT - 10740
 - P L F C K L C H Y M A E H R R T S I L L
 - L Y F V S F V T T W L S I V E L P F Y F
 - S I L * A L S L H G * A S * N F H S T S

10741 - CAGCCTGAGGCACACACTTGATAGCCTTTGGATTTCCAATGTCATGAAGAACTGGAAACT - 10800
 - Q P E A H T * * P L D F Q C H E E L E T
 - S L R H T L D S L W I S N V M K N W K L
 - A * G T H L I A F G F P M S * R T G N L

10801 - TATCAGCAAGCAATGCAGACTTCACAACCATGTGTTGTACTTTTCTGCAAGCAGAATTA - 10860
 - Y Q Q A M Q T S Q P C V V L F C K Q N *
 - I S K Q C R L H N H V L Y F S A S R I N
 - S A S N A D F T T M C C T F L Q A E L T

10861 - CCCTCAGTTCATCTCCTATAATAGGGTATTCAACAGACCAATCAACGCGCTTAACAAAGC - 10920
 - P S V H L L * * G I Q Q T N Q R A * Q S
 - P Q F I S Y N R V F N R P I N A L N K A
 - L S S S P I I G Y S T D Q S T R L T K H

FIG. 12 Con't

10921 - ACTCATGGACTGCTAAACATCTAGTCATGATAGCATCACAAC TAGCCACATGTGCATTTC - 10980
 - T H G L L N I * S * * H H N * P H V H F
 - L M D C * T S S H D S I T T S H M C I S
 - S W T A K H L V M I A S Q L A T C A F P
 10981 - CATGTACCTGGCAATGTTGGTCATGGTTACTCTGAAGTTACCCGTAAGCCCCACTGCT - 11040
 - H V P G N V G H G Y S E G Y P * S P T A
 - M Y L A M L V M V T L K V T R K A P L L
 - C T W Q C W S W L L * R L P V K P H C *
 11041 - GAACATCAATCATAAATGGGTTATAGACATAGTCAAAACCCACAGAATGATTCCAGCAGG - 11100
 - E H Q S * M G Y R H S Q N P Q N D S S R
 - N I N H K W V I D I V K T H R M I P A G
 - T S I I N G L * T * S K P T E * F Q Q A
 11101 - CATAAGTATCTGATGAAGTAGAAAAGCAAGTTCACACAGACAACACGTTTC - 11160
 - H K Y L M K * K S K L H V C H T D N T F
 - I S I * * S R K A S C T F V T Q T T R S
 - * V S D E V E K Q V A R L S H R Q H V L
 11161 - TTTCAGGTCCAATCTTGACAAAGTACTTCATTGATGTAAGCTCAAAGCCATGCGCCCAA - 11220
 - F Q V Q S * Q S T S L M * A Q S H A P K
 - F R S N L D K V L H * C K L K A M R P K
 - S G P I L T K Y F I D V S S K P C A Q R
 11221 - GGACGAACACGACTCTGTCTGACAATCCTTTCAGTGTATCACTGAGCATTGTACTATCT - 11280
 - G R T R L C L T I L S V Y H * A F V L S
 - D E H D S V * Q S F Q C I T E H L Y Y L
 - T N T T L S D N P F S V S L S I C T I L
 11281 - TAATACGCACTACATTCCAGGCAAGCCTTTATACATGAGTGGTATAAGATGTTAAACT - 11340
 - * Y A L H S R A S L Y T * V V * D V * T
 - N T H Y I P G Q A F I H E W Y K M F K L
 - I R T T F Q G K P L Y M S G I R C L N W
 11341 - GGTCACTGGTGGAGGTTTTCATTAAGTCTGGTGAATTCTGTGTTATTTTCAGTGTCAA - 11400
 - G H L V E V L H * L W * I L C Y F Q C Q
 - V T P W W R F C I N S G E F C V I F S V N
 - S P G G G F A L T L V N S V L F S V S T
 11401 - CATAACCAGTGGTACAGTACTAAGTAAACCTGTAGAAAATCCTAGCTGGAGAGGTA - 11460
 - H N Q S V Q L L S * H L * K I L A G E V
 - I T S R Y S Y * V N T C R K S * L E R *
 - * P V G T A T K L T P V E N P S W R G R
 11461 - GGTTAGTACCCACAGCATCTCTAGTTGCATGACGCCCTCTACATCAAAGCCAATCCAG - 11520
 - G * Y P Q H L * L H D S P L H Q S Q S T
 - V S T H S I S S C M T A L Y I K A N P R
 - L V P T A S L V A * Q P S T S K P I H A
 11521 - CACGAACGTGACGAATAGCTTCTTCGCGGGTGATAAACATATTAGGGTAACCATTGACTT - 11580
 - H E R D E * L L R G * * T Y * G N H * L
 - T N V T N S F F A G D K H I R V T I D L
 - R T * R I A S S R V I N I L G * P L T W
 11581 - GGTAATTCATTTGAAACCCATCATAGAGATGAGTCTACGGTAGGTCATGTCCTTTGGTA - 11640
 - G N S F * N P S * R * V Y G R S C P L V
 - V I H F E T H H R D E S T V G H V L W Y
 - * F I L K P I I E M S L R * V M S F G M
 11641 - TGCCTGGTATGTCAACACATAATCCTTCAGTCTTGAATTTTATATCAACGCTGAGGTGTG - 11700
 - C L V C Q H I I L Q S * I L Y Q R * G V
 - A W Y V N T * S F S L E F Y I N A E V C
 - P G M S T H N P S V L N F I S T L R C V
 11701 - TAGGTGCTGTGTAGGATGAAGACCAGTAATGATCTTACTACAGTCCCTTAAAAAGTCCAG - 11760
 - * V P V * D E D Q * * S Y Y S P * K V Q
 - R C L C R M K T S N D L T T V L K K S S
 - G A C V G * R P V M I L L Q S L K S P V

FIG. 12 Con't

11761 - TTACATTTTCTGCTTGTAAATGTAGCCACATTGCGACGTGGTATTTCTAGACTTGAAATT - 11820
 - L H F L L V M * P H C D V V F L D L * I
 - Y I F C L * C S H I A T W Y F * T C K L
 - T F S A C N V A T L R R G I S R L V N C
 11821 - GCAGTTGTGCATAAAGATCTCTATCAGACATTATGCACAAAATGCCAATTTTGGCCCTTG - 11880
 - A V C H K D L Y Q T L C T K C Q F L P L
 - Q F V I K I S I R H Y A Q N A N F C P C
 - S L S * R S L S D I M H K M P I F A L V
 11881 - TGATAGCCACATTGAAGCGGTTGACATTACAAGAGTGTGCTGTTTCAGTAGTTTGTGTGA - 11940
 - * * P H * S G * H Y K S V L F Q * F V *
 - D S H I E A V D I T R V C C F S S L C E
 - I A T L K R L T L Q E C A V S V V C V N
 11941 - ATATGACATAGTCATATTAGAACCCTGTGATGAATCAACAGTCTGCGTAGGCAATCCTA - 12000
 - I * H S H I Q N P V M N Q Q S A * A I L
 - Y D I V I F R T L * * I N S L R R Q S *
 - M T * S Y S E P C D E S T V C V G N P K
 12001 - AGATTTTGAAGCTACAGCGTTCGTGAATTATAAGGTGAGATAAAAACAGCTTTTCTCC - 12060
 - R F L K L Q R S V N Y K V R * K Q L F S
 - D F * S Y S V L * I I R * D K N S F S P
 - I F E A T A F C E L * G E I K T A F L Q
 12061 - AAGCAGATTGCGTGTAAAGAAATCTCTTACAACGCCTATTTGAGGTCTGTTGATTGCAG - 12120
 - K Q D C V * E I L L Q R L F E V C * L Q
 - S R I A C K K F S Y N A Y L R S V D C R
 - A G L R V R N S L T T P I * G L L I A D
 12121 - ATGAACATCATGTGTAATAACACCTTTGTAGAACATTTGAAGCATTGAGCTGACTTAT - 12180
 - M K H H V * * H L C R T F * S I E L T Y
 - * N I M C N N T F V E H F E A L S * L I
 - E T S C V I T P L * N I L K H * A D L S
 12181 - CCTTGTGTGCTTTTAGCTTATTGTGCATAAACTAAAGCACTCAGAGTGTCAACAATTTAG - 12240
 - P C V L L A Y C H K L K H S Q C Q Q F Q
 - L V C F * L I V I N * S T H S V N N F S
 - L C A F S L L S * T K A L T V S T I S A
 12241 - CAGGACAACGGCGACAAGTTCCAAGGAACATGTCTGGACCTATTGTTTTCATAAGTCTGC - 12300
 - Q D N G D K F Q G T C L D L L F S * V C
 - R T T A T S S K E H V W T Y C F H K S A
 - G Q R R Q V P R N M S G P I V F I S L H
 12301 - AACTGAATTAATAATTTCTGGTCTAGTGTGCCTTTAGTACGAATGTGCGGGGGCTG - 12360
 - T L N * N I L V L V C L * S A M C G G L
 - H * I K I F W F * C A F S Q Q C A G G W
 - T E L K Y S G S S V P L V S N V R G A G
 12361 - GTAATTGAGCAGGATCGCCAATATAGACGTAGTGTGTTGCACGAAGTCTAGCATTGACAA - 12420
 - V I E Q D R Q Y R R S V L H E V * H * Q
 - * L S R I A N I D V V F C T K S S I D N
 - N * A G S P I * T * C F A R S L A L T T
 12421 - CACTCAAGTCATAATTAGTAGCCATAGAGATTTTCATCAAAGACTACAATGTCAGCAGTTG - 12480
 - H S S H N * * P * R F H Q R L Q C Q Q L
 - T Q V I I S S H R D F I K D Y N V S S C
 - L K S * L V A I E I S S K T T M S A V V
 12481 - TTTCTGGCAATGCATTTACAGTGCAGAAAACATACTGTTCTAGTGTGAATTCATTTGA - 12540
 - F L A M H L Q C R K H T V L V L N S L *
 - F W Q C I Y S A E N I L F * C * I H F E
 - S G N A F T V Q K T Y C S S V E F T L N
 12541 - ATTTATCAAACACTCTACGCGCGCAGCGGATGATTCTACTACATTTATCTATGG - 12600
 - I Y Q N T L R A H A Q V * F Y Y I Y L W
 - F I K T L Y A R T R R Y D S T T F I Y G
 - L S K H S T R A R A G M I L L H L S M G

FIG. 12 Con't

12601 - GCAAATATTTTAAATGCCTTTTCACATAGGGCATCAACAGCTGCATGAGAGCATGCCGTAT - 12660
 - A N I L M P F F H I G H Q Q L H E S M P Y
 - Q I F * C L F T * G I N S C M R A C R I
 - K Y F N A F S H R A S T A A * E H A V Y
 12661 - ACACATGCGAGCAGATGGGTAATAGAGAGCAAGTCCGATGGCAAATGACTCTTACCAG - 12720
 - T L C E Q M G N R E Q V R W Q N D S Y Q
 - H Y A S R W V I E S K S D G K M T L T S
 - T M R A D G * * R A S P M A K * L L P V
 12721 - TACCAGGTGGTCCCTGGAGTGTAGACTTTTTGCATGCCGACCTTTTGATAATTTGCAA - 12780
 - Y Q V V L G V * S T F A C R P F D N L Q
 - T R W S L E C R V L L H A D L L I I C N
 - P G G P W S V E Y F C M P T F * * F A T
 12781 - CATTGCTAGAAAACATCTGAGATGTTGAGTGTGGGTACAAGCCAGTAATTCTCATAT - 12840
 - H C * K T H L R C * V L G T S Q * F S H
 - I A R K L I * D V E C W V Q A S N S H I
 - L L E N S S E M L S V G Y K P V I L T *
 12841 - AGTGCTCTTGTGGCACTAGAGTAGGTGCACTAAGTGGCATTACAGTGTGAGATGTCAACA - 12900
 - S A L V A L E * V H * V A L Q C E M S T
 - V L L W H * S R C T K W H Y S V R C Q H
 - C S C G T R V G A L S G I T V * D V N T
 12901 - CAAAGTAATCACCAACATTCAACTTGTATGTCGTAGTACCTCTGTACACAACAGCATCAC - 12960
 - Q S N H Q H S T C M S * Y L C T Q Q H H
 - K V I T N I Q L V C R S T S V H N S I T
 - K * S P T F N L Y V V V P L Y T T A S P
 12961 - CATAGTCACCTTTTCAAGGTGACTCTCCAATCTGTACTTTACTATTTTGTAGTTACAC - 13020
 - H S H L F Q R C T L Q S V L Y Y F * L H
 - I V T F F K G V L S N L Y F T I F S Y T
 - * S P F S K V Y S P I C T L L F L V T R
 13021 - GGTAACCAGTAAAGACATAGTTTCTGTTCAATGGTGGTCTAGGTTTTCCAACCTCCCATG - 13080
 - G N Q * R H S F C S M V V * V F Q P P M
 - V T S K D I V S V Q W W S R F S N L P *
 - * P V K T * F L F N G G L G F P T S H E
 13081 - AAAGATGCAATTCTCTGTGAGAGTACTTCGCGTACAGTGGCAATACCATATGACAGCT - 13140
 - K D A I L C Q R V L R V Q W Q Y H M T A
 - K M Q F S V R E Y F A Y S G N T I * Q L
 - R C N S L S E S T S R T V A I P Y D S L
 13141 - TAAATGTTTCCCTCAGTGGCTTTGAGCGTTTCTGCTGCGAAAAGCTTGAGTCTCTCAGTAC - 13200
 - * M F P Q W L * A F L L R K A * V S Q Y
 - K C F L S G F E R F C C E K L E S L S T
 - N V S S V A L S V S A A K S L S L S V Q
 13201 - AAGTGTGGCAAGTATGTAATCGCCAGCATTAGTCCAATCACATGTTGCTATCGCATTGA - 13260
 - K C W Q V C N R Q H * S N H M L L S H *
 - S V G K Y V I A S I S P I T C C Y R I E
 - V L A S M * S P A L V Q S H V A I A L K
 13261 - AGTCAGTGACATTGTCACTGCCTACACATGTGTTTTGTATAAACCAAAAACCTGACCAT - 13320
 - S Q * H C H C L H M C F C I N Q K P D H
 - V S D I V T A Y T C V F V * T K N L T I
 - S V T L S L P T H V F L Y K P K T * P L
 13321 - TAGCACATAATGGAAAACATAATGGGAGGCTTATGTGACTTGCAATAATAGCTCATACCTC - 13380
 - * H I M E N * W E A Y V T C N N S S Y L
 - S T * W K T N G R L M * L A I I A H T S
 - A H N G K L M G G L C D L Q * * L I P P
 13381 - CTAGATACAGTTGTGTCACATCAGTGACATCACAACTGGGGCATTGCAAACATAGGGAT - 13440
 - L D T V V S H Q * H H N L G H C K H R D
 - * I Q L C H I S D I T T W G I A N I G I
 - R Y S C V T S V T S Q P G A L Q T * G L

FIG. 12 Con't

13441 - TAACAGACAACACTAATTTGTGTGATGTTGAAATGACATGGTCATAGCAGCACTTGCAAC - 13500
 - * Q T T L I C V M L K * H G H S S T C N
 - N R Q H * F V * C * N D M V I A A L A T
 - T D N T N L C D V E M T W S * Q H L Q H

13501 - ATAGGAATGGTCTCCTAATACAGGCACCGCAACGAAGTGAAGTCTGTGAATTGCACAATA - 13560
 - I G M V S * Y R H R N E V K S V N C T I
 - * E W S P N T G T A T K * S L * I A Q Y
 - R N G L L I Q A P Q R S E V C E L H N T

13561 - CACAAGCACCTACAGCCTGCAAGACTGTATGTGGTGTGTACATAGCCTCATAAAACTCAG - 13620
 - H K H L Q P A R L Y V V C T * P H K T Q
 - T S T Y S L Q D C M W C V H S L I K L R
 - Q A P T A C K T V C G V Y I A S * N S G

13621 - GTTCCCAGTACCGTGGGTTATCATTAGTTAGCATTACGGAATACATGTCCAACATGT - 13680
 - V P S T V R C Y H * L A L R N T C P T C
 - F P V P * G V I I S * H Y G I H V Q H V
 - S Q Y R E V L S L V S I T E Y M S N M W

13681 - GGCCAGTAAGCTCATCATGTAACCTTTCTAATGTATTGTAATACAAGTAAAAGACATCAG - 13740
 - G Q * A H H V T F * C I V N T S E R H Q
 - A S K L I M * L S N V L * I Q V K D I S
 - P V S S S C N F L M Y C K Y K * K T S A

13741 - CATACTCCTGATTAGGATGTTTTGTAAGTGGGTAAGCATCAATAGCCAGTGACACGAACC - 13800
 - H T P D * D V L * V G K H Q * P V T R T
 - I L L I R M F C K W V S I N S Q * H E P
 - Y S * L G C F V S G * A S I A S D T N L

13801 - TTTCAATCATAAGTGTACCATCTGTTTTGACAATATCATCGACAAAACAGCCTGCGCCTA - 13860
 - F Q S * V Y H L F * Q Y H R Q N S L R L
 - F N H K C T I C F D N I I D K T A C A *
 - S I I S V P S V L T I S S T K Q P A P N

13861 - ATATTCTTGATGGATCTGGGTAAGGCAGGTACACGTAATCATCTCCTTGTTTAACTAGCA - 13920
 - I F L M D L G K A G T R N H L L V * L A
 - Y S * W I W V R Q V H V I I S L F N * H
 - I L D G S G * G R Y T * S S P C L T S I

13921 - TTGTATGCTGTGAGCAAATTCGTGAGGTCCTTTAGTAAGTCTCAGTCTCAGTCCAACATT - 13980
 - L Y A V S K I R E V L * * G Q S Q S N I
 - C M L * A K F V R S F S K V S L S P T F
 - V C C E Q N S * G P L V R S V S V Q H F

13981 - TTGCCTCAGACATGAACACATATTTTGATAATAAAGAACTGCCTTAAAGTTCTTAATGC - 14040
 - L P Q T * T H Y F D N K E L P * S S * C
 - C L R H E H I I L I I K N C L K V L N A
 - A S D M N T L F * * * R T A L K F L M L

14041 - TAGCTACTAAACCTTGAGCCGCATAGTTACTGTTATAGCACACAACGGCATCATCAGAAA - 14100
 - * L L N L E P H S Y C Y S T Q R H H Q K
 - S Y * T L S R I V T V I A H N G I I R K
 - A T K P * A A * L L L * H T T A S S E R

14101 - GAATCATCATGGAGAAATGTTTACGCAGGTAAGCGTAAAACCTCATCCACGAATTCATGAT - 14160
 - E S S W R N V Y A G K R K T H P R I H D
 - N H H G E M F T Q V S V K L I H E F M I
 - I I M E K C L R R * A * N S S T N S * S

14161 - CAACATCCCTATTTCTATAGAGACTCATAGGCCTGTGTTGTAGATTGCGGACATACT - 14220
 - Q H P Y F Y R D T H R A C V V D C G H T
 - N I P I S I E T L I E P V L * I A D I L
 - T S L F L * R H S * S L C C R L R T Y L

14221 - TGCAGCTATCTTATTACCATCAGTTGAAAGAAGTGCATTTACATTTGCTGTACAGCTT - 14280
 - C Q L S Y Y H Q L K E V H L H W L * Q L
 - V S Y L I T I S * K K C I Y I G C N S L
 - S A I L L P S V E R S A F T L A V T A *

FIG. 12 Con't

14281 - GACAAATGTTAAAGACACTATTAGCATAAGCAGTTGTAGCATCACCGGATGATGTTCCAC - 14340
 - D K C * R H Y * H K Q L * H H R M M F H
 - T N V K D T I S I S S C S I T G * C S T
 - Q M L K T L L A * A V V A S P D D V P P
 14341 - CTGGTTTAAACATATAGTGAGCCGCCACACATGACCATCTCACTTAATACTTGCGCACACT - 14400
 - L V * H I V S R H T * P S H L I L A H T
 - W F N I * * A A T H D H L T * Y L R T L
 - G L T Y S E P P H M T I S L N T C A H S
 14401 - CGTTAGCTAACCTGTAGAAAACGGTGTGATAAGTTACAGCAAGTGTATGTTTGCAGCAA - 14460
 - R * L T C R N G V I S Y S K C Y V C E Q
 - V S * P V E T V * * V T A S V M F A S K
 - L A N L * K R C D K L Q Q V L C L R A R
 14461 - GAACAAGAGAGGCCATTATCCTAAGCATGTTAGGCATGGCTCTGTACATTTTGGATAAT - 14520
 - E Q E R P L S * A C * A W L C H I L D N
 - N K R G H Y P K H V R H G S V T F W I I
 - T R E A I I L S M L G M A L S H F G * S
 14521 - CCCAACCCATAAGGTGTGGAGTTTCTACATCACTGTAAACAGTTTTTAAACATATTATGCC - 14580
 - P N P * G V E F L H H C K Q F L T Y Y A
 - P T H K V W S F Y I T V N S F * H I M P
 - Q P I R C G V S T S L * T V F N I L C Q
 14581 - AGCCACCGTAAAACCTTGCTTGTCCAATTACCACAGTAGCTCCTCTAGTGGCGGCTATTG - 14640
 - S H R K T C L F Q L P Q * L L * W R L L
 - A T V K L A C S N Y H S S S S S G G Y *
 - P P * N L L V P I T T V A P L V A A I D
 14641 - ACTTCAATAATTTCTGATGAACTGTCTATTTGTCATAGTACTACAGATAGAGACACCAG - 14700
 - T S I I S D E T V Y L S * Y Y R * R H Q
 - L Q * F L M K L S I C H S T T D R D T S
 - F N N F * * N C L F V I V L Q I E T P A
 14701 - CTACGGTGCAGCTCTATTCCTTGCACATAATGGCATACTTAAGATTCATTTGAGTTATAG - 14760
 - L R C E L Y S L H * W H T * D S F E L *
 - Y G A S S I L C T N G I L K I H L S Y S
 - T V R A L F F A L M A Y L R F I * V I V
 14761 - TAGGGATGACATTACGCTTAGTATACGCGAAAAGTGCATCTTGATCCTCATAACTCATG - 14820
 - * G * H Y A * Y T R K V H L D P H N S L
 - R D D I T L S I R E K C I L I L I T H *
 - G M T A L R L V Y A K S A S * S S * L I E
 14821 - AGTCATAAAGTCTAGCCTTACCCATTATTAATGGGAAACCAGCTGATTATCCA - 14880
 - S H N K V * P Y P I Y * M G N Q L I Y P
 - V I I K S S L T P F I K W E T S * F I Q
 - S * * S L A L P H L L N G K P A D L S R
 14881 - GATTGTTAACGATTACTTGGTTGGCATTAAATACAGCCACCATCGTAACAATCAAAGTATT - 14940
 - D C * R L L G W H * Y S H H R N N Q S I
 - I V N D Y L V G I N T A T I V T I K V F
 - L L T I T W L A L I Q P P S * Q S K Y L
 14941 - TATCAACAACTTCAACTACGAATAGGAGTTGTCTGATATCACACATGTTGGCAGATTAT - 15000
 - Y Q Q L Q L R I G V V * Y H T L L A D Y
 - I N N F N Y E * E L S D I T H C W Q I I
 - S T T S T T N R S C L I S H I V G R L *
 15001 - AACGATAATAGTCATAATCACTGATAGCAGCGTTGCCATCCTGAGCAAAGAAGAAGTGT - 15060
 - N D N S H N H * * Q R C H P E Q R R S V
 - T I I V I I T D S S V A I L S K E E V F
 - R * * S * S L I A A L P S * A K K K C F
 15061 - TTAGTTCAACAGAACTTCTTCCTTAAAGAACTTTAGACACAGCAAAGTCATAAAAGT - 15120
 - L V Q Q N F L P * R N L * T Q Q S H K S
 - * F N R T S F L K E T F R H S K V I K V
 - S S T E L P S L K K P L D T A K S * K S

FIG. 12 Con't

15121 - CTTTATTAATAATTACCGGTTTGACAGTTTGAAAAGCAACATTGTTTGTAGTGCAGCTA - 15180
 - L Y * N Y R V * Q F E K Q H C L L V Q L
 - F I K I T G F D S L K S N I V C * C S Y
 - L L K L P G L T V * K A T L F V S A A T
 15181 - CTGAAAAGCATGTAGTGCCTTATCTAGCAATAAATTGCCAGAAGCTGCATGCATAGCTG - 15240
 - L K S M * C V Y L A I N C Q K L H A * L
 - * K A C S A F I * Q * I A R S C M H S W
 - E K H V V R L S S N K L P E A A C I A G
 15241 - GATCAGCAGCATACACTAAAAGTTCCCTGAAACTGAGACGCGAGCTATGTAAGTTTACAT - 15300
 - D Q Q H T L K V P * N * D A S Y V S L H
 - I S S I H * K F L E T E T R A M * V Y I
 - S A A Y T K S S L K L R R E L C K F T S
 15301 - CCTGATTATGTACGACTCCTAACTCACGAAAATGGTATCCAGTTGAAACAACAAAAGGAA - 15360
 - P D Y V R L L T H E N G I Q L K Q Q K E
 - L I M Y D S * L T K M V S S * N N K R N
 - * L C T T P N S R K W Y P V E T T K G T
 15361 - CACCATCTACAAATATTTTCTTACTAGTGGTCCAAAACCTGTAGGTGGAACACAGTAG - 15420
 - H H L Q I F F L L V V Q N L * V E T Q *
 - T I Y K Y F S Y * W S K T C R W K H S R
 - P S T N I F L T S G P K L V G G N T V E
 15421 - AAAATAACACATTAAGTTTGCACAATGAAGGATACACCTATCATCCAAACAGTTAATAC - 15480
 - K I T H * S L H N E G Y T Y H P N S * Y
 - K * H I K V C T M K D T P I I Q T V N T
 - N N T L K F A Q * R I H L S S K Q L I Q
 15481 - AATTGGGATGGTATGTCTGGTCCCAATATTTAAAATAACGGTCCGAGAGACAAAAGTCTCT - 15540
 - N W D G M S G P N I * N N G R R D K V S
 - I G M V C L V P I F K I T V E E T K S L
 - L G W Y V W S Q Y L K * R S K R Q S L S
 15541 - CTTCGGTAAAATCATATTTTCAGCAAATCCCACTTAATAAGTGGTTTTGCGAGATCAGCAT - 15600
 - L P * N H I S A N P T * * V V L R D Q H
 - F R K I I F Q Q I P L N K W F C E I S I
 - S V K S Y F S K S H L I S G F A R S A S
 15601 - CCATATGGGACTCAGCAGCCAATGCCCTAGTCAAAGTGAGGATGGGCATCAGCAATGAGT - 15660
 - P Y G T Q Q P M P * S K * G W A S A M S
 - H M G L S S Q C P S Q S E D G H Q Q * V
 - I W D S A A N A L V K V R M G I S N E *
 15661 - AATATGAATCCACAATAGGAACTCCGCAGCCTGGTCTACTTGTACGAAATCACCAGAAAT - 15720
 - N M N P Q * E L R S L V L L V R N H R N
 - I * I H N R N S A A W C Y L Y E I T E I
 - Y E S T I G T P Q P G A T C T K S P K S
 15721 - CGTACCAGTCCCATTAAAGATCTGATTATCTAATGTCAGTACGCCTACAATGCCTGCAT - 15780
 - R T S S H * D P D Y L M S V R L Q C L H
 - V P V P I K I L I I * C Q Y A Y N A C I
 - Y Q F P L R S * L S N V S T P T M P A S
 15781 - CACGCATAGCATCGCAGAATTGTACAGTCTTTAATAATGATTGGCGTACACGCTCACCTA - 15840
 - H A * H R R I V Q S L I M I G V H A H L
 - T H S I A E L Y S L * * * L A Y T L T *
 - R I A S Q N C T V F N N D W R T R S P K
 15841 - AGTTAGCATATACGCGTAAGATGTCAGGATTCTCTACGAAGTCATACCAATCCTTCTTAT - 15900
 - S * H I R V R C Q D S L R S H T N P S Y
 - V S I Y A * D V R I L Y E V I P I L L I
 - L A Y T R K M S G F S T K S Y Q S F L L
 15901 - TGAAATAATCATCATCACAGCAATTGTATGTGACGAGTATTTCTTTAATGTATCACAAT - 15960
 - * N N H H H S N C M * R V F L L M Y H N
 - E I I I I T A I V C D E Y F F * C I T I
 - K * S S S Q Q L Y V T S I S F N V S Q L

FIG. 12 Con't

15961 - TACCCTCATCAAATGACGTAGAGCATAGACTAAATCAGCCATTGTGTATTTAGTTAGAC - 16020
 - Y P H Q N D V E H R L N Q P L C I * L D
 - T L I K M T * S I D * I S H C V F S * T
 - P S S K * R R A * T K S A I V Y L V R R
 16021 - GCTGACGTGATATATGTGGTACCATGTCACCATCTACTCTAAACTGAAAAAGTCATGGA - 16080
 - A D V I Y V V P C H H L L * T * K S H G
 - L T * Y M W Y H V T I Y S K L E K V M D
 - * R D I C G T M S P S T L N L K K S W T
 16081 - CAGCAACCGCTGGACAATCTTTAACCAAGTTATAAATAGTCTCTTCATGTTGGTAGTTAG - 16140
 - Q Q P L D N L * P S Y K * S L H V G S *
 - S N R W T I F N Q V I N S L F M L V V R
 - A T A G Q S L T K L * I V S S C W * L D
 16141 - ACATAGTATGCCTCTTAAC TACAAAGTAAGAGTCTAATAAATGCCTTCCTCATCCTTCT - 16200
 - T * Y A S * L Q S K S L I N C L P H P S
 - H S M P L N Y K V R V * * I A F L I L L
 - I V C L L T T K * E S N K L P S S S F S
 16201 - CCTGGAAGCGACAGCAATTAGTTTTAGGAACTTTGCAAACCAGCACTTTTTTCGTTGT - 16260
 - P G S D S N * F L G T L Q N Q H F F R C
 - L E A T A I S F * E L C K T S T F F V V
 - W K R Q Q L V F R N F A K P A L F S L *
 16261 - AAATATCAAAGCCCTGTAGACGACATCAGTACTAGTGCTGTGCCGCACGGTGAAGAC - 16320
 - K Y Q K P C R R H Q Y * C L C R T V * D
 - N I K S P V D D I S T S A C A A R C K T
 - I S K A L * T T S V L V P V P H G V R R
 16321 - GGGCTGCCTTACACCGCAAACCCGTTAAAAACGTTGATGCATCCGCAGACTGCATCAA - 16380
 - G L H L H R K P V * K R * C I R R L H Q
 - G C T Y T A N P F K N V D A S A D C I K
 - A A L T P Q T R L K T L M H P Q T A S R
 16381 - GGGTTCGCGGAGTTGGTCACAAC TACAGCCATAACCTTTCCACATTCCGCAGACGGTACA - 16440
 - G F A E L V T T T A I T F P H S A D G T
 - G S R S W S Q L Q P * P F H I P Q T V Q
 - V R G V G H N Y S H N L S T F R R R Y R
 16441 - GACTGTGTTTCTAAGTGTA AAAACCCACTGGGT CATTAGCACAAGTGGTAGGTATTTGGAC - 16500
 - D C V S K C K T H W V I S T S G R Y L D
 - T V F L S V K P T G S L A Q V V G I W T
 - L C F * V * N P L G H * H K W * V F G R
 16501 - GTACTTACCTTTCAAGTCACAGAATCCTTTAGGATTTGGATGGTCAATGTGGCATCTACA - 16560
 - V L T F Q V T E S F R I W M V N V A S T
 - Y L P F K S Q N P L G F G W S M W H L Q
 - T Y L S S H R I L * D L D G Q C G I Y N
 16561 - ATACAGACAACATGAAGCACCACCAAGGACTCTTGGTCCATGTAGCTTCGGTGTAC - 16620
 - I Q T T * S T T K G L L V H V S F W C Y
 - Y R Q H E A P P K D S W S M L A S G V T
 - T D N M K H H Q R T L G P C * L L V L Q
 16621 - AGTAATTGCCTGTCTGTACCAGTGTGTACACAACATCTTCACACAGTTGGTGATTGG - 16680
 - S N C L S C T S V C T Q H L H T V G D W
 - V I A C P V P V C V H N I F T Q L V I G
 - * L P V L Y Q C V Y T T S S H S W * L V
 16681 - TTGTCCTCCACTTGCTAGGTAATCCTTATATGCTTTAGCAGGCTCTACTGCAAAGCACA - 16740
 - L S S T C * V I L I C F S R V Y C K S T
 - C P P L A R * S L Y A L A G S T A K A Q
 - V L H L L G N P Y M L * Q G L L Q K H R
 16741 - GAAGGAAAGCACAGTTGAATTGGCAGTACTTCTGTAGCATTCCAGCCTGAAGACGTAC - 16800
 - E G K H S * I G R Y F C S I S S L K T Y
 - K E S T V E L A G T S V A F P A * R R T
 - R K A Q L N W Q V L L * H F Q P E D V L

FIG. 12 Con't

16801 - TGTAGCAGCTAAACTGCCAGCACCATACTCTATTTAGGTTGTTTAAAGCCTTTGATGAA - 16860
 - C S S * T A Q H H T S I * V V * A F D E
 - V A A K L P S T I P L F R L F K P L M K
 - * Q L N C P A P Y L Y L G C L S L * * S
 16861 - GTACAAGTATTTCACTTTAGGCCCTTTTGGTGTGTCTGTAACAAACCTACAAGGTGGTTC - 16920
 - V Q V F H F R P F W C V C N K P T R W F
 - Y K Y F T L G P F G V S V T N L Q G G S
 - T S I S L * A L L V C L * Q T Y K V V P
 16921 - CAGTTCTGTGTA AATTGTACCTGTACCATCACTCTTAGGG AATCTAGCCATTGAGATC - 16980
 - Q F C V N C T C T I T L R E S S P F E I
 - S S V * I V P V P S L L G N L A H L R S
 - V L C K L Y L Y H H S * G I * P I * D L
 16981 - TTGGTGGTCTGATAGTAATGCCAGCACAAACCTACCTCCCTCGAATTGTTATAGTAGGC - 17040
 - L V V * * * C Q H K P T S L R I V I V G
 - W W S D S N A S T N L P P F E L L * * A
 - G G L I V M P A Q T Y L P S N C Y S R Q
 17041 - AAGTGCATTGTCATCAGTACAAGCTGTTTGTGGTACCAGCCGCACAGGACATCTGTCG - 17100
 - K C I V I S T S C L C G T S R T G H L S
 - S A L S S V Q A V C V V P A A Q D I C R
 - V H C H Q Y K L F V W Y Q P H R T S V V
 17101 - TAGTGCTACTGGACTCAGTTCATTATTCTGTAGTTTAAACAGCTGAGTTGGCTCTTAGAGC - 17160
 - * C Y W T Q F I I L * F N S * V G S * S
 - S A T G L S S L F C S L T A E L A L R A
 - V L L D S V H Y S V V * Q L S W L L E L
 17161 - TGTAACAATAAGAGGCCAAGCCAAATTTGGTGAATTGTCCATGTTAATTTCACTAAGTTG - 17220
 - C N N K R P S Q I W * I V H V N F T K L
 - V T I R G Q A K F G E L S M L I S L S *
 - * Q * E A K P N L V N C P C * F H * V E
 17221 - AACAACTTCTGCTATCCGCATCAACAACCTTGGTGGATTCCCAGAGTGCAGATGCATATGT - 17280
 - N N L A I R I N N L L D F P E C R C I C
 - T I L L S A S T T C W I S Q S A D A Y V
 - Q S C Y P H Q Q L A G F P R V Q M H M *
 17281 - AAAGGTGTTACCATCACAAGTGTCTTGTAGGTACCATAATCAGGGACAACAACCATGAG - 17340
 - K G V T I T S V L V G T I I R D N N H E
 - K V L P S Q V F L * V P * S G T T T M S
 - R C Y H H K C S C R Y H N Q G Q Q P * V
 17341 - TTTGGCTGCTGATGCAATGGTATGATGTTGAGTGGAAACACAACCATCACGGCATTGTT - 17400
 - F G C C S Q W Y D V E W N T T I T R I V
 - L A A V V N G M M L S G T Q P S R A L L
 - W L L * S M V * C * V E H N H H A H C *
 17401 - GATAATGTTGTTAAGTGCATCATTATCAAGCTTCCTAAGCATAGTGAAGAGCATTGTTT - 17460
 - D N V V K C I I I K L P K H S E E H C L
 - I M L L S A S L S S F L S I V K S I V C
 - * C C * V H H Y Q A S * A * * R A L F A
 17461 - CATAGCACTAGTACTTTTGGCCCTTGTCTCAGATCTTGCCCTGTTTGTACATTTGGGT - 17520
 - H S T S Y F C P L V L R S C L F V H L G
 - I A L V T F A L L S S D L A C L Y I W V
 - * H * L L L P S C P Q I L P V C T F G S
 17521 - CATAGCCTGATCTGCCATCTTTTCCAACCTGCGTTGCATGGCAGCATCACGGTCAAAC - 17580
 - H S L I C H L F Q L A L H G S I T V K L
 - I A * S A I F S N L R C M A A S R S N S
 - * P D L P S F P T C V A W Q H H G Q T Q
 17581 - AGATTTAGCCACATTC AAGATTTCTTTAACTTTTTGAGAACGACTTCAGAATCACCATT - 17640
 - R F S H I Q R F L * L F E N D F R I T I
 - D L A T F K D F F N F L R T T S E S P L
 - I * P H S K I S L T F * E R L Q N H H *

FIG. 12 Con't

17641 - AGCTACAGCCTGCTCATAGGCCTCCTGGGCAGTGGCATAAGCGGCATATGATGGTAAAGA - 17700
 - S Y S L L I G L L G S G I S G I * W * R
 - A T A C S * A S W A V A * A A Y D G K E
 - L Q P A H R P P G Q W H K R H M M V K N
 17701 - ACTAAATCTGAAGCAATAGCCTGAAGAGTAGCACGGTTATCGAGCATTTCCTCGCACAA - 17760
 - T K F * S N S L K S S T V I E H F L A Q
 - L N S E A I A * R V A R L S S I S S H N
 - * I L K Q * P E E * H G Y R A F P R T T
 17761 - CCTATTAATGTCTACAGCACCTGCATGGATAGCAAACAGACAAAAGAGAAAACCATCTT - 17820
 - P I N V Y S T L H G * Q N R Q K R N H L
 - L L M S T A P C M D S K T D K R E T I F
 - Y * C L Q H P A W I A K Q T K E K P S S
 17821 - CTCGAAAGCTTCAGTTGTGTCTTTTGAAGAAGAATATCATTGTGGAGTTGTACACATTG - 17880
 - L E S F S C V F C K K N I I V E L Y T L
 - S K A S V V S F A R R I S L W S C T H C
 - R K L Q L C L L Q E E Y H C G V V H I V
 17881 - TGCCCAATTTAGAAGATGACTCTACTCTAAGTTGTTGAAGAACCGAGAGCAGTACCAC - 17940
 - C P Q F R R * L Y S K L L K N R E Q Y H
 - A H N L E D D S T L S C * R T E S S T T
 - P T I * K M T L L * V V E E P R A V P Q
 17941 - AGATGTGCACTTTACGTCAGACATTTTAGACTGTACAGTAGCAACCTTGATACATGGTTT - 18000
 - R C A L Y V R H F R L Y S S N L D T W F
 - D V H F T S D I L D C T V A T L I H G L
 - M C T L R Q T F * T V Q * Q P * Y M V Y
 18001 - ACCTCCAATACCCAACTTAATGTTAAGCTTGAAAGCATCAATACTACTCTTAGGAGG - 18060
 - T S N T Q Q L N V K L E S I N T T L R R
 - P P I P N N L M L S L K A S I L L L G G
 - L Q Y P T T * C * A * K H Q Y Y S * E A
 18061 - CAAAAGCCCTGGGAGTTTCATATACCTAAATCTTGTGTAGAGACCAAGTAGTCATAAAC - 18120
 - Q K P L G V H I P K F L C R D Q V V I N
 - K S P W E F I Y L N S C V E T K * S * T
 - K A P G S S Y T * I L V * R P S S H K H
 18121 - ACCAAGAGTAAGCCTGAAGTAACGGTTGAGTAAACAGAAAAGGCCAAAGTAGCAGCAGCA - 18180
 - T K S K P E V T V E * T E K A K V A A A
 - P R V S L K * R L S K Q K R P K * Q Q Q
 - Q E * A * S N G * V N R K G Q S S S S N
 18181 - ACAATAGCCTAAGAAACAATAAACAAGCATGATACACTGTAAGGTGTTGCCAGTAATAAA - 18240
 - T I A * E T I N K H D T L * G V A S N K
 - Q * P K K Q * T S M I H C K V L P V I N
 - N S L R N N K Q A * Y T V R C C Q * * I
 18241 - TAACAATGGGTAATACTCAACACACAAACACTATAGCTTAGCTAAAAACATGATAGT - 18300
 - * Q W V I L N T H K H Y S S S * K H D S
 - N N G * Y S T H T N T I A L A K N M I V
 - T M G N T Q H T Q T L * L * L K T * * S
 18301 - CGTAACGACACCAGAATAGTTAGAGGTTACAGAAATAACTAAGGCCCATGGAATAGC - 18360
 - R N D T R I V R G Y R N N * G P H G N S
 - V T T P E * L E V T E I T K A H M E I A
 - * R H Q N S * R L Q K * L R P T W K * L
 18361 - TTGATCTAAAGCATTACCATAGTAGACTTTGTAAACAAGTGAATGACATTCATCAGTGT - 18420
 - L I * S I T I V D F V N K C N D I H Q C
 - * S K A L P * * T L * T S V M T F I S V
 - D L K H Y H S R L C K Q V * * H S S V S
 18421 - CCAAACAGTCTAGCAGCATCATATAACAGTGGAGCTGTCATGAGAATAAGCAAAC - 18480
 - P N T S S S I I I N S A S C H E N K Q N
 - Q T R L A A S S * T V R A V M R I S K T
 - K H V * Q H H H K Q C E L S * E * A K L

FIG. 12 Con't

18481 - TAAAGCTGAAGCATACATAACACAATCCCTTAAGCCTATAACCAGACAAGCTAGTGTGTCAGC - 18540
 - * S * S I H N T I L K P I T R Q A S V S
 - K A E A Y I T Q S L S L * P D K L V S A
 - K L K H T * H N P * A Y N Q T S * C Q P
 18541 - CAATTCAAGCCATGTCATGATACGCATCACCCAGCTAGCAGGCATGTAGACCATATATAA - 18600
 - Q F K P C H D T H H P A S R H V D H I K
 - N S S H V M I R I T Q L A G M * T I L K
 - I Q A M S * Y A S P S * Q A C R P Y * S
 18601 - GTAAGCAACTGTGCAAGAGAAGTAACGAAACAAGCACAAGAATGCGTGCTTATGCTT - 18660
 - V S N C C K R R * Q K Q A Q E C V L M L
 - * A T V A R E G N R N K H K N A C L C L
 - K Q L L Q E K V T E T S T R M R A Y A *
 18661 - AACAAGCAGCATAGCACATGCAGCAATTGCCATAATACCAAGAGTAAATGGCAAGAAAGC - 18720
 - N K Q H S T C S N C H N T K S K W Q E S
 - T S S I A H A S A I A I I P R V N G K K A
 - Q A A * H M Q Q L P * Y Q E * M A R K H
 18721 - ATTCTCGTAAACAAAGAAAACAGTGACCCTGTGTACTTTGAACAAGAATCAATAGTGA - 18780
 - I L V N K E K Q * P L C T L N K N Q * *
 - F S * T K K N S D H C V L * T R I N S D
 - S R K Q R K T V T T V Y F E Q E S I V M
 18781 - TGTCAAGAAAGTAAAAGCATCCAATGATGAGTGCCTTAAACAATTTCTTGAACCTACC - 18840
 - C Q E S * K H P M M S A L N N F L E L T
 - V K K V K S I Q * * V P L T I F L N L P
 - S R K L K A S N D E C P * Q F S * T Y L
 18841 - TTGGAAGGTAACACCAGAGCATTGTCTAACAACATCAAATGGTGTAACCTCATCTTCTAA - 18900
 - L E G N T R A L S N N I K W C K L I F *
 - W K V T P E H C L T T S N G V N S S S K
 - G R * H Q S I V * Q H Q M V * T H L L K
 18901 - AATAGTGTACCAAGGATAGTACGACCATTACATACCATTCTGCAGCAGCTCTTCAAGC - 18960
 - N S A T K D S T T I H T I L Q Q L F Q S
 - I V L P R I V R P F I P F C S S S F K A
 - * C Y Q G * Y D H S Y H S A A A L S K Q
 18961 - AGCACACATATCTAAGACGGCAATTCCTGTTTGGAGCAGAAAGAGGTCCCAATATGTCAAC - 19020
 - S T H I * D G N S C L S R K R S Q Y V N
 - A H I S K T A I P V * A E R G P N M S T
 - H T Y L R R Q F L F E Q K E V P I C Q H
 19021 - ATGATCTGTGTCAAAGGTTTCATAGTTGTACTTCATTGCCACAAGGTTAAAGTCATTCAA - 19080
 - M I L C Q R F I V V L H C H K V K V I Q
 - * S C V K G S * L Y F I A T R L K S F K
 - D L V S K V H S C T S L P Q G * S H S K
 19081 - AGTAGTGGTGAATCTATTAAGAAACCACCTATCACCATTGATAACAGCAGCATAACGCCA - 19140
 - S S G E S I K K P P I T I D N S S I Q P
 - V V V N L L R N H L S P L I T A A Y S H
 - * W * I Y * E T T Y H H * * Q Q H T A M
 19141 - TGCCAAAACATTTAATGTTATGGTTGTGTCTGTACTGTCAGCCTGTGCAGTTTGTCTGTC - 19200
 - C Q N I * C Y G C V C T C S L C S L S V
 - A K T F N V M V V S V P A A C A V C L S
 - P K H L M L W L C L Y L Q P V Q F V C Q
 19201 - AACAAATGGACCATAGAATTTACCTTCTAAGTACAGTACCAGCGTGTACTCCTGTTGGAAG - 19260
 - N K W T I E F T F * V S T S V Y S C W K
 - T N G P * N L P S K S V P A C T P V G S
 - Q M D H R I Y L L S Q Y Q R V L L L E A
 19261 - CTCCATATGATGCATATAGCAGAAAGACACGCAATCATAATCAATGTTAAACCAACT - 19320
 - L H M M H I A E R H A I I I N V K T N T
 - S I * C I * Q K D T Q S * S M L K P T L
 - P Y D A Y S R K T R N H N Q C * N Q H Y

FIG. 12 Con't

19321 - ACCACATGATCCATTAAGGAAAGAACCTTTAATGGTATGATTAGGTCTCATGGCACACTG - 19380
 - T T * S I K E R T F N G M I R S H G T L
 - P H D P L R K E P L M V * L G L M A H *
 - H M I H * G K N L * W Y D * V S W H T D
 19381 - ATAAACACCAGATGGTGAACCATTGTAGCATGCTAGAACTGAAAATGTTTGACCAGGTTG - 19440
 - I N T R W * T I V A C * N * K C L T R L
 - * T P D G E P L * H A R T E N V * P G W
 - K H Q M V N H C S M L E L K M F D Q V G
 19441 - GATACGGACAATTATACTTGGGTGTCTTAGGGTTAGAAGTATCAACTTAAGCCTAAG - 19500
 - D T D K F I L G C L R V R S I N F K P K
 - I R T N L Y L G V L G L E V S T L S L S
 - Y G Q I Y T W V S * G * K Y Q L * A * A
 19501 - CAGACAATTTGCGATAGAATGGCCAATAACACGAAGTGAACATGCCAGCCTGAACAAG - 19560
 - Q T I L H R M A N N T K L N I A S L N K
 - R Q F C I E W P I T R S * T L P A * T R
 - D N F A * N G Q * H E V E H C Q P E Q E
 19561 - AAAGCTATGGTTGGATTTGCGAATGAGCAGATCTTCATAGTTAGGATTAAGCATGTCTTC - 19620
 - K A M V G F A N E Q I F I V R I K H V F
 - K L W L D L R M S R S S * L G L S M S S
 - S Y G W I C E * A D L H S * D * A C L L
 19621 - TGCTGTGCAAATGACATGTCTTGGACAGTATACTGTGTATCCAACCACAATCCATTAAG - 19680
 - C C A N D M S W T V Y C V I Q P Q S I K
 - A V Q M T C L G Q Y T V S S N H N P L R
 - L C K * H V L D S I L C H P T T I H * E
 19681 - AGTTGTAGTTCACAGGTTACTTGTACCATGCACCCTCAACTTGCCTGACGGGAATGC - 19740
 - S C S S T G Y L Y H A P F N F A * R E C
 - V V V P Q V T C T M H P S T L P D G N A
 - L * F H R L L V P C T L Q L C L T G M P
 19741 - CATTTTCCTAAAACCACTCTGCAGAACAGCAAGTGATTGATGTCTGTGGTGGTTGGTA - 19800
 - H F P K T T L Q N S R S D * C L W W L V
 - I F L K P L C R T A E V I D V C G G W *
 - F S * N H S A E Q Q K * L M S V V V G R
 19801 - GAGAACATCAGCAGCTGAGTTGCTAAAGTCATTTAGAGCCTTTGCTAAGTGGCAGCAAGC - 19860
 - E N I S T * V A K V I * S L C * V A A S
 - R T S A P E L L K S F R A F A K W Q Q A
 - E H Q H L S C * S H L E P L L S G S K L
 19861 - TGCTTCACGATAGCTGGTAGTATCTAAGGCTCCACTGAAATACTGTACTTGTATATAG - 19920
 - C F T I A G S I * G S T E I L V L V I *
 - A S R * L V V S K A P L K Y L Y L L Y R
 - L H D S W * Y L R L H * N T C T C Y I E
 19921 - AGCAAGATACCTGTATACTGTGTAAGTGGCAACAGTGTCTCGCTACGCAATTTTAGGTA - 19980
 - S K I P V I L C K W Q Q C L A T Q F * V
 - A R Y L L Y C V S G N S V S L R N F R Y
 - Q D T C Y T V * V A T V S R Y A I L G T
 19981 - CATTTCTGTGAGCAAAAAGGTACACAAAGCAGCCTCCTCGAAGGTACTAAATGTAAC - 20040
 - H F L V E Q K G T Q S S L L E G T K C N
 - I S L L S K K V H K A A S S K V L N V T
 - F P C * A K R Y T K Q P P R R Y * M * L
 20041 - TCCATTAACATGACTCTTTTCCTAAGATAGTTGTTAAGAACCAATGGCAGTGCCTCAG - 20100
 - S I K H D S F P K I V V K E P M A V L Q
 - P L N M T L F L R * L L K N Q W Q C F R
 - H * T * L F S * D S C * R T N G S A S E
 20101 - AGAAATACAGAATACATAGATTGCTGTTATCCAAAAAGGCACAATAGGAGAAAACATGGC - 20160
 - R N T E Y I D C C Y P K R H N R R K H G
 - E I Q N T * I A V I Q K G T I G E N M A
 - K Y R I H R L L L S K K A Q * E K T W Q

FIG. 12 Con't

20161 - AAACCATTGAAGGTGAGCCAAGAATGAAACATCATTGGTGAATAGAATGTCAAGTACAA - 20220
 - K P L K V S Q E * N I I G E I E C Q V Q
 - N H * R * A K N E T S L V K * N V K Y K
 - T I E G E P R M K H H W * N R M S S T S

20221 - GTAAAAGACTGAGTAGACTCCCGGCAGAAAGCTGTAAGCTGGTACCAGACAGAGTATAGT - 20280
 - V K D * V D S R Q K A V S W Y Q T E Y S
 - * K T E * T P G R K L * A G T R Q S I V
 - K R L S R L P A E S C K L V P D R V * *

20281 - GAAAGACATCAAAAACAAAAGTGCATTAGCAGCAACAACATGGTTGTACTIONCACCAAAAC - 20340
 - E R H Q K Q K C I S S N N M V V L T K N
 - K D I K N K S A L A A T T W L Y S P K T
 - K T S K T K V H * Q Q Q H G C T H Q K H

20341 - ACGTCTGAATTTTCATAAAGTAGTAGGCAGCACAAGTCACCAATATGGCAATAATACCACC - 20400
 - T S E F H K V V G S T S H Q Y G N N T T
 - R L N F I K * * A A Q V T N M A I I P P
 - V * I S * S S R Q H K S P I W Q * Y H Q

20401 - AGCCACTACTGAAGCAGACACATCTAAAGCACCCACAGGTGCACAAGAGGAGTAAAGAT - 20460
 - S H Y * S R H I * S T H R L H K R S K D
 - A T T E A D T S K A P T G C T R G V K M
 - P L L K Q T H L K H P Q V A Q E E * R C

20461 - GTTAGCTATGAGATTCATCGCATCAACACCACAGAAAACCTCTGATAGAGCTCTGTAATG - 20520
 - V S Y E I H R I N T T E N S * * S S V M
 - L A M R F I A S T P Q K T P D R A L * C
 - * L * D S S H Q H H R K L L I E L C N A

20521 - CTCATTATTAAGAACCCTACTACCCTGGTAGATAGGCAAAATACCTACTTCTGACCTTTC - 20580
 - L I I K N P S T T G R * A N T Y F * P F
 - S L L R T H L P L V D R Q I P T S D L S
 - H Y * E P I Y H W * I G K Y L L L T F R

20581 - GCATGTACTGTCTACAGTACTCAGCATCAAAAAGTTGTTACTACTCTAACAGAACCCCTC - 20640
 - A C T M S T V L S I K S C Y Y S N R T L
 - H V P C L Q Y S A S K V V T T L T E P S
 - M Y H V Y S T Q H Q K L L L L * Q N P P

20641 - CAGGTAAGTGTAGGAACTGTATGATGGAACCATCCATAAGCACATAACGAGTGTCTGG - 20700
 - Q V S V R K L Y D G T I H K H I T S V W
 - R * V L G N C M M E P S I S T * R V S G
 - G K C * E T V * W N H P * A H N E C L D

20701 - ACGAAGCTCACTATAAGAAATAGAACCCTCTAGCAAATTAGTGTACATAACAATATGGCAC - 20760
 - T K L T I R N R T L * Q I S V I T I W H
 - R S S L * E I E P S S K L V S * Q Y G T
 - E A H Y K K * N P L A N * C H N N M A Q

20761 - AGGTTTGCCCATAGCATCCTTAAAAATTGTACACTCAGCAGCAAGAACGCAAGCAGAGGT - 20820
 - R F A H S I L K N C T L S S K N A S R G
 - G L P I A S L K I V H S A A R T Q A E V
 - V C P * H P * K L Y T Q Q Q E R K Q R *

20821 - AGCAAAATCACTATACTCAATGAGTTTGGGAAGGTGTGTAGCAAATGTTGCCAACAGCACT - 20880
 - S K I T I L N E F G R C V A N V A N S T
 - A K S L Y S M S L E G V * Q M L P T A L
 - Q N H Y T Q * V W K V C S K C C Q Q H *

20881 - AAAAAACGAGGTAGAAAATGCAAGAAGTACCATTGATTGCTCTCAGCACAGTACCCGG - 20940
 - K N T R * K M Q E V T I D C S Q H S T R
 - K T R G R K C K K S P L I A L S T V P G
 - K H E V E N A R S H H * L L S A Q Y P V

20941 - TAAGCCAGGCACTATGAAACCAATCTCTCTGTAAATGATAGCAGCTACTACAGGCAGCT - 21000
 - * A R H Y E T N L S C N D S S Y Y R A A
 - K P G T M K P I S L V M I A A T T G Q L
 - S Q A L * N Q S L L * * * Q L L Q G S F

FIG. 12 Con't

21001 - TTTGTCATTTTTGTATGAACCACCACGCTGGCTAAACCATGCGTCAAACCAGCATGTTT - 21060
 - F V I F V * T T T L A K P C V K T S M F
 - L S F L Y E P P R W L N H A S K P A C L
 - C H F C M N H H A G * T M R Q N Q H V Y

21061 - ATTTGCAAAACAATCATCAGTAGAAATGATGTCACGAGTGACACCATCCTGAATGGCTTT - 21120
 - I C K T I I S R N D V T S D T I L N G F
 - F A K Q S S V E M M S R V T P S * M A L
 - L Q N N H Q * K * C H E * H H P E W L C

21121 - GTAACCAATGATTTTCATTGTGTAACCATCATGGATTGACAATGTATGTACTGGCATAAC - 21180
 - V T N D F I C V T I M D * Q C M Y W H N
 - * P M I S F V * P S W I D N V C T G I T
 - N Q * F H L C N H H G L T M Y V L A * R

21181 - GATATAACAAACCAATGCAGCAAGAACGCACAATAATGTGGCCTTAAGCATAAGTTTAAA - 21240
 - D I T N Q C S K N A Q * C G L K H K F K
 - I * Q T N A A R T H N N V A L S I S L K
 - Y N K P M Q Q E R T I M W P * A * V * N

21241 - ACAAGTACTAACAATCTTACCACCCTTGAGTGAGATTTTAGTAGTTATGACATTGACAAC - 21300
 - T S T N N L T T L E * D F S S Y D I D N
 - Q V L T I L P P L S E I L V V M T L T T
 - K Y * Q S Y H P * V R F * * L * H * Q P

21301 - CTGTCTAGTTGTAGCACAAAGTTAGTGTAAGGTTAGTTGTTCTTCTGGCAGCAGTACG - 21360
 - L S S C S T S * C K R Y V V L L G S S T
 - C L V V A Q V S V K G M L F F L A A V R
 - V * L * H K L V * K V C C S S W Q Q Y E

21361 - AATTTGTTTACGCAGCTGTTTCAGATAAAGCATGTAGTCTTTTACATTCCAGATGAGTGA - 21420
 - N L F T Q L F R * R H V V F Y I P D E *
 - I C L R S C S D K D M * S F T F Q M S E
 - F V Y A A V Q I K T C S L L H S R * V K

21421 - AACATTGTGACTTTTTGCTACTTGGGCATTGATATGCCTTGCATTACAGTCAATACATGC - 21480
 - N I V T F C Y L G I D M P C I T V N T C
 - T L * L F A T W A L I C L A L Q S I H A
 - H C D F L L L G H * Y A L H Y S Q Y M R

21481 - GCCAAGATCTCTGGGCGTCATGTTTTCAACCTTATTATAGGTGAGCATGAAATTGTTACA - 21540
 - A K I S G R H V F N L I I G E H E I V T
 - P R S L G V M F S T L L * V S M K L L Q
 - Q D L W A S C F Q P Y Y R * A * N C Y N

21541 - ACTGTCACCTGTCACCTTCTAAGTCAGAGTGATGTGAAAGTTGAGACATTCAATAACATC - 21600
 - T V T C H F * V R V M * K F E T F N N I
 - L S P V T S K S E * C E S L R H S I T S
 - C H L S L S Q S D V K V * D I Q * H P

21601 - CTTTGTGTCAACATCGGTATCAACAACACCTGTGCGGCAGCTGACACGAATGTAGAAAG - 21660
 - L C V N I G I N N T L S G S * H E C R K
 - F V S T S V S T T P C R A A D T N V E R
 - L C Q H R Y Q Q H L V G Q L T R M * K G

21661 - GACACCATCTAAAGCTACACCCTTGCTAACTCGCTGTGAGCTGTAGCAACAAGTGCCTT - 21720
 - D T I * S Y T L C * L A V S C S N K C L
 - T P S K A T P F A N S L * A V A T S A L
 - H H L K L H P L L T R C E L * Q Q V P *

21721 - AAGTTTTTCCATAGGAACACTAAAAGTTGCTGAAAAGGTGTCGACATAAGCATCAAACAT - 21780
 - K F F H R N T K S C * K G V D I S I K H
 - S F S I G T L K V A E K V S T * A S N I
 - V F P * E H * K L L K R C R H K H Q T S

21781 - CTTAACGGAACTTCAGTACTATCTCCAACGTTTGATACAAGAGCTTGGTCAAGCAACAG - 21840
 - L N G N F S T I S N V * Y K S L V K Q Q
 - L T E T S V L S P T F D T R A W S S N R
 - * R K L Q Y Y L Q R L I Q E L G Q A T E

FIG. 12 Con't

21841 - AATAGGTTGGCACATCAGCTGACTGTAGTACACAGAAGCAGACTTAGAAGCAGACTCGTC - 21900
 - N R L A H Q L T V V H R S R L R S R L V
 - I G W H I S * L * Y T E A D L E A D S S
 - * V G T S A D C S T Q K Q T * K Q T R R

21901 - GCATTTGGACTTGCCATCAAAAATGACATTAATAGGCAGTGAACCTTAGTGTGTT - 21960
 - A F G L A I K N Y D I N R Q * T F S V V
 - H L D L P S K T M T L I G S E P L V L L
 - I W T C H Q K L * H * * A V N L * C C *

21961 - AGCTCTCAAATGTCTAAATGACAAAATGGGAGAGCGGATGTCTCTCATAGGTCTTTTG - 22020
 - S S Q I V * I D K M G E R M S L I G L L
 - A L K L S K L T K W E S G C L S * V F *
 - L S N C L N * Q N G R A D V S H R S F D

22021 - ACCAGCCTTGTCAAAGTAGAGGTGAAGCGGCCATTTTCACAGCAACTATCAACAAT - 22080
 - T S L V K V E V K R A I F H S N T I N N
 - P A L S K * R * S A P F F T A T L S T I
 - Q P C Q S R G E A R H F S Q Q H Y Q Q Y

22081 - ATACGATGACTGGTCAGTAGGGTGTGATTGGTCTTTAAACTGGAGTGACAAATCAGAGC - 22140
 - I R * L V S R V D W S F K L E * Q I T S
 - Y D M W S V G L I G L L N W S D K S R A
 - T M T G Q * G * L V F * T G V T N H E Q

22141 - AACTTCATCACTAATGAATGTACTACCAGTGCAAAAATGTGTCACAATTGAGACAATTCCA - 22200
 - N F I T N E C T T S A K C V T I E T I P
 - T S S L M N V L P V Q N V S Q L R Q F Q
 - L H H * * M Y Y Q C K M C H N * D N S N

22201 - ATGTGAGTCTTGCAAGCCACGGCCTCCATTTGCATAGACATAGAAAGATCTCTTCAT - 22260
 - I V S L A E A T A S I C I D I E R S L H
 - L * V L Q K P R P P F A * T * K D L F M
 - C E S C R S H G L H L H R H R K I S S C

22261 - GCCATTAACAATAGTTGTACTCAACGGTGTGGCAGATTGCGCTTATAGCACATCAT - 22320
 - A I N N S C T L N A C G T I A L I A H H
 - P L T I V V H S T R V A R L R L * H I M
 - H * Q * L Y T Q R V W H D C A Y S T S C

22321 - GCAAGTCGAAGAGGTGCAACCATCCATGATATGAACATAGCTCTTCCATATGTAGTAGAA - 22380
 - A S R R G A T I H D M N I A L P Y V V E
 - Q V E E V Q P S M I * T * L F H M * * K
 - K S K R C N H P * Y E H S S S I C S R K

22381 - AGAAGCAAAGAAGATGTACATCCTAACCTGACAGAAACGGGTGCCATTTGTACAATACT - 22440
 - R S K E D V H P N H C R N G C H L Y N T
 - E A K K M Y I L T I A E T G A I C T I L
 - K Q R R C T S * P L Q K R V P F V Q Y *

22441 - AATGATAAACCATGAGCCAAGAATTGCTGATGAAATGACTAGCAAAATAGCCAAGAA - 22500
 - N D K P H E P R I A D E M T S K I A K E
 - M I N H M S Q E L L M K * L A K * P K N
 - * * T T * A K N C * * N D * Q N S Q R T

22501 - CACCTGCATTATAGCTGAAAGACCTAATAAATAAAGAATTTTGTGAACAACATATATGC - 22560
 - H L H Y S * K T * * I K E F C E Q H I C
 - T C I I A E R P N K * K N F V N N I Y A
 - P A L * L K D L I N K R I L * T T Y M P

22561 - CAAAACCACTCAGCGCCAGACCTAAAATGTCAAGTCTAGCTTGTACGATGAAATCGT - 22620
 - Q N P L S G Q T * N C Q V * L V R * N R
 - K T H S A A R P K I V K S S L Y D E I V
 - K P T Q R P D L K L S S L A C T M K S S

22621 - CACCTGAATGGTTCAAGAGCTGGATAAGAATCAAGGGAGTCTAATCCACTTAAACAAAT - 22680
 - H L N G F K S W I R I K G V * S T * T N
 - T * M V S R A G * E S R E S N P L K Q M
 - P E W F Q E L D K N Q G S L I H L N K C

FIG. 12 Con't

22681 - GCTGCAAGGAAAAGAACCTTCACAGAAATCCATAGTAGTAACGTTAGACGAATTAAGATA - 22740
 - A A R K R T F T E I H S S N V R R I K I
 - L Q G K E P S Q K S I V V T L D E L R Y
 - C K E K N L H R N P * * * R * T N * D T

22741 - CAATTCTTAACGCCATTACAATAAGAAGGAGCACCAAATTAGATAAGAGTACACCAAA - 22800
 - Q F S N A I T I R R S T K I R * E Y T K
 - N S L T P L Q * E G A P K L D K S T P K
 - I L * R H Y N K K E H Q N * I R V H Q K

22801 - AGCAGCAGTTACACAGATTAGAGAACCTAAGCAAATACTTAACAACAATAGCCACATAGC - 22860
 - S S S Y T D * R T * A N T * Q Q * P H S
 - A A V T Q I R E P K Q I L N N N S H I A
 - Q Q L H R L E N L S K Y L T T I A T * R

22861 - GATTGTGAACAATTTAGAAAATTTGGGTGACTTCACATAATTAATGCCGGCATCCAACA - 22920
 - D C E Q F R K F G * L H I I N A G I Q T
 - I V N N L E N L G D F T * L M P A S K H
 - L * T I * K I W V T S H N * C R H P N I

22921 - TAATTTAGCAACACTCTTAACACTATTTTTAGCAATAGTTGTAGGTAGTGAAGCTCTAAT - 22980
 - * F S N T L N T I F S N S C R * * S S N
 - N L A T L L T L F L A I V V G S E A L I
 - I * Q H S * H Y F * Q * L * V V K L * F

22981 - TCTAGAATTGGTACTTTTAGTAAAAGTACACAATTGGAACAATAATGTAAACACATAAGG - 23040
 - S R I G T F S K S T Q L E Q * C K H I R
 - L E L V L L V K V H N W N N N V N T * G
 - * N W Y F * * K Y T I G T I M * T H K A

23041 - CATATAATTGTTAAACACACGTTGTGCTAATCTCTTAGCGCAATTTGATGTTGTAATTGC - 23100
 - H I I V K H T L C * S L S A I * C C N C
 - I * L L N T R C A N L L A Q F D V V I A
 - Y N C * T H V V L I S * R N L M L * L L

23101 - TGCTTGTCTAAGAATGGTTGACATAAGCCAAAATTTACTCCAAGGAACACTATTAAT - 23160
 - C L S * E W F D I S Q N F T P R N T I N
 - A C P K N G L T * A K I L L Q G T L L I
 - L V L R M V * H K P K F Y S K E H Y * L

23161 - TGCAGCAATACCATGAGTGGCAATGTTTTAAACCTAAGGCTAGTGAAGCTCATTAGG - 23220
 - C S N T M S G N C F * T * G * * K L I R
 - A A I P * V A I V F K P K A S E S S L G
 - Q Q Y H E W Q L F L N L R L V K A H * V

23221 - TTTCTTAATGGTAATGCTTGTGTTTTCCACATAAGCAGCCATAAGATCCTCATGACCTAA - 23280
 - F L N G N A C V F H I S S H K I L M T *
 - F L M V M L V F S T * A A I R S S * P N
 - S * W * C L C F P H K Q P * D P H D L T

23281 - CTCTTGTGTTACTTTAACACCTTCATCTGATGGTTTAAAGTATGACATTGCCTACAATT - 23340
 - L L C Y F N T F I * W F K Y D I A Y N F
 - S C V T L T P S S D G L S M T L P T T S
 - L V L L * H L H L M V * V * H C L Q L R

23341 - GGTAGTTTTACGTCACACTCTATGACTTCCTTCTGTATGGTAGGATTTCCACTACTTC - 23400
 - G S F H V T L Y D F L L Y G R I F H Y F
 - V V F T S H S M T S F C M V G F S T T S
 - * F S R H T L * L P S V W * D F P L L L

23401 - TTCAGAGGTGGGTGTTGACTTTCAAGCAAGATTGTCCATTCTTGTGTCTTCTAC - 23460
 - F R G G L L T F T S K I V H S L C V F Y
 - S E V G C * L S Q A R L S I P C V S S T
 - Q R W V V D F H K Q D C P F L V C L L L

23461 - TGCCAGAACTTCAAATGAATTTGAAGTATCTACTGGCTTTGTACTCCAAGACAACGTAA - 23520
 - C Q N F K * I * S I Y W L C T P K T T *
 - A R T S N E F E V S T G F V L Q R Q R K
 - P E L Q M N L K Y L L A L Y S K D N V N

FIG. 12 Con't

23521 - ACACCAAGTGTGGTTTGAACGTTGTCTTGGTTGTAGCCTGGTTAATGTGCCAAACAAT - 23580
 - T P S V W F E R C L G C S L V N V P N N
 - H Q V F G L N V V L V V A W L M C Q T I
 23581 - TGGCTTATGCAGTAATTTAGCACCTTCTTGAAACTCGCTGAATAGTGTCTATAGTCAAT - 23640
 - W L M Q * F S T F L E T R * I V S I V N
 - G L C S N L A P F L K L A E * C L * S I
 - A Y A V I * H L S * N S L N S V Y S Q *
 23641 - AGCCACTACATCGCCATTCAAGTCTGGGAAGAATGTGACAGATAGCTCTCGTGAAGCTGG - 23700
 - S H Y I A I Q V W E E C D R * L S * S W
 - A T T S P F K S G K N V T D S S R E A G
 - P L H R H S S L G R M * Q I A L V K L A
 23701 - CTTTGTGAAGCCTGTCAATTTGATTTAAATCATCAGCAAATTTTGTGTTAGAACATGTGAG - 23760
 - L C E A C H L I * I I S K F C V R T C E
 - F V K P V I * F K S S A N F V L E H V S
 - L * S L S F D L N H Q Q I L C * N M * V
 23761 - TTTGAAATTATCAAACCTCGCATTGGTAATGGTTGAGTTGGTACAAGGTCTATAGGCTG - 23820
 - F E I I K T R I W * W L S W Y K V Y R L
 - L K L S K L A F G N G * V G T R S I G C
 - * N Y Q N S H L V M V E L V Q G L * A A
 23821 - CTCTGTATAGTAAGCATTATCCTTTTTATAATACCCATCCAATTTTGGTTCAATCTCTGT - 23880
 - L C I V S I I L F I I P I Q F W F N L C
 - S V * * A L S F L * Y P S N F G S I S V
 - L Y S K H Y P F Y N T H P I L V Q S L C
 23881 - GTAAGTAACTCCATCGAGTTTATACGACACAGGCTTGATGGTTGTAGTGAAGATGTTTC - 23940
 - V S N S I E F I R H R L D G C S V R C F
 - * V T P S S L Y D T G L M V V V * D V S
 - K * L H R V Y T T Q A * W L * C K M F P
 23941 - CTTGTAGAAAACATCAGTCACTGGTCCTTTGACTCTGACATCTTTGTAAGGTGAGCTCC - 24000
 - L V E N I S H W S F V L * H L C K V S A S
 - L * K T S V T G P L Y S D I F V R * A P
 - C R K H Q S L V L C T L T S L * G E L R
 24001 - GTCAATACGATAGAGGGTCTCCTTAGCAGTTATATGAGTGAATGACCACACTGATAGTT - 24060
 - V N T I E G L L S S Y M S V M T T L I V
 - S I R * R V S L A V I * V * * P H * * L
 - Q Y D R G S P * Q L Y E C N D H T D S Y
 24061 - ACCAGTGTACTCATTTCGCACATAAGAATGTACCTTGCTGTAATTTATACTCAGCAGGTGG - 24120
 - T S V L I R T * E C T L L * F I L S R W
 - P V Y S F A H K N V P C C N L Y S A G G
 - Q C T H S H I R M Y L A V I Y T Q Q V V
 24121 - TGCAGACATCATAACAAAAGAAGACTCTTGTGTACTAGATATTGTGTAGCATCAGCACC - 24180
 - C R H H N K R R L L L Y * I L C S I T T
 - A D I I T K E D S C C T R Y C V A S R P
 - Q T S * Q K K T L V V L D I V * H H D H
 24181 - ACACACACATGGAATGGAACACCTGTCTTAAGATTATCATAAGATAGAGTACCCATATA - 24240
 - T H T W N G N T C L K I I I R * S T H I
 - H T H G M E T P V L R L S * D R V P I Y
 - T H M E W K H L S * D Y H K I E Y P Y T
 24241 - CATCACAGCTTACACCCGTTAAGGTAGTAGTTTTCTGACCACAATGTTTACACACCAC - 24300
 - H H S F Y T R * G S S F L T T M F T H H
 - I T A S T P V K V V V F * P Q C L H T T
 - S Q L L H P L R * * F S D H N V Y T P H
 24301 - ATTAAGAACTCGCTTTGCAGATTCCAATTAGCATGCTGTAGAAGATGGGTCATAGTTTC - 24360
 - I K N S L C R F Q I S M L * K M G H S F
 - L R T R F A D S K L A C C R R W V I V S
 - * E L A L Q I P N * H A V E D G S * F L

FIG. 12 Con't

24361 - TCTGACATCACCAAGCTCGCCAACAGTTTTATTACTGTAAGCGAGTATGAGTGCACAAAA - 24420
 - S D I T K L A N S F I T V S E Y E C T K
 - L T S P S S P T V L L L * A S M S A Q K
 - * H H Q A R Q Q F Y Y C K R V * V H K S

24421 - GTTAGCAGCATCACCAGCACGGGCTCTATAATAAGCCTCTGAAGTGCTGGTGCATTGAA - 24480
 - V S S I T S T G S I I S L L K C W C I E
 - L A A S P A R A L * * A S * S A G A L N
 - * Q H H Q H G L Y N K P L E V L V H * I

24481 - TTTGACTTCAAGCTGTTGAAGTGCTAATAAAACACTAGACAAATAACAATTGTTATCAGC - 24540
 - F D F K L L K C * * N T R Q I T I V I S
 - L T S S C * S A N K T L D K * Q L L S A
 - * L Q A V E V L I K H * T N N N C Y Q P

24541 - CCATTTAATTGAAGTTAAACCACCAACTTGAGGAAATTTCCATTTCTTTGTGTGGTTTAA - 24600
 - P F N * S * T T N L R K F P F L C V V *
 - H L I E V K P P T * G N F H F F V W F K
 - I * L K L N H Q L E E I S I S L C G L K

24601 - AGCAGACATGTACCTACCAAGAAAACCTCTCATCAAGAGTATGGTAGTACTCGAAAGCTTC - 24660
 - S R H V P T K K T L I K S M V V L E S F
 - A D M Y L P R K L S S R V W * Y S K A S
 - Q T C T Y Q E N S H Q E Y G S T R K L H

24661 - ACTACGTAGTGTGCATCACTAGGTAGTACAAAGAAAGTCTTACCCTCATGATTTACATG - 24720
 - T T * C V I T R * Y K E S L T L M I Y M
 - L R S V S S L G S T K K V L P S * F T *
 - Y V V C H H * V V Q R K S Y P H D L H E

24721 - AGGTTTAAATTTTTGTAACATCAGCACCATCCAAGTATGTTGACCAAACCTGCTGTCCATA - 24780
 - R F N F C N I S T I Q V C W T K L L S I
 - G L I F V T S A P S K Y V G P N C C P Y
 - V * F L * H Q H H P S M L D Q T A V H M

24781 - TGTCATAGACATATCCACAAGCTGTGTGTGGAGATTAGTGTGTCCACAGTTGTGAACAC - 24840
 - C H R H I H K L C V E I S V V H S C E H
 - V I D I S T S C V W R L V L S T V V N T
 - S * T Y P Q A V C G D * C C P Q L * T L

24841 - TTTTATAGTCTTAACTCCCGCAGGGATAAGAGACTCTTTAGTTTGTCAAGTGAAGAAGC - 24900
 - F Y S L N L P Q G * E T L * F V K * K N
 - F I V L T S R R D K R L F S L S S E R T
 - L * S * P P A G I R D S L V C Q V K E P

24901 - CTCACCGTCAAGATGAAACTCGACGGGGCTCTCCAGAGTGGTACACAATTTGTCCACC - 24960
 - L T V K M K L D G A L Q S V V H N F V T
 - S P S R * N S T G L S R V W Y T I L S P
 - H R Q D E T R R G S P E C G T Q F C H H

24961 - ACGCTTAAGAAATCAACACCTAACTCTGTACGCTGCTGAATAGGACCAATCTCTGTA - 25020
 - T L K K F N T * L C T L S * I G P I S V
 - R L R N S T P N S V R C P E * D Q S L *
 - A * E I Q H L T L Y A V L N R T N L C K

25021 - AGAGCCAGCCAAAGAAACTGTTTCTACAAAGTGCTCCTCAGATGTCTTTGATGACGAAGT - 25080
 - R A S Q R N C F Y K V L L R C L * * R S
 - E P A K E T V S T K C S S D V F D D E V
 - S Q P K K L F L Q S A P Q M S L M T K *

25081 - GAGGTATCCATTATATGTAGTAACAGCATCTGGTGATGATACTGACACTACGGCAGGAGC - 25140
 - E V S I I C S N S I W * * Y * H Y G R S
 - R Y P L Y V V T A S G D D T D T T A G A
 - G I H Y M * * Q H L V M I L T L R Q E L

25141 - TTTAAGAGAACGCATACAGCGCGCAGCCTCTCAAGATTAACCATGTGTACATAACC - 25200
 - F K R T H T A R S L F K I K T M C H I T
 - L R E R I Q R A A S S R L K P C V T * P
 - * E N A Y S A Q P L Q D * N H V S H N Q

FIG. 12 Con't

25201 - AATTGGCATTGTGACAAGCGGCTCATTAGAGAGTTGAGCTTCGTAATAATAGAAGCTAC - 25260
 - N W H C D K R L I * R V Q L R N N R S Y
 - I G I V T S G S F R E F S F V I I E A T
 - L A L * Q A A H L E S S A S * * * K L Q

25261 - AGGCTCTTTACTAGTATAAAAGAAGAATCGGACACCATAGTCAACGATGCCCTCTGAAT - 25320
 - R L F T S I K E E S D T I V N D A L L N
 - G S L L V * K K N R T P * S T M P S * I
 - A L Y * Y K R R I G H H S Q R C P L E F

25321 - TTTAATTCCTTTATACTTACGTTGGATGGTTGCCATTATGGCTCTAACATCCATGCATAT - 25380
 - F N S F I L T L D G C H Y G S N I H A Y
 - L I P L Y L R W M V A I M A L T S M H I
 - * F L Y T Y V G W L P L W L * H P C I *

25381 - AGGCATTAATTTCTGTCTCTTCAGCATGAGCAAGCATTCTCTCAAATTCAGGATAC - 25440
 - R H * F S C L F S M S K H F S Q I P G Y
 - G I N F L V S S A * A S I S L K F Q D T
 - A L I F L S L Q H E Q A F L S N S R I Q

25441 - AGTTCTAGAACTCTTCTTAGCATTAGGTGCTTCTGAAGGTAGTACATAAAATGCAGA - 25500
 - S S * N L F L S I R C F * R * Y I K C R
 - V P R I S S L A L G A S E G S T * N A D
 - F L E S L P * H * V L L K V V H K M Q I

25501 - TTTGCATTCTTAAGAGCAGTCTTAGCTTCTCAAGTGATAACCAGCACATCCTTGTC - 25560
 - F A F L K S S L S F L K C I T S T S L S
 - L H F L R A V L A S S S V * P A H P C P
 - C I S * E Q S * L P Q V Y N Q H I L V Q

25561 - AGGGTACGTGGTTATATACTCATCAACTGGCACTTCTTCAAAGCTCTTGAGAGCATCTC - 25620
 - R V R G Y I L I N W H F L Q S S * E H L
 - G Y V V I Y S S T G T F F K A L E S I S
 - G T W L Y T H Q L A L S S K L L R A S Q

25621 - AGTAGTCCACCAGCCTTTTGGAGGTATTACAACAAGTGATATCACCAGTATGAT - 25680
 - S S A T S L F G G Y Y N T S D I T T S D
 - V V P P A F L E G I T T Q V I S P L V I
 - * C H Q P F W R V L Q H K * Y H H * * *

25681 - AACATCACCTACCATGTAAGGTGCATCCTTCTCAAGGAAAGACATATCTTCACCTCAAG - 25740
 - N I T Y H V R C I L L K E R H I F T S K
 - T S P T M * G A S F S R K D I S S P L S
 - H H L P C K V H P S Q G K T Y L H L * A

25741 - CATGTTCTGAGAATCATGGTAAAGCTTACCATTGATATCAGCAAACAAGAGTAACTTATT - 25800
 - H V L R I M V K L T I D I S K Q E * L I
 - M F * E S W * S L P L I S A N K S N L L
 - C S E N H G K A Y H * Y Q Q T R V T Y W

25801 - GGTAAGAACTTAGTTTCTCCAGTGTGTGGTAACCTCATCAATGCAGGCCTTAATTTT - 25860
 - G K K L S F F Q C C G N L I N A G L N F
 - V R N L V S S S V V V T S S M Q A L I F
 - * E T * F L P V L W * P H Q C R P * F L

25861 - TGGCTTCACATCGACAGGCTTCTGTACGACAGATTTCTCCTCAGTTTTGGAATCTTCTGT - 25920
 - W L H I D R L L Y D R F L L S F G I F C
 - G F T S T G F C T T D F S S V L E S S V
 - A S H R Q A S V R Q I S P Q F W N L L C

25921 - GTTGGTGGCTCCTCTGTTTAGGTGCTTCCACTCTAGGCTTCAAGGTTATCAAGATAATC - 25980
 - V W W L L L F R C F H S R L Q V I K I I
 - F G G S S C L G A S T L G F R L S R * S
 - L V A P L V * V L P L * A S G Y Q D N P

25981 - CATGACAACCTGCTCATAAAGAGCTTTGTGCTGACTGCAATATAAACCTGTGTACGAAC - 26040
 - H D N L L I K S F V I D C N I N L C T N
 - M T T C S * R A L S L T A I * T C V R T
 - * Q P A H K E L C H * L Q Y K P V Y E P

FIG. 12 Con't

26041 - CGTCTGCACGCACACTTGTAAGACTGAAGTGGTTTAGCACCAAATATGCCTGCTGACAA - 26100
 - R L H A H L * R L K W F S T K Y A C * Q
 - V C T H T C K D * S G L A P N M P A D N
 - S A R T L V K T E V V * H Q I C L L T T
 26101 - CAATGGTCAAGTAAGATGTCCTGTGAATTGAAATTTTCATATGCTGCCTTAAGAAGCTG - 26160
 - Q W C K * D V L * I E I F I C C L K K L
 - N G A S K M S C E L K F S Y A A L R S W
 - M V Q V R C P V N * N F H M L P * E A G
 26161 - GATGTCCTCACCTGCATTTAGGTTAGGTCACAACATGCAGACACTTCTTAGCAAGATT - 26220
 - D V L T C I * V R S N N M Q T L L S K I
 - M S S P A F R L G P T T C R H F L A R L
 - C P H L H L G * V Q Q H A D T S * Q D Y
 26221 - ATGTCCAGAAAGCAAACAAGACCTCTACTGTAAGAGGCCATTAGCTTAATGTAATC - 26280
 - M S R K Q T R P S Y C K R A I * L N V I
 - C P E S K Q D P P T V R G P F S L M * S
 - V Q K A N K T L L L * E G H L A * C N H
 26281 - ATCACTCTCTTTTGCATGGCACCATTGGTTGCCTTGTGAGTGCACCTGTACACCACC - 26340
 - I T L L L H G T I G C L V E C T C Y T T
 - S L S F C M A P L V A L L S A P A T P P
 - H S P F A W H H W L P C * V H L L H H H
 26341 - ACCATGTTTCAGGTGTATGTTAGCAGCATTACAATCACCATAGGATTAGCACTTTGTGC - 26400
 - T M F Q V Y V S S I Y N H H R I S T L C
 - P C F R C M L A A F T I T I G L A L C A
 - H V S G V C * Q H L Q S P * D * H F V P
 26401 - CTCCTTAACGATGTCAACACATTTAATGGCAACATGTGCAGTAAGTTTTAAATAACAGT - 26460
 - L L N D V N T F N G N I V S K F * I T S
 - S L T M S T H L M A T L S V S F K * P V
 - P * R C Q H I * W Q H C Q * V L N N Q *
 26461 - AAAGTAACTGTTCTTCAGGTGTAGGTTCTGGTTCTGGCTCAATCTCTGATTGCTC - 26520
 - K L I N W F F R C R F W F W L N L * L L
 - N * L T G S S G V G S G S G S I S D C S
 - T D * L V L Q V * V L V L A Q S L I A Q
 26521 - AGTAGTATCATCCAGCCAGTCTTCTCTTCTTCTCTCAACTCGAACTGTTTCAGCTGA - 26580
 - S S I I Q P V F L F F F L N S N C F S *
 - V V S S S Q S S S S S S S S T R T V S A E
 - * Y H P A S L P L L P Q L E L F Q L R
 26581 - GGCACCAATTCAGAGGAGACCTTGATAATCATCCTCTGTACCGTACTCATGTCACA - 26640
 - G T K F Q R E T L I I I L C T V L M F T
 - A P N S R G R P * * S S S V P Y S C S Q
 - H Q I P E G D L D N H P L Y R T H V H R
 26641 - GGTTTCATCAATTTCTTCTCTCACACTCTGCATCGTCTCTTCTTCTCTCATCTGGAGG - 26700
 - G F I N F F F L T L C I V L F F L I W R
 - V S S I S S S S H S A S S S S S S S G G
 - F H Q F L L P H T L H R P L L P H L E G
 26701 - GTAAAAGGAACAATACATACGTGATGAAAAGTTTTCTTACCAGCATCATCAATAAGTA - 26760
 - V K G T I H T * * K V F F T S I I K * V
 - * K E Q Y I R D E K F S S P A S S N K *
 - K R N N T Y V M K S F L H Q H H Q I S R
 26761 - GAATGTAGCTACTCCACTCATCAAGATCAATACCCATGTTGGTAAGGAGATCAGAAAC - 26820
 - E C S Y T P L I K I N T H V G K E I R N
 - N V A T L H S S R S I P M L V R R S E T
 - M * L H S T H Q D Q Y P C W * G D Q K L
 26821 - TGGTTGTAAGTCTTCACAACAGCCTCTGCTACAACACATGCAAACCTCAGTAACCTCGGT - 26880
 - W L * S L H N S L C Y N T C K L S N F G
 - G C K V F T T A S A T T H A N S V T S V
 - V V K S S Q Q P L L Q H M Q T Q * L R Y

FIG. 12 Con't

26881 - ACCGGATTCAACAGTGTAGACAGAGCACTTTTCATTAAGCACTTTGTCAACACGTTTCATC - 26940
 - T G F N S V D R A L F I K H F V N T F I
 - P D S T V * T E H F S L S T L S T R S S
 - R I Q Q C R Q S T F H * A L C Q H V H Q
 26941 - AAGCTCAAATGTGATTCTCACATTCTTGTAACCTGAACTCCCAAACAGTATCTTCTCC - 27000
 - K L K C D S H I L V T L N F P N S I F S
 - S S N V I L T F L * P * T S Q T V S S P
 - A Q M * F S H S C N L E L P K Q Y L L Q
 27001 - AAAGGTTACACCTTTAATTGGTGACCCCTTTTAAAGCGAAAGACATTGTTTGTAGCCAG - 27060
 - K G Y T F N W C T P F * A K D I V C S Q
 - K V T P L I G A P P F K R K T L F V A S
 - R L H L * L V H P L L S E R H C L * P V
 27061 - TAAACCAGGAGACAATGCGCAGTATTGTCTTTGTCTTAATCTCTAAGAGCATGAGGCC - 27120
 - * T R R Q C A V L F F V L N L * E H E A
 - K P G D N A Q Y C S L S L I S K S M R P
 - N Q E T M R S I V L C P * S L R A * G H
 27121 - ATTTACACAGACTGGTGTGCCGACGATAGCTCCATTGTGAAGCTATCAACGGCGCTC - 27180
 - I Y T D W C A D D S S I C E A I N G R L
 - F T Q T G V P T I A P F V K L S T G V S
 - L H R L V C R R * L H L * S Y Q R A S R
 27181 - GAGTGCCTTCGAGTTCACCGTTCTTGAGAAACCTCCTCAGAGGTAAGTACTGTGTCATG - 27240
 - E C F E F T V L E N N L L R G K Y C V M
 - S A S S P F L R T T S S E V S T V S C
 - V L R V H R S * E Q P P Q R * V L C H V
 27241 - TGAATCACCTTCAAGAAAGGTTACTTCTTTGGTGCCTTAAGAGGCATGAGTAGTTGCAG - 27300
 - * I T F K K G Y F F W C L K R H E * L Q
 - E S P S R K V T S F G A L R G M S S C S
 - N H L Q E R L L L L V P * E A * V V A A
 27301 - CTGCTCCTTGCCACGTATACACTGACGGTAAAGTCCCTTGCTTTGAGCGATGAAGACTTC - 27360
 - L L A T Y T L T V K S L A L S D E D F
 - C S L P R I H * R * S P L L * A M K T S
 - A P C H V Y T D G K V P C F E R * R L H
 27361 - ACCTAAGTTGAGTGATCGCAACTTTCGCCAGCGATAGTGACTTGATCAATGCACATTTC - 27420
 - T * V E * S Q L C A S D S D L I N A H F
 - P K L S D R N F A P A I V T * S M H I S
 - L S * V I A T L R Q R * * L D Q C T F R
 27421 - GAGTGCCTTGTTAACAACATCAATGAAGCATTTTACACAATCCTTGATGTTATCTGAAGC - 27480
 - E C L V N N I N E A F Y T I L D V I * S
 - S A L L T T S M K H F T Q S L M L S E A
 - V P C * Q H Q * S I L H N P * C Y L K Q
 27481 - AACCTGATTTGACCCTTGACGATGTCAAAAACACCTGTAATGAGAAATTTGAGAATCTC - 27540
 - N L Y L T L D D V K N T C N E K F E N L
 - T C I * P L T M S K T P V M R N L R I S
 - P V F D P * R C Q K H L * * E I * E S P
 27541 - CCAAGCATCCTTGAGAAATTCACCTCCTGCACTAAGTTTCGCCTCAATCCATTCAAAGAT - 27600
 - P S I L E K F N S C T K F R L N P F K D
 - Q A S L R N S T P A L L S F A S I H S K I
 - K H P * E I Q L L H * V S P Q S I Q R *
 27601 - AGGCCTGAGTTTTTCAACAGTAGTGCCCAAAGATTAGACAACCACTGAGAAGTCTGTTG - 27660
 - R P E F F N S S A Q K I R Q P L R S L L
 - G L S F S T V V P K R L D N H * E V C C
 - A * V F Q Q * C P K D * T T T E K S V V
 27661 - TACAAGACCACGATTACATATGCCATAATAATGACACTGTTGGTGAGCAGGCTGAAGT - 27720
 - Y K T T S Y I C H N N D T V G E Q V * S
 - T R P V T Y A I I M T L L V S R S E V
 - Q D H Q L H M P * * * H C W * A G L K Y

FIG. 12 Con't

27721 - ATAACCATGGCGTCGACAAGACGTAATGACTGTTTCAGAAATACCATCAAGTATGGTGAC - 27780
 - I N H G V D K T * * L F R N T I K Y G D
 - * T M A S T R R N D C S E I P S S M V T
 - K P W R R Q D V M T V Q K Y H Q V W * Q
 27781 - AGCTGCTCTTTGCAAATCAGGAATTGAGTGGTTTGTGCATCAAGTGTGCGCGCAAAAAT - 27840
 - S C S L Q I R N * V V C C I K C A R K N
 - A A L C K S G I E W F A A S S V R A K I
 - L L F A N Q E L S G L L H Q V C A Q K L
 27841 - TGATCTGATAACACCAGCAGCCTGTGAGGGAAAACCACACAGTGGTGTAAAAGTATCT - 27900
 - * S D N T S S L * G K T T Q W C * N * S
 - D L I T P A A C E G K P H S G V K T D L
 - I * * H Q Q P V R E N H T V V L K L I S
 27901 - CTGTTGTCCAATGTTCCAAGCACCTTTTACGGGCTTTCCCTTGGTAACTTTATAGTTACC - 27960
 - L L S N V P S T F Y G L S L G N F I V T
 - C C P M F Q A P F T G F P L V T L * L Y P
 - V V Q C S K H L L R A F P W * L Y S Y R
 27961 - GCAGGACTCAACAATGGTTTTGAAAGACTTGAATCAAGACTCTTTATAGTGTCAATAAAA - 28020
 - A G L N N G F E R L V I K T L Y S V N K
 - Q D S T M V L K D L * S R L F I V S I K
 - R T Q Q W F * K T C N Q D S L * C Q * R
 28021 - GGCCTTGTAGAAGCAGAGAAAGATGCCAAAATGATGGCAACCTCTTCATTCAAATGAAA - 28080
 - G T C R S R E R C Q N D G N L F I Q M K
 - A L V E A E K D A K M M A T S S F K * K
 - H L * K Q R K M P K * W Q P L H S N E N
 28081 - ATCGCCAACAATGTTAATGTTAACAGTTCACGACTCAGTATCTCAAGGAGATCCTCATT - 28140
 - I A N N V N V N T F T T Q Y L K E I L I
 - S P T M L M L T R S R L S I S R R S S F
 - R Q Q C * C * H V H D S V S Q G D P H S
 28141 - CAAGGTCTCCACATTGTCCAGTAATGCCAGTATGGCCTGAGCCAATATCAGCACTAGC - 28200
 - Q G L H I V T S N A S M A * A N I S T S
 - K V S T L S P V M P V W P E P I S A L A
 - R S P H C H Q * C Q Y G L S Q Y Q H * H
 28201 - ACGAGGAACCCAGTAGGCAGCCTTATTATAGCAGCCAACATAGGCAACACACAGCCTCC - 28260
 - T R N P V G T L I I A A N I G K H T A S
 - R G T Q * A R L L * Q P T * A N T Q P P
 - E E P S R H A Y Y S S Q H R Q T H S L Q
 28261 - AAAACATCTAGTCCTACCTCCCTTGCAGGAGTTCAGTTCATGTTGAGTGGTTGTGATA - 28320
 - K T S S P T S L A E S S F N V * V V V I
 - K H L V L P P L R S R V S M F E W L * *
 - N I * S Y L P C G V E F Q C L S G C D N
 28321 - ATCTGCAACACTATGCTCAGGTCCAATCTCTGGGTCTTGACAGGCAGGACATGGCATT - 28380
 - I C N T M L R S N L W V L T G R T W H F
 - S A T L C S G P I S G S * Q A G H G I F
 - L Q H Y A Q V Q S L G L D R Q D M A F S
 28381 - CACTACAGCATTAGTAGGTAGGTACCCACATGTAGTGGTCTCAATAACTAAATTTTC - 28440
 - H Y S I S R * V P T C S R S F N N * I F
 - T T A L V G R Y P H V V G P S I T K F S
 - L Q H * * V G T H M * * V L Q * L N F Q
 28441 - AGTGCCACAATGTTACAAAGTGGCTTTAGAAAGTCCGACGTCGCCATGAAACTTCATC - 28500
 - S A T M F T S G F Q K V A R L P * N F I
 - V P Q C S Q V A F R K S H V C H E T S S
 - C H N V H K W L S E S R T S A M K L H R
 28501 - GCAATGATTACATTTTCATCAAGGTAGACAAGTGCATATTGTTACTCCTGTGGAGATGC - 28560
 - A M I T F H Q G R Q V H I V T L L W R C
 - Q * L H F I K V D K C I L L H S C G D A
 - N D Y I S S R * T S A Y C Y T P V E M Q

FIG. 12 Con't

28561 - AACAGGGTACACAGAGCGTATACGCCCATGAAACCCTCAGTCTTTTCTTTTCAACAG - 28620
 - N R V H R A Y T P H E T L S L F L F N T
 - T G Y T E R I R P M K P S V F F F S T R
 - Q G T Q S V Y A P * N P Q S F S F Q H V
 28621 - TGGTTGAATGACTTTGACTTTTGAGTTAAGAGGAAACACAAACTTTGGGCATTCCCTTT - 28680
 - W L N D F D F * V K R K H K L W A F P F
 - G * M T L T F E L R G N T N F G H S P L
 - V E * L * L L S * E E T Q T L G I P L *
 28681 - GAAAGTGTCAAATTTCTTGGCACTCTTAATTTGGAAGGGTGTCTGGTGCTCGTAGCTCTT - 28740
 - E S V K F L G T L N F E G C L V L V A L
 - K V S N F L A L L I S K G V W C S * L L
 - K C Q I S W H S * F R R V S G A R S S Y
 28741 - ATCAGAGCGCTCAGTGAACCAGGCAATTTTCATGCTCATGGTCACGGCAGCAGTAGACAC - 28800
 - I R A L S E P G N F M L M V T A A V D T
 - S E R S V N Q A I S C S W S R Q Q * T P
 - Q S A Q * T R Q F H A H G H G S S R H L
 28801 - TCTCTTCGACTCGATGTAATCAAGTTGTTTCGGAAAGAGTGCACATTGACTTGCCCGCGG - 28860
 - S L R L D V I K L F G K S A H * L A R A
 - L F D S M * S S C S E R V H I D L P A R
 - S S T R C N Q V V R K E C T L T C P R V
 28861 - TGCAGAAAATCTTTGATGCAATCAAGAGGGTACCCATCTGGGCCACAGAAATTTGTGTC - 28920
 - C E K I F D A I K R V P I W A T E I V V
 - A R K S L M Q S R G Y P S G P Q K L L S
 - R E N L * C N Q E G T H L G H R N C C R
 28921 - GACATAGCGAGTGACTGCACCTCCATTGAGCTCAGGAGTTCACGGAGTGCACCACT - 28980
 - D I A S D C T S I E L T S E F T E C T T
 - T * R V T A P P L S S R V S S R S A P L
 - H S E * L H L H * A H E * V H G V H H C
 28981 - GCCATGCTTAGTGTCCAGTTTGTTCATAATCTTCAATGGGATCAGTGCCAAGCTCGTC - 29040
 - A M L S V P V L F I I F N G I S A K L V
 - P C L V F Q F C S * S S M G S V P S S S
 - H A * C S S F V H N L Q W D Q C Q A R H
 29041 - ACCTAAGTCATAAGACTTTAGATCGATGCCATAGCTATGACCACGGCTCCCTTATTACC - 29100
 - T * V I R L * I D A I A M T T G S L I T
 - P K S * D F R S M P * L * P P A P L L P
 - L S H K T L D R C H S Y D H R L P Y Y R
 29101 - GTTCTTACGAAGAAGCAATTCGCGGTATGCAATTTGGGGTTTCGCCACATGTGGCAGGAG - 29160
 - V L T K K N I A V C N W G F A H M W H E
 - F L R R R T L R Y A I G V S P T C G T S
 - S Y E E E H C G M Q L G F R P H V A R V
 29161 - TACTCCCAGTGTATACCGCTACGACCGTACTGAATGCCGTCCATTTCTGCAACCAGCTC - 29220
 - Y S Q C Y T A T T V L N A V H F C N Q L
 - T P S V I P L R P Y * M P S I S A T S S
 - L P V L Y R Y D R T E C R P F L Q P A Q
 29221 - AACGACCTTGTGGCCGTGATGGTGCCTTAAGGCATCAGAACGTTAATGAACACATAGGG - 29280
 - N D L V A V I G A * G I R T F N E H I G
 - T T L W P * L V L K A S E R L M N T * G
 - R P C G R D W C L R H Q N V * * T H R A
 29281 - CTGTTCAAGCTGGGGCAGTACGCCTTTTCCAGCTCTACTAGACCACAAGTGCCATTTTT - 29340
 - L F K L G Q Y A F F Q L Y * T T S A I F
 - C S S W G S T P F S S S T R P Q V P F L
 - V Q A G A V R L F P A L L D H K C H F *
 29341 - GAGGTGTTACGTCCTCCGATAGGGCTCTTCCACAGAGTCCCGAAGCCACGCACTAG - 29400
 - E V F T C L R * G L F H R V P E A T H *
 - R C S R A S D R A S S T E S P K P R T S
 - G V H V P P I G P L P Q S P R S H A L A

FIG. 12 Con't

29401 - CACGTCTTAACCTGAAGGACAGGCAAACCTGAGTTGGACGTGTGTTTTCTCGTTGACACC - 29460
- H V S N L K D R Q T E L D V C F L V D T
- T S L T * R T G K L S W T C V F S L T P
- R L * P E G Q A N * V G R V F S R * H Q
29461 - AAGAACAAGGCTCTCCATCTTACCTTTCGGTCACACCCGGACGAAACCTAGGTATGCTGA - 29520
- K N K A L H L T F R S H P D E T * V C *
- R T R L S I L P F G H T R T K P R Y A D
- E Q G S P S Y L S V T P G R N L G M L M
29521 - TGATCGACTGCAACACGGACGAAACCGTAAGCAGTCTGCAGAAGAGGGACGAGTTACTCG - 29580
- * S T A T R T K P * A V C R R G T S Y S
- D R L Q H G R N R K Q S A E E G R V T R
- I D C N T D E T V S S L Q K R D E L L V
29581 - TTTCTTGCAACGACAGTAAAATTTATTATTGTTTATACTGCGTAGGTGCACTAGGCATG - 29640
- F L V N D S K I Y Y C L Y C V G A L G M
- F L S T T V K F I I V Y T A * V H * A C
- S C Q R Q * N L L L F I L R R C T R H A
29641 - CAGCCGAGCGACAGCTACACAGATTTTAAAGTTCGTTTAGAGAACAGATCTACAAGAGAT - 29700
- Q P S D S Y T D F K V R L E N R S T R D
- S R A T A T Q I L K F V * R T D L Q E I
- A E R Q L H R F * S S F R E Q I Y K R S
29701 - CGAGGTTGGTTGGCTTTTCCTGGGTAGGTAAAAACCTAATAT - 29742
- R G W L A F P G * V K T * Y X
- E V G W L F L G R * K P N X
- R L V G F S W V G K N L I X

FIG. 12 Con't

N-gene primers (nucleotide position 29247-29410)

150# (5'-gactgatgaagctcaggcctt-3')

200# (5'-cttgtgtggatcatcatgagtg-3')

S-gene primers (nucleotide position 24751-25049)

131# (5'-cacagaggaacttctttt-3')

132# (5'-tcccaattcttgaaggtcaatgag-3')

FIG. 13

ATGTCTGATAATGGACCCCAATCAAACCAACGTAGTGCCCCCGCATTACATTTGGTGGAC
CCCACAGATTCAACTGACAATAACCAGAATGGAGGACGCAATGGGGCAAGGCCAAAACAG
CGCCGACCCCAAGGTTTACCCAATAATACTGCGTCTTGGTTCACAGCTCTCACTCAGCAT
GGCAAGGAGGAAGTTAGATTCCCTCGAGGCCAGGGCGTTCCAATCAACACCAATAGTGGT
CCAGATGACCAATTGGCTACTACCGAAGAGCTACCCGACGAGTTCGTGGTGGTGACGGC
AAAATGAAAGAGCTCAGCCCCAGATGGTACTTCTATTACCTAGGAACTGGCCCAGAAGCT
TCACTTCCCTACGGCGCTAACAAAGAAGGCATCGTATGGGTTGCAACTGAGGGAGCCTTG
AATACACCCAAAGACCACATTGGCACCCGCAATCCTAATAACAATGCTGCCACCGTGCTA
CAACTTCCTCAAGGAACAACATTGCCAAAAGGCTTCTACGCAGAGGGAAGCAGAGGCGGC
AGTCAAGCCTCTTCTCGCTCCTCATCACGTAGTCGCGGTAATTCAAGAAATTCAACTCCT
GGCAGCAGTAGGGGAAATTCTCCTGCTCGAATGGCTAGCGGAGGTGGTGAAACTGCCCTC
GCGCTATTGCTGCTAGACAGATTGAACCAGCTTGAGAGCAAAGTTTCTGGTAAAGGCCAA
CAACAACAAGGCCAAACTGTCACTAAGAAATCTGCTGCTGAGGCATCTAAAAAGCCTCGC
CAAAAACGTACTGCCACAAAACAGTACAACGTCACTCAAGCATTGGGAGACGTGGTCCA
GAACAAACCCAAGGAAATTTCCGGGGACCAAGACCTAATCAGACAAGGAACTGATTACAAA
CATTGGCCGCAAATTGCACAATTTGCTCCAAGTGCCTCTGCATTCTTTGGAATGTCACGC
ATTGGCATGGAAGTCACACCTTCGGGAACATGGCTGACTTATCATGGAGCCATTAATTG
GATGACAAAGATCCACAATTCAAAGACAACGTACTGCTGAACAAGCACATTGACGCA
TACAAAACATTCCCACCAACAGAGCCTAAAAAGGACAAAAAGAAAAGACTGATGAAGCT
CAGCCTTTGCCGAGAGACAAAAGAAGCAGCCACTGTGACTCTTCTCCTGCGGCTGAC
ATGGATGATTTCTCCAGACAACCTTCAAATTCATGAGTGGAGCTTCTGCTGATTCAACT
CAGGCATAA

FIG. 14A

MSDNGPQSNQRSAPRITFGGPTDSTDNNQNGGRNGARPKQRRPQGLPNNTASWFTALTQH
GKEELRFPRGQGVPIINTNSGPDDQIGYYRRATRRVRGGDGKMKELSPRWYFYLLGTGPEA
SLPYGANKEGIVVATEGALNTPKDHIGTRNPNNNAATVLQLPQGTTLPKGFYAEGSRGG
SQASSRSSSRSGNSRNSTPGSSRGNSPARMASGGGETALALLLLDRLNQLESKVSQKQ
QQQQTVTKKSAAEASKKPRQKRTATKQYNVTQAFGRRGPEQTQGNFGDQDLIRQGTDYK
HWPQIAQFAPSASAFFGMSRIGMEVTPSGTWLTYHGAIKLDDKDPQFKDNVILLNKHIDA
YKTFPPTPEPKKDKKKKTDEAQPLPQRQKQPTVTLTPAADMDDFSRQLQNSMSGASADST
QA

FIG. 14B

ATGTTTATTTCTTATTATTTCTTACTCTCACTAGTGGTAGTGACCTTGACCGGTGCACCACCTT
TGATGATGTTCAAGCTCCTAATTACACTCAACATACTTCATCTATGAGGGGGTTTACTATCCTG
ATGAAATTTTAGATCAGACACTCTTTATTTAACTCAGGATTTATTTCTTCCATTTTATTCTAAT
GTTACAGGGTTTCATACTATTAATCATACTGTTTGGCAACCCTGTCATACCTTTTAAGGATGGTAT
TTATTTTGCTGCCACAGAGAAATCAAATGTTGTCCGTGGTTGGGTTTTTGGTTCTACCATGAACA
ACAAGTCACAGTCGGTGATTATTATTAACAATTCTACTAATGTTGTTATACGAGCATGTAACCTT
GAATTGTGTGACAACCCCTTTCTTTGCTGTTTCTAAACCCATGGGTACACAGACACATACTATGAT
ATTCGATAATGCATTTAATTGCACCTTCGAGTACATATCTGATGCCTTTTCGCTTGATGTTTCAG
AAAAGTCAGGTAATTTTAAACACTTACGAGAGTTTGTGTTTAAAAATAAAGATGGGTTTTCTCTAT
GTTTATAAGGGCTATCAACCTATAGATGTAGTTCGTGATCTACCTTCTGGTTTTAACACTTTGAA
ACCTATTTTAAAGTTGCCTCTTGGTATTAACATTACAAATTTTAGAGCCATTCTTACAGCCTTTT
CACCTGCTCAAGACATTTGGGGCACGTCAGCTGCAGCCTATTTTGTGGCTATTTAAAGCCAACT
ACATTTATGCTCAAGTATGATGAAAATGGTACAATCACAGATGCTGTTGATTGTTCTCAAATCC
ACTTGCTGAACTCAAATGCTCTGTTAAGAGCTTTGAGATTGACAAAGGAATTTACCAGACCTCTA
ATTTACAGGGTTGTTCCCTCAGGAGATGTTGTGAGATTCCTAATATTACAAACTTGTGTCCTTTT
GGAGAGGTTTTTAAATGCTACTAAATTCCTTCTGTCTATGCATGGGAGAGAAAAAATTTCTAA
TTGTGTTGCTGATTACTCTGTGCTCTACAACCTCAACATTTTTTTCAACCTTTAAGTGTATGGCG
TTTCTGCCACTAAGTTGAATGATCTTTGCTTCTCCAATGTCTATGCAGATTCTTTTGTAGTCAAG
GGAGATGATGTAAGACAAATAGCGCCAGGACAACTGGTGTATTGCTGATTATAATTATAAATT
GCCAGATGATTTTCATGGGTTGTGTCCTTGCTTGAATACTAGGAACATTGATGCTACTTCAACTG
GTAATTATAATTATAAATATAGGTATCTTAGACATGGCAAGCTTAGGCCCTTTGAGAGAGACATA
TCTAATGTGCCTTTCTCCCCTGATGGCAAACCTTGCAACCCACCTGCTCTTAATTGTTATTGGCC
ATTAATGATTATGGTTTTTACACCACTACTGGCATTGGCTACCAACCTTACAGAGTTGTAGTAC
TTTCTTTTGAACCTTTTAAATGCACCGGCCACGGTTTGTGGACCAAATTTACTGACCTTATT
AAGAACCAGTGTGCAATTTTAAATTTAATGGACTCACTGGTACTGGTGTGTTAACTCCTTCTTC
AAAGAGATTTCAACCATTTCAACAATTTGGCCGTGATGTTTCTGATTTCACTGATTCCGTTTCGAG
ATCCTAAAACATCTGAAATATTAGACATTTACCTTGCTCTTTTGGGGGTGTAAGTGTAAATTACA
CCTGGAACAAATGCTTCATCTGAAGTTGCTGTTCTATATCAAGATGTAACTGCACTGATGTTTC
TACAGCAATTCATGCAGATCAACTCACACCAGCTTGGCGCATATATTCTACTGGAACAATGTAT

FIG. 15A

TCCAGACTCAAGCAGGCTGTCTTATAGGAGCTGAGCATGTCGACACTTCTTATGAGTGCGACATT
CCTATTGGAGCTGGCATTGTGTAGTTACCATACAGTTTCTTTATTACGTAGTACTAGCCAAA
ATCTATTGTGGCTTATACTATGTCTTTAGGTGCTGATAGTTCAATTGCTTACTCTAATAACACCA
TTGCTATACTACTAACTTTTCAATTAGCATTACTACAGAAGTAATGCCTGTTTCTATGGCTAAA
ACCTCCGTAGATTGTAATATGTACATCTGCGGAGATTCTACTGAATGTGCTAATTTGCTTCTCCA
ATATGGTAGCTTTTGCACACAATAATCGTGCACCTCTCAGGTATTGCTGCTGAACAGGATCGCA
ACACACGTGAAGTGTTGCTCAAGTCAAACAAATGTACAAAACCCCAACTTTGAAATATTTTGGT
GGTTTTAATTTTTCACAAATATTACCTGACCCTCTAAAGCCAACTAAGAGGTCTTTTTATTGAGGA
CTTGCTCTTTAATAAGGTGACACTCGCTGATGCTGGCTTCATGAAGCAATATGGCGAATGCCTAG
GTGATATTAATGCTAGAGATCTCATTGTGCGCAGAAGTTCAATGGACTTACAGTGTTGCCACCT
CTGCTCACTGATGATATGATTGCTGCCTACACTGCTGCTCTAGTTAGTGGTACTGCCACTGCTGG
ATGGACATTTGGTGCTGGCGCTGCTCTTCAAATACCTTTTGCTATGCAAATGGCATATAGGTTCA
ATGGCATTGGAGTTACCCAAAATGTTCTCTATGAGAACCAAAAACAAATCGCCAACCAATTTAAC
AAGGCGATTAGTCAAATTCAGAATCACTTACAACAACATCAACTGCATTGGGCAAGCTGCAAGA
CGTTGTTAACCAGAATGCTCAAGCATTAAACACACTTGTTAAACAACCTTAGCTCTAATTTTGGTG
CAATTTCAAGTGCTAAATGATATCCTTTGCGGACTTGATAAAGTCGAGGCGGAGGTACAAATT
GACAGGTTAATTACAGGCAGACTTCAAAGCCTTCAAACCTATGTAACACAACAACCTAATCAGGGC
TGCTGAAATCAGGGCTTCTGCTAATCTTGCTGCTACTAAAATGTCTGAGTGTGTTCTTGGACAAT
CAAAAAGAGTTGACTTTTGTGGAAAGGGCTACCACCTTATGTCCTTCCCACAAGCAGCCCCGCAT
GGTGTGCTTCTTACATGTACGTATGTGCCATCCCAGGAGAGGAACTTACCACAGCGCCAGC
AATTTGTCATGAAGGCAAAGCATACTTCCCTCGTGAAGGTGTTTTTGTGTTAATGGCACTTCTT
GGTTTATTACACAGAGGAACTTCTTTTCTCCACAAATAATTACTACAGACAATACATTTGTCTCA
GGAAATGTGATGTCGTTATTGGCATCATTAAACAACACAGTTTATGATCCTCTGCAACCTGAGCT
TGACTCATTCAAAGAAGAGCTGGACAAGTACTTCAAAAATCATAACATCACCAGATGTTGATCTTG
GCGACATTTCAGGCATTAACGCTTCTGTGCTCAACATTCAAAAGAAATGACCGCCTCAATGAG
GTCGCTAAAAATTTAAATGAATCACTCATTGACCTTCAAGAAATGGGAAAATATGAGCAATATAT
TAAATGGCCTTGGTATGTTTGGCTCGGCTTCAATTGCTGGACTAATGCCATCGTCATGGTTACAA
TCTTGCTTTGTTGCATGACTAGTTGTTGCAGTTGCCCAAGGGTGCATGCTCTTGTGGTTCTTGC
TGCAAGTTTGATGAGGATGACTCTGAGCCAGTTCTCAAGGGTGTCAAATTACATTACACATAA

FIG. 15A Con't

MFIFLLFLTLTSGSDLDRCTTFDDVQAPNYTQHTSSMRGVVYPDEIFRSDTLYLTQDLFL
PFYSNVTGFHTINHTFGNPVIPPFDGIYFAATEKSNVVRGWVFGSTMNKSQSVIIINNS
TNVVIRACNFELCDNPPFAVSKPMGTQHTMI FDNAFNCTFEYISDAFSLDVSEKSGNFK
HLREFVFKNKDGFYVYKGYQPIDVVRDLPSGFNTLKPIFKLPLGINITNFRAILTAFSP
AQDIWGTSAAYFVGYLKPTTFMLKYDENGITDAVDCSQNPLAELKCSVKSEIDKGIY
QTSNFRVVPDGDVVRFPNITNLCPFGEVFNATKFPVYAWERKKISNCVADYSVLYNSTF
FSTFKCYGVSATKLNLDLCSNVYADSFVVKGDDVRQIAPGQTGVIADYNYKLPDDFMGCV
LAWNTRNIDATSTGNVNYKYRYLRHGKLRPFERDISNVFSPDGKPCPPALNCYWPLND
YGFYTTTGIGYQPYRVVLSFELLNAPATVCGPKLSTDLIKNQCVNFNFNGLTGTGVLTP
SSKRFQPFQFGRDVSDFDTSVRDPKTSEILDISPSCSFGGVSVITPGTNASSEVAVLYQD
VNCTDVSTAIHADQLTPAWRIYSTGNVVFQTQAGCLIGAHEVDTSYECDIPIGAGICASY
HTVSLLRSTSQKSIVAYTMSLGADSSIAYSNTTIAIPTNFSISITTEVMPVSMAKTSVDC
NMYICGDSTECANLLLQYGSFCTQLNRALSGIAAEQDRNTREVFAQVKQMYKTPTLKYFG
GFNFSQILPDPLKPTKRSFIEDLLFNKVTLADAGFMKQYGECLGDINARDLICAQKFNGL
TVLPPLLTDDMIAAYTAALVSGTATAGWTFGAGAALQIPFAMQMAYRFNGIGVTQNVLYE
NQKQIANQFNKAISQIQESLTTTSTALGKLQDVVNQNAQALNTLVKQLSSNFGAISSVLN
DILSRDKVEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSK
RVDFCGKGYHLMSFPQAAPHGVVFLHVTVVPSQERNFTTAPAICHEGKAYFPREGVFEVN
GTSWFITQRNFFSPQIITTDNTFVSGNCDVVIGIINNTVYDPLQPELDSFKEELDKYFKN
HTSPDVLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYVWL
GFIAGLIAIVMVTILLCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT

FIG. 15B

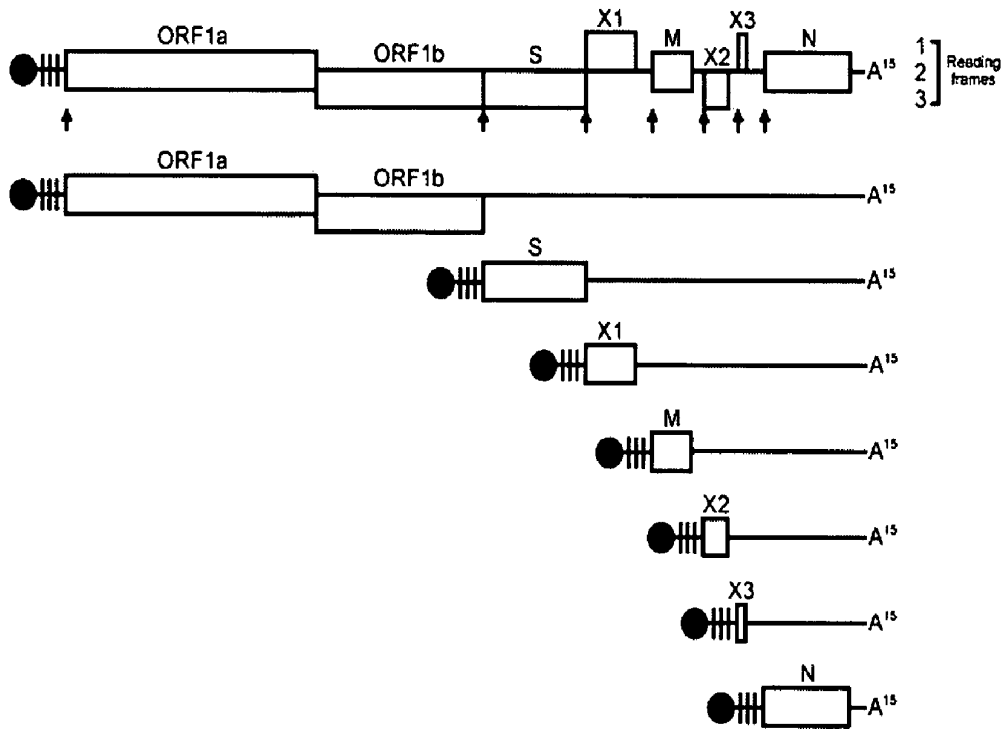


FIG. 16

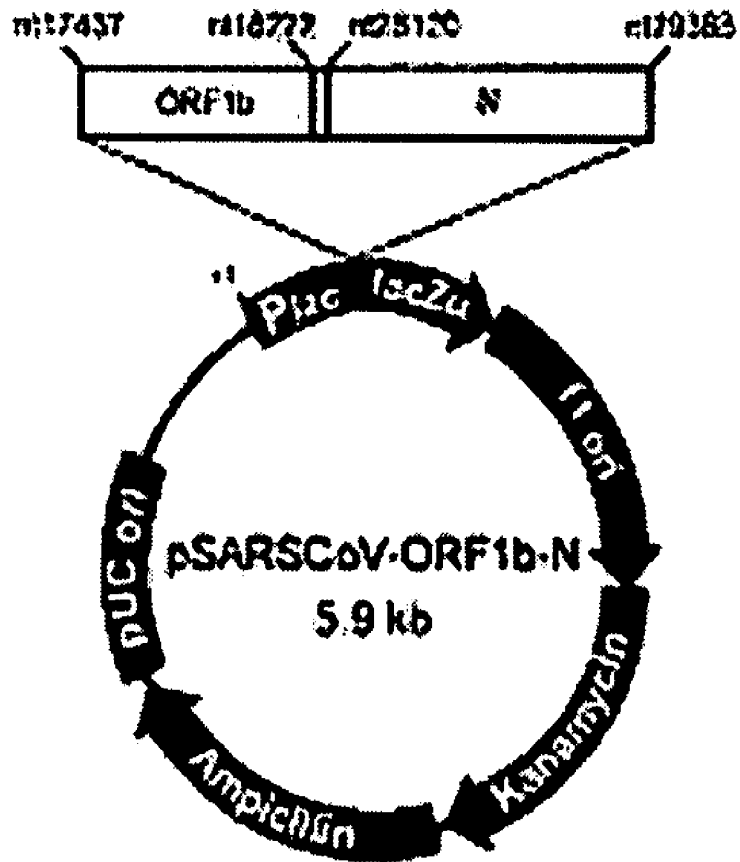


FIG. 17

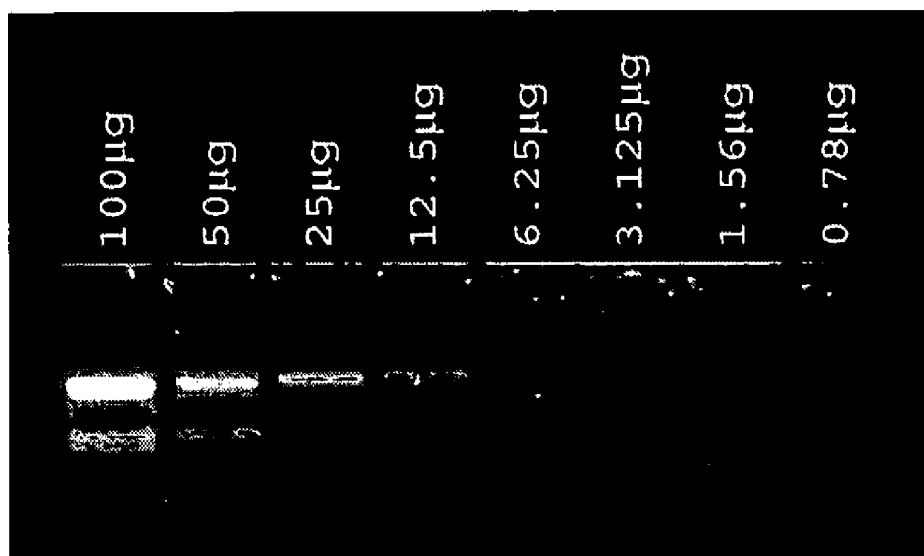


FIG. 18

	-ve control	+ve control	No EIOH Precipitation			After EIOH Precipitation			
			1.0x10e4	2.5x10e4	5.0x10e4	1.0x10e4	2.5x10e4	5.0x10e4	
11									




FIG. 19

- Primers for a 225-bp fragment of the region of N-gene that showed no homology to other coronavirus:

SRS251: 5'-GCAGTCAAGCCTCTTCTCG-3' (SEQ ID NO:2480)

SRS252: 5'-GCCTCAGCAGCAGATTTC-3' (SEQ ID NO:2481)

- Primers for 181-bp fragment of the region of 1b-gene:

coro3: 5'-TACACACCTCAGCGTTG-3' (SEQ ID NO:3)

coro4: 5'-CACGAACGTGACGAAT-3' (SEQ ID NO:4)

- Primers for a 745-bp fragment from pig β -actin gene:

Actin-F: 5'-TGAGACCTTCAACACGCC-3' (SEQ ID NO:2482)

Actin-R: 5'-ATCTGCTGGAAGGTGGAC-3' (SEQ ID NO:2483)

FIG. 20

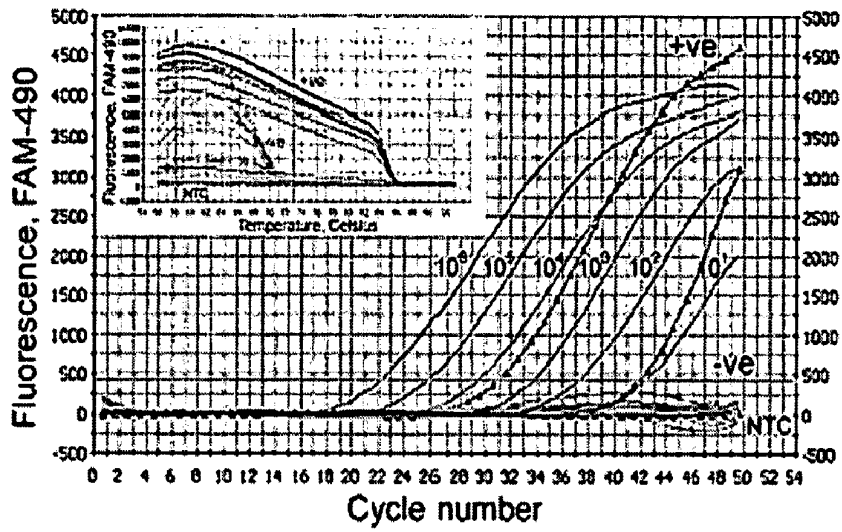


FIG. 21A

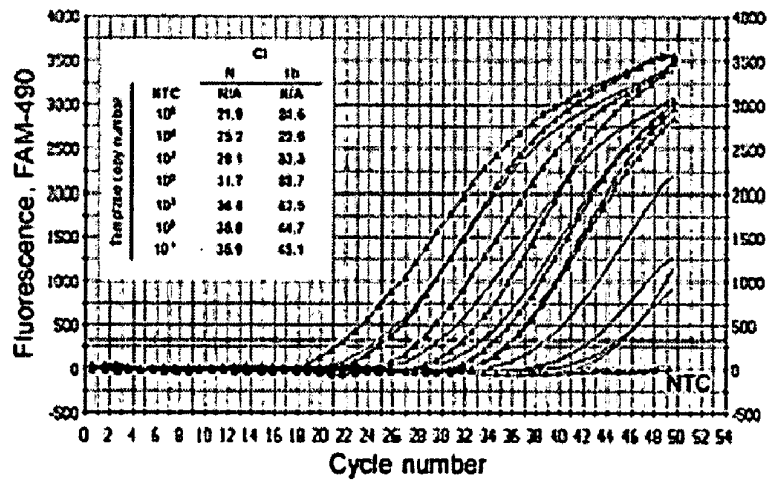


FIG. 21B

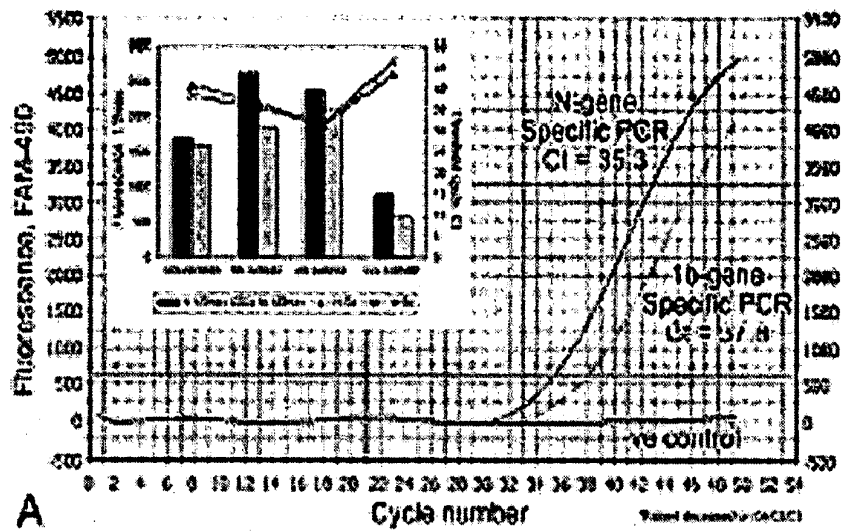


FIG. 22A

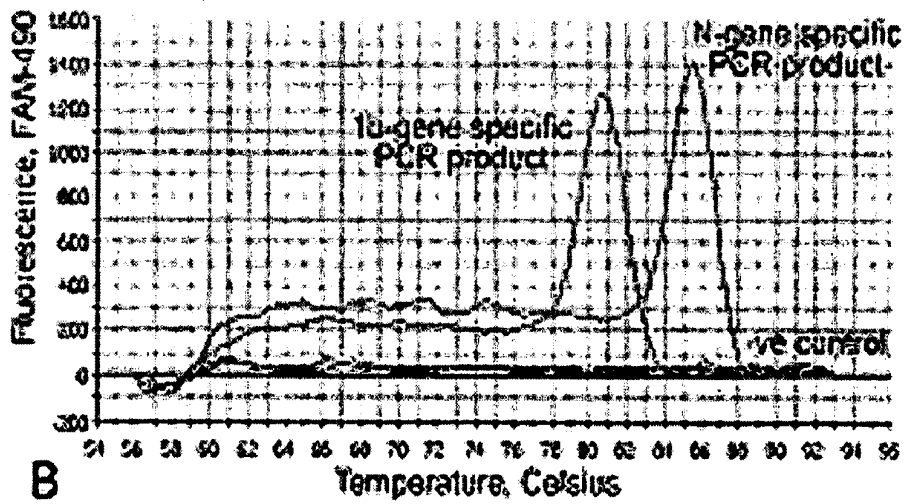


FIG. 22B

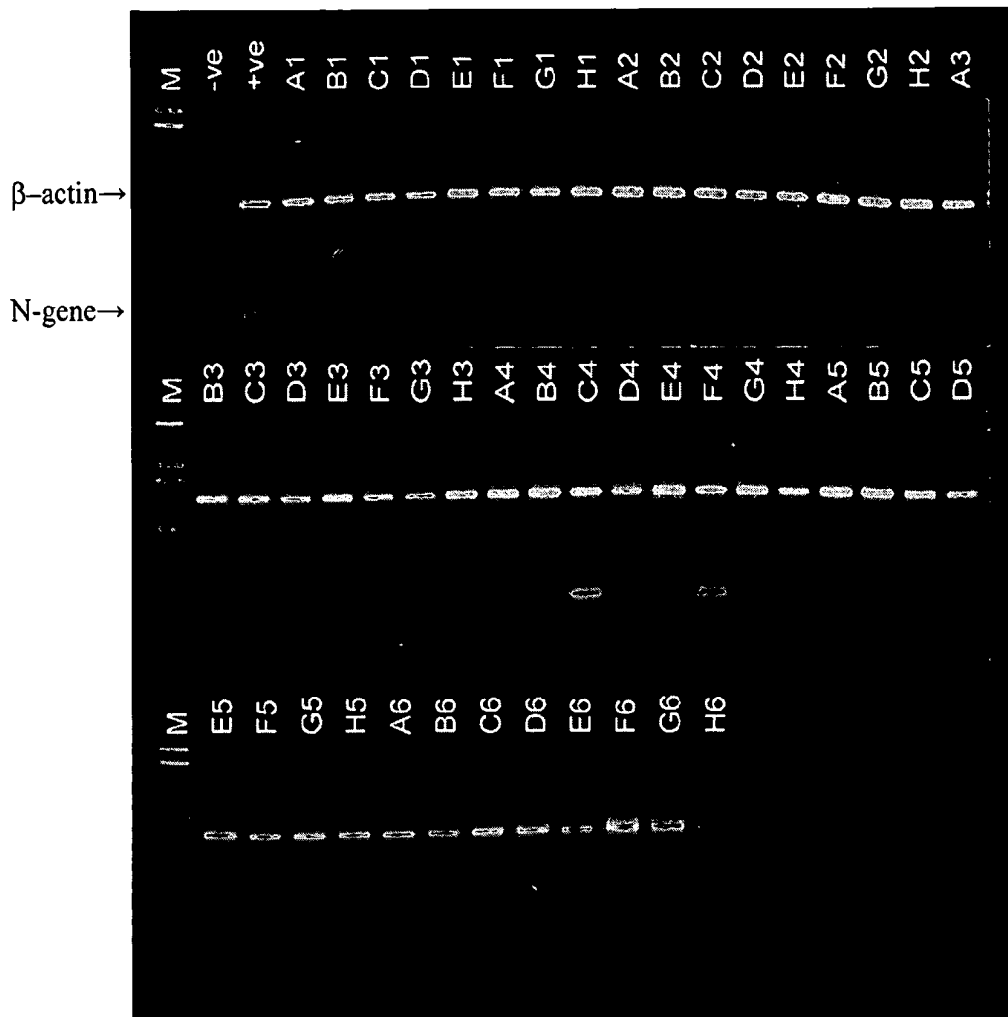


FIG. 23

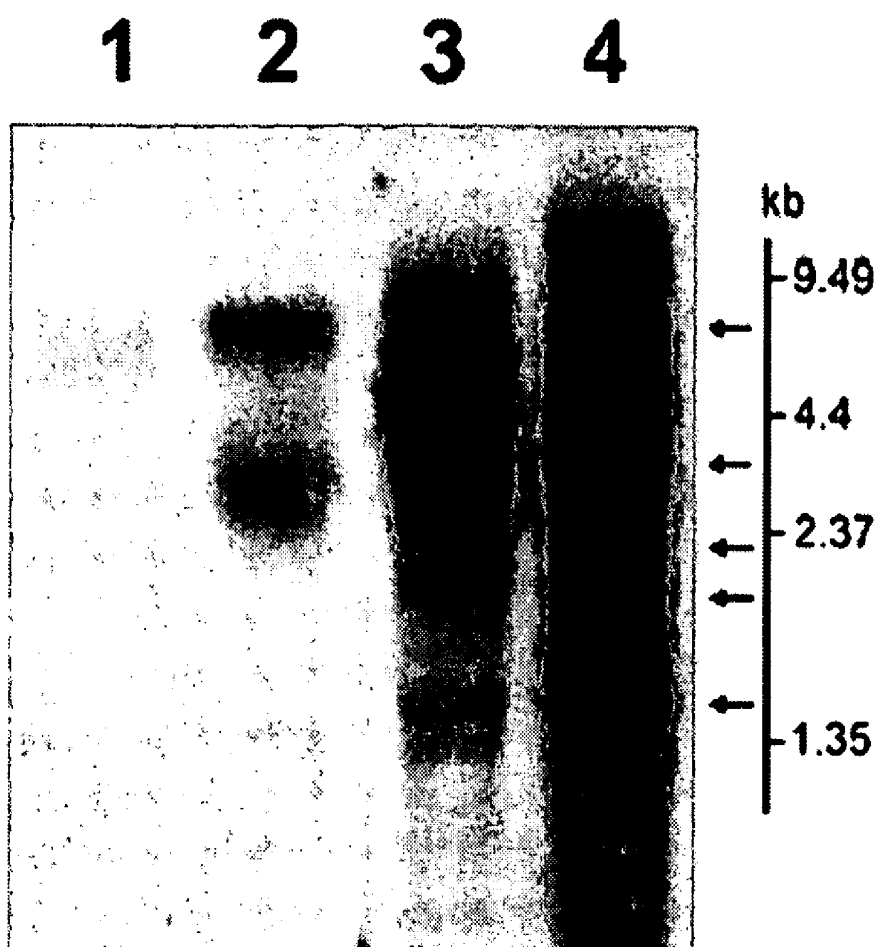


FIG. 24

<u>Probe</u>	<u>Region</u>	<u>SEQ ID NO</u>	<u>Sequence</u>
1b	18057 – 18222	2484	gatataaaattcaagactgaaggattatgtggtgacataccaggcatacceaaggacat gacctaccgtagactcatctctatgatgggttcaaaatgaattaccaagtcaatggttac cctaatatgttatcaccgcgaagaagctattcgtcacggtcgtg
S	21920 – 22107	2485	catgggtacacagacacatactatgatattcgataatgcatttaattgcactttcgagtaca tatctgatgccttttcgcttgatgtttcagaaaagtcaggtaattttaaacacttacgagagt ttgtgttaaaaaataaagatgggttctctatgtttataagggtatcaacctatagatgtag
M	26867 – 26996	2486	gctgtgacattaaggacctgccaaaagagatcactgtggctacatcacgaacgctttctt attacaaattaggagcgtcgcagcgtgtaggcactgattcaggttttgctgcatacaacc gctaccgtat
N	28658 – 28883	2487	gcagtcaagcctcttctcgctcctcatcacgtagtcgcggttaattcaagaaattcaactc ctggcagcagtaggggaaattctctgctcgaatggctagcggaggtggtgaaactgc cctcgcgctattgctgctagacagattg

FIG. 25

HIGH-THROUGHPUT DIAGNOSTIC ASSAY FOR THE HUMAN VIRUS CAUSING SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

[0001] This application claims priority benefit to U.S. provisional application No. 60/457,031, filed Mar. 24, 2003; U.S. provisional application No. 60/457,730, filed Mar. 26, 2003; U.S. provisional application No. 60/459,931, filed Apr. 2, 2003; U.S. provisional application No. 60/460,357, filed Apr. 3, 2003; U.S. provisional application No. 60/461,265, filed Apr. 8, 2003; U.S. provisional application No. 60/462,805, filed Apr. 14, 2003; U.S. provisional application No. 60/464,886 filed Apr. 23, 2003, U.S. provisional application No. 60/465,738, filed Apr. 25, 2003; and U.S. provisional application No. 60/470,935, filed May 14, 2003, each of which is incorporated herein by reference in its entirety.

[0002] The instant application contains a lengthy Sequence listing which is being concurrently submitted via triplicate CD-R in lieu of a printed paper copy, and is hereby incorporated by reference in its entirety. Said CD-R, recorded on Mar. 22, 2004, are labeled "CRF", "Copy 1" and "Copy 2", respectively, and each contains only identical 1.6 MB file (V9661077.APP).

1. INTRODUCTION

[0003] The present invention relates to a high-throughput diagnostic assay for the virus causing Severe Acute Respiratory Syndrome (SARS) in humans ("hSARS virus"). In particular, the invention relates to a high-throughput reverse transcription-PCR diagnostic test for SARS associated *coronavirus* (SARS-CoV). The present assay is a rapid, reliable assay which may be used for diagnosis and monitoring the spread of SARS. The present method eliminates false negative results and provides increased sensitivity for the assay. The invention further relates to nucleotide sequences and portions thereof, useful for the diagnosis of SARS. The invention further relates to nucleotide sequences and portions thereof, useful for assessing genetic diversity of SARS. The nucleotide sequences of the present invention comprise the (Nucleocapsid) N-gene and the S-gene sequences of the hSARS virus. The invention relates to a diagnostic kit that comprises nucleic acid molecules for the detection of the N-gene or S-gene of hSARS virus. The invention also relates to the deduced amino acid sequences of the N-gene and S-gene products of the hSARS virus. The invention further relates to the use of the N-gene and S-gene products in diagnostic methods. The invention further encompasses diagnostic assays and kits comprising antibodies generated against the N-gene or S-gene product.

2. BACKGROUND OF THE INVENTION

[0004] Recently, there has been an outbreak of atypical pneumonia in Guangdong province in mainland China. Between November 2002 and March 2003, there were 792 reported cases with 31 fatalities (WHO. Severe Acute Respiratory Syndrome (SARS) *Weekly Epidemiol Rec.* 2003; 78: 86). Patients with SARS show various clinical symptoms, including fever (of 38 degrees Celsius or above for over 24 hours), malaise, chills, headache and body ache. Chest X-rays show changes compatible with pneumonia. Other symptoms include coughing, shortness of breath or difficulty in breathing. By 3 May 2003, a cumulative total number of 1621 cases and 179 deaths had been occurred in

Hong Kong, which contributed to 26% and 41% of the global reported cases (6234) and deaths (435) respectively. As the disease is highly contagious and spreads in daily-life activities, it is important to develop a rapid and reliable diagnosis test to monitor and control the disease. In response to this crisis, the Hospital Authority in Hong Kong has increased the surveillance on patients with severe atypical pneumonia. In the course of this investigation, a number of clusters of health care workers with the disease were identified. In addition, there were clusters of pneumonia incidents among persons in close contact with those infected. The disease was unusual in its severity and its progression in spite of the antibiotic treatment typical for the bacterial pathogens that are known to be commonly associated with atypical pneumonia. The present inventors were one of the groups involved in the investigation of these patients. All tests for identifying commonly recognized viruses and bacteria were negative in these patients. Furthermore, diagnostic tests for the detection of other genes in the hSARS virus, such as the 1b-gene are not useful to accurately diagnose SARS. The disease was given the acronym Severe Acute Respiratory Syndrome ("SARS"). This virus mutates and changes rapidly and hence the diagnostic of SARS was extremely difficult until the isolation of particular regions of the virus, the N-gene and S-gene, of the hSARS virus from the SARS patients by the present inventors as disclosed herein. Namely, the present invention discloses a diagnostic assay using particular regions in the genome of the virus for rapid, accurate, reliable and specific identification of the hSARS virus. The invention is useful in both clinical and scientific research applications. Furthermore, the present invention provides a high-throughput assay which can be used as a sensitive method for diagnosis and monitoring the spread of the SARS.

3. SUMMARY OF INVENTION

[0005] The present invention is based upon the inventors' identification of a specific region of the hSARS virus, specifically, the 3' region of the hSARS viral genome, and in particular, the (nucleocapsid) N-gene of the hSARS virus that may be used in diagnostic assay to detect hSARS. In particular, the N-gene is useful for the diagnosis of SARS because the N-gene has the most abundant copy number during viral infection compared to any other gene in the hSARS virus, especially when the cells are lysed. Thus, the nucleic acid sequences of the N-gene of the hSARS virus are particularly useful in a rapid and reliable diagnostic assay for the hSARS virus. Furthermore, the present method eliminates false negative results and increases the sensitivity of the assay.

[0006] The hSARS virus was isolated from patients suffering from SARS in the recent outbreak of severe atypical pneumonia in China. The isolated virus is an enveloped, single-stranded RNA virus of positive polarity which belongs to the order, Nidovirales, of the family, Coronaviridae. The hSARS virus is a very large RNA virus consisting of approximately 29,742 nucleotides. The complete genomic sequence of the hSARS virus was deposited in Genbank, NCBI with Accession No: AY278491 (SEQ ID NO:15), which is incorporated by reference. The isolated hSARS virus was deposited with China Center for Type Culture Collection (CCTCC) on Apr. 2, 2003 and accorded an accession number, CCTCC-V200303, as described in Section 7, *infra*, which is incorporated by reference. Also,

the entire genome sequence of the hSARS virus, CCTCC-V200303, and characterization thereof are disclosed in a United States patent application with Attorney Docket No. V9661.0069 filed concurrently herewith on Mar. 24, 2004, which is incorporated by reference in its entirety. The virus mutates and changes rapidly and hence making the diagnostic of SARS very difficult. The present inventors have designed a diagnostic assay for detecting the presence of N-gene nucleic acid sequence or protein to rapidly, accurately, and specifically identify the hSARS virus. Furthermore, the present inventors have designed a diagnostic assay for detecting the presence of S-gene nucleic acid sequence or protein to determine the genetic diversity of the hSARS virus. Accordingly, the invention relates to methods of detecting nucleotide sequences of the N-gene and S-gene of the hSARS virus.

[0007] The present invention provides a rapid, reliable assay for the detection of hSARS virus. In preferred embodiment, the detection of hSARS virus includes the use of the nucleic acid molecules of the present invention in a polymerase chain reaction, Reverse transcription-Polymerase Chain Reaction (RT-PCR), Southern analysis, Northern analysis, or other nucleic acid hybridization for the detection of hSARS nucleic acids. In one embodiment, the invention provides methods for detecting the presence, activity or expression of the hSARS virus of the invention in a biological material, such as cells, nasopharyngeal aspirate, sputum, blood, saliva, urine, stool and so forth. In preferred embodiments, the biological material is nasopharyngeal aspirate or stool. The increased or decreased activity or expression of the hSARS virus in a sample relative to a control sample can be determined by contacting the biological material with an agent which can detect directly or indirectly the presence, activity or expression of the hSARS virus. In a specific embodiment, the detecting agents are the nucleic acid molecules of the present invention.

[0008] The present invention also relates to a method for identifying a subject infected with the hSARS virus, said method comprising obtaining total RNA from a biological sample obtained from the subject; reverse transcribing the total RNA to obtain cDNA; and subjecting the cDNA to PCR assay using a set of primers derived from a nucleotide sequence of the hSARS. In preferred embodiments, the primers are derived from the (nucleocapid) N-gene. In most preferred embodiments, the primers comprise the nucleotide sequences of SEQ ID NOS:2475 and/or 2476 or SEQ ID NOS:2480 and/or 2481. In another preferred embodiments, the primers are derived from the (spike) S-gene. In more preferred embodiments, the primers comprise the nucleotide sequences of SEQ ID NOS:2477 and/or 2478.

[0009] The invention further relates to the use of the sequence information of the isolated virus for diagnostic and therapeutic methods. In a specific embodiment, the invention provides nucleic acid molecules which are suitable for use as primers consisting of or comprising the nucleotide sequence of SEQ ID NO:1, 11, 13, 15, 2471, or 2473, or a complement thereof, or at least a portion of the nucleotide sequence thereof. In the most preferred embodiment, the primers comprise the nucleic acid sequence of SEQ ID NOS:2475 and/or 2476 or SEQ ID NOS:2480 and/or 2481 for the detection of N-gene. In another most preferred embodiment, the primers comprise the nucleic acid sequence of SEQ ID NO:2477 and/or 2478 for the detection

of S-gene. In another specific embodiment, the invention provides nucleic acid molecules which are suitable for hybridization to hSARS nucleic acid, including, but not limited to, as PCR primers, Reverse Transcriptase primers, probes for Southern analysis or other nucleic acid hybridization analysis for the detection of hSARS nucleic acids, e.g., consisting of or comprising the nucleotide sequence of SEQ ID NO:1, 11, 13, 15, 2471, 2473, 2475, 2476, 2477, 2478, 2480 or 2481, or a complement thereof, or a portion thereof. In a preferred embodiment, primers that amplify fragments comprising (nucleotide position 18057 to 18222 or portions thereof of SEQ ID NO:15) 1b gene; (nucleotide position 21920-22107, or portions thereof of SEQ ID NO:15) M-gene; and (nucleotide position 28658-28883, or portions thereof of SEQ ID NO:15) N-gene may be used for probe synthesis for detection of hSARS nucleic acids. In a specific embodiment, the invention provides a diagnostic kit comprising nucleic acid molecules which are suitable for use to detect the N-gene of hSARS. In a specific embodiment, the N-gene comprises nucleic acid sequence of SEQ ID NO: 2471. In specific embodiment, the nucleic acid molecules comprise nucleic acid sequence of SEQ ID NOS:2475 and/or 2476 or SEQ ID NOS:2480 and/or 2481. In preferred embodiments, the diagnostic kit further comprises a control for amplification of 1b gene. In specific embodiments, the primers used for amplifying 1 b gene are SEQ ID NOS:3 and/or 4. In another specific embodiments, the diagnostic kit further comprises an internal control using pig β -actin gene. In specific embodiments, the primers used for amplifying β -actin gene are SEQ ID NOS:2482 and/or 2483.

[0010] In a specific embodiment, the invention provides a diagnostic kit comprising nucleic acid molecules which are suitable for use to detect the S-gene of hSARS. In a specific embodiment, the S-gene comprises nucleic acid sequence of SEQ ID NO: 2473. In specific embodiment, the nucleic acid molecules comprise nucleic acid sequence of SEQ ID NOS: 2477 and/or 2478. The invention further encompasses chimeric or recombinant viruses encoded in whole or in part by said nucleotide sequences.

[0011] In another specific embodiment, the invention provides nucleic acid molecules comprising a nucleotide sequence of SEQ ID NO:1, 11, 13, 2471, and/or 2473. In a specific embodiment, the present invention provides isolated nucleic acid molecules comprising or, alternatively, consisting of the nucleotide sequence of SEQ ID NO:1, a complement thereof or a portion thereof, preferably at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:1, or a complement thereof. In another specific embodiment, the present invention provides isolated nucleic acid molecules comprising or, alternatively, consisting of the nucleotide sequence of SEQ ID NO:11, a complement thereof or a portion thereof, preferably at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1,000, 1,050, 1,100, 1,150, 1,200, or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:11, or a complement thereof. In yet another specific embodiment, the present invention provides isolated nucleic acid molecules comprising or, alternatively, consisting of the nucleotide sequence of SEQ ID NO:13, a complement thereof or a portion thereof, preferably at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, 650, 700, or more contiguous nucleotides of the

nucleotide sequence of SEQ ID NO:13, or a complement thereof. In another specific embodiment, the present invention provides isolated nucleic acid molecules comprising or, alternatively, consisting of the nucleotide sequence of SEQ ID NO:15, a complement thereof or a portion thereof, preferably at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1,000, 1,050, 1,100, 1,150, 1,200, 2,000, 3,000, 4,000, 5,000, 6,000, 7,000, 8,000, 9,000, 10,000, 11,000, 12,000, 13,000, 14,000, 15,000, 16,000, 17,000, 18,000, 19,000, 20,000, 21,000, 22,000, 23,000, 24,000, 25,000, 26,000, 27,000, 28,000, 29,000 or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:15, or a complement thereof. In another specific embodiment, the present invention provides isolated nucleic acid molecules comprising or, alternatively, consisting of the nucleotide sequence of SEQ ID NO:2471, a complement thereof or a portion thereof, preferably at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1,000, 1,050, 1,100, 1,150, 1,200 or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:2471, or a complement thereof. In another specific embodiment, the present invention provides isolated nucleic acid molecules comprising or, alternatively, consisting of the nucleotide sequence of SEQ ID NO:2473, a complement thereof or a portion thereof, preferably at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1,000, 1,050, 1,100, 1,150, 1,200, 2,000, 3,000, or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:2473, or a complement thereof. Furthermore, in another specific embodiment, the invention provides isolated nucleic acid molecules which hybridize under stringent conditions, as defined herein, to a nucleic acid molecule having the sequence of SEQ ID NO:1, 11, 13, 15, 2471, or 2473, or a complement thereof. In one embodiment, the invention provides an isolated nucleic acid molecule which is antisense to the coding strand of a nucleic acid of the invention. In another specific embodiment, the invention provides isolated polypeptides or proteins that are encoded by a nucleic acid molecule comprising or, alternatively consisting of a nucleotide sequence that is at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:1, or a complement thereof. In yet another specific embodiment, the invention provides isolated polypeptides or proteins that are encoded by a nucleic acid molecule comprising or, alternatively consisting of a nucleotide sequence that is at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1,000, 1,050, 1,100, 1,150, 1,200 or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:11, or a complement thereof. In yet another specific embodiment, the invention provides isolated polypeptides or proteins that are encoded by a nucleic acid molecule comprising or, alternatively consisting of a nucleotide sequence that is at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, 650, 700, or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:13, or a complement thereof. In yet another specific embodiment, the invention provides isolated polypeptides or proteins that are encoded by a nucleic acid molecule comprising or, alternatively consisting of a nucleotide sequence that is at least 5,

10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1,000, 1,050, 1,100, 1,150, 1,200, 2,000, 3,000, 4,000, 5,000, 6,000, 7,000, 8,000, 9,000, 10,000, 11,000, 12,000, 13,000, 14,000, 15,000, 16,000, 17,000, 18,000, 19,000, 20,000, 21,000, 22,000, 23,000, 24,000, 25,000, 26,000, 27,000, 28,000, 29,000 or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:15, or a complement thereof. In yet another specific embodiment, the invention provides isolated polypeptides or proteins that are encoded by a nucleic acid molecule comprising or, alternatively consisting of a nucleotide sequence that is at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1,000, 1,050, 1,100, 1,150, 1,200 or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:2471, or a complement thereof. In yet another specific embodiment, the invention provides isolated polypeptides or proteins that are encoded by a nucleic acid molecule comprising or, alternatively consisting of a nucleotide sequence that is at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1,000, 1,050, 1,100, 1,150, 1,200, 2,000, 3,000, or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:2473, or a complement thereof. The invention further provides proteins or polypeptides that are isolated from the hSARS virus, including viral proteins isolated from cells infected with the virus but not present in comparable uninfected cells. The invention further provides proteins or polypeptides shown in FIGS. 11 (SEQ ID NOS:17-239, 241-736 and 738-1107) and 12 (SEQ ID NOS:1109-1589, 1591-1964 and 1966-2470). The invention further provides proteins or polypeptides having the amino acid sequence of SEQ ID NO:2472 or 2474. The polypeptides or the proteins of the present invention preferably have a biological activity of the protein (including antigenicity and/or immunogenicity) encoded by the sequence of SEQ ID NO:1, 11, 13, 2471, or 2473. In other embodiments, the polypeptides or the proteins of the present invention have a biological activity of the protein (including antigenicity and/or immunogenicity) encoded by a nucleotide sequence that is at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1,000, 1,050, 1,100, 1,150, 1,200, 2,000, 3,000, 4,000, 5,000, 6,000, 7,000, 8,000, 9,000, 10,000, 11,000, 12,000, 13,000, 14,000, 15,000, 16,000, 17,000, 18,000, 19,000, 20,000, 21,000, 22,000, 23,000, 24,000, 25,000, 26,000, 27,000, 28,000, 29,000 or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:15, or a complement thereof. In other embodiments, the polypeptides or the proteins of the present invention have a biological activity of the protein (including antigenicity and/or immunogenicity) of FIGS. 11 (SEQ ID NOS:17-239, 241-736 and 738-1107) and 12 (SEQ ID NOS:1109-1589, 1591-1964 and 1966-2470). The invention further provides proteins or polypeptides having a biological activity of the protein having amino acid sequence of SEQ ID NO: 2472 or 2474.

[0012] In one aspect, the invention provides a method for propagating the hSARS virus in host cells comprising infecting the host cells with the isolated hSARS virus, culturing the host cells to allow the virus to multiply, and harvesting the resulting virions. Also provided by the present invention are host cells that are infected with the hSARS virus.

[0013] In one aspect, the invention relates to the use of the isolated hSARS virus for diagnostic and therapeutic methods. In a specific embodiment, the invention provides a method of detecting in a biological sample an antibody immunospecific for the hSARS virus using the isolated hSARS virus or any proteins or polypeptides thereof. In another specific embodiment, the invention provides a method of screening for an antibody which immunospecifically binds and neutralizes hSARS. Such an antibody is useful for a passive immunization or immunotherapy of a subject infected with hSARS.

[0014] The invention further provides antibodies that specifically bind a polypeptide of the invention encoded by the nucleotide sequence of SEQ ID NO:1, 11, 13, 2471, or 2473, or a fragment thereof, or encoded by a nucleic acid comprising a nucleotide sequence that hybridizes under stringent conditions to the nucleotide sequence of SEQ ID NO:1, 11, 13, 2471, or 2473, and/or any hSARS epitope, having one or more biological activities of a polypeptide of the invention. The invention further provides antibodies that specifically bind polypeptides of the invention encoded by the nucleotide sequence of SEQ ID NO:15, or a fragment thereof. These polypeptides include those shown in FIGS. 11 (SEQ ID NOS:17-239, 241-736 and 738-1107) and 12 (SEQ ID NOS:1109-1589, 1591-1964 and 1966-2470). In another embodiment, the polypeptide comprises amino acid sequence of SEQ ID NO:2472, or 2474. The invention further provides antibodies that specifically bind polypeptides of the invention encoded by a nucleic acid comprising a nucleotide sequence that hybridizes under stringent conditions to the nucleotide sequence of SEQ ID NO:15, and/or any hSARS epitope, having one or more biological activities of a polypeptide of the invention. Such antibodies include, but are not limited to polyclonal, monoclonal, bi-specific, multi-specific, human, humanized, chimeric antibodies, single chain antibodies, Fab fragments, F(ab')₂ fragments, disulfide-linked Fvs, intrabodies and fragments containing either a VI or VH domain or even a complementary determining region (CDR) that specifically binds to a polypeptide of the invention.

[0015] In another embodiment, the invention provides vaccine preparations, comprising the hSARS virus, including recombinant and chimeric forms of said virus, or protein subunits of the virus. In a specific embodiment, the vaccine preparations of the present invention comprise live but attenuated hSARS virus with or without adjuvants. In another specific embodiment, the vaccine preparations of the invention comprise an inactivated or killed hSARS virus. Such attenuated or inactivated viruses may be prepared by a series of passages of the virus through the host cells or by preparing recombinant or chimeric forms of virus. Accordingly, the present invention further provides methods of preparing recombinant or chimeric forms of hSARS. In another specific invention, the vaccine preparations of the present invention comprise a nucleic acid or fragment of the hSARS virus, e.g., the virus having accession no. CCTCC-V200303, or nucleic acid molecules having the sequence of SEQ ID NO. 1, 11, 13, 15, 2471 or 2473, or a fragment thereof. In another embodiment, the invention provides vaccine preparations comprising one or more polypeptides isolated from or produced from nucleic acid of hSARS virus, for example, of deposit accession no. CCTCC-V200303. In a specific embodiment, the vaccine preparations comprise a polypeptide of the invention encoded by the nucleotide

sequence of SEQ ID NO:1, 11, 13, 2471 or 2473, or a fragment thereof. In a specific embodiment, the vaccine preparations comprise polypeptides of the invention as shown in FIGS. 11 (SEQ ID NOS:17-239, 241-736 and 738-1107) and 12 (SEQ ID NO:1109-1589, 1591-1964 AND 1966-2470) or encoded by the nucleotide sequence of SEQ ID NO:15, or a fragment thereof. In a specific embodiment, the vaccine preparations comprise polypeptides comprising amino acid sequence of SEQ ID NO:2472 or 2474. Furthermore, the present invention provides methods for treating, ameliorating, managing or preventing SARS by administering the vaccine preparations or antibodies of the present invention alone or in combination with adjuvants, or other pharmaceutically acceptable excipients.

[0016] In another aspect, the present invention provides pharmaceutical compositions comprising anti-viral agents of the present invention and a pharmaceutically acceptable carrier. In a specific embodiment, the anti-viral agent of the invention is an antibody that immunospecifically binds hSARS virus or any hSARS epitope. In preferred embodiments, such antibodies neutralize the hSARS virus. In a specific embodiment, the anti-viral agent of the invention binds a fragment, variant, homolog of N-gene or S-gene of hSARS virus. In a specific embodiment, the anti-viral agent of the invention binds a fragment, variant, homolog of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2472 or 2474. In another specific embodiment, the anti-viral agent is a polypeptide or protein of the present invention or nucleic acid molecule of the invention. The invention also provides kits containing a pharmaceutical composition of the present invention.

[0017] 3.1 Definitions

[0018] The term "an antibody or an antibody fragment that immunospecifically binds a polypeptide of the invention" as used herein refers to an antibody or a fragment thereof that immunospecifically binds to the polypeptide encoded by the nucleotide sequence of SEQ ID NO:1, 11, 13, 15, 2471 2473, or the polypeptides shown in FIGS. 11 and 12, or a fragment thereof, and does not non-specifically bind to other polypeptides. An antibody or a fragment thereof that immunospecifically binds to the polypeptide of the invention may cross-react with other antigens. Preferably, an antibody or a fragment thereof that immunospecifically binds to a polypeptide of the invention does not cross-react with other antigens. An antibody or a fragment thereof that immunospecifically binds to the polypeptide of the invention, can be identified by, for example, immunoassays or other techniques known to those skilled in the art.

[0019] An "isolated" or "purified" peptide or protein is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of a polypeptide/protein in which the polypeptide/protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, a polypeptide/protein that is substantially free of cellular material includes preparations of the polypeptide/protein having less than about 30%, 20%, 10%, 5%, 2.5%, or 1%, (by dry weight) of contaminating protein. When the polypeptide/protein is recombinantly produced, it is also

preferably substantially free of culture medium, i.e., culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When polypeptide/protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, i.e., it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly, such preparations of the polypeptide/protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than polypeptide/protein fragment of interest. In a preferred embodiment of the present invention, polypeptides/proteins are isolated or purified.

[0020] An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized. In a preferred embodiment of the invention, nucleic acid molecules encoding polypeptides/proteins of the invention are isolated or purified. The term "isolated" nucleic acid molecule does not include a nucleic acid that is a member of a library that has not been purified away from other library clones containing other nucleic acid molecules.

[0021] The term "portion" or "fragment" as used herein refers to a fragment of a nucleic acid molecule containing at least about 25, 30, 35, 40, 45, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150, 1200, 1250, 1300, 1350, 2,000, 3,000, 4,000, 5,000, 6,000, 7,000, 8,000, 9,000, 10,000, 11,000, 12,000, 13,000, 14,000, 15,000, 16,000, 17,000, 18,000, 19,000, 20,000, 21,000, 22,000, 23,000, 24,000, 25,000, 26,000, 27,000, 28,000, 29,000, or more contiguous nucleic acids in length of the relevant nucleic acid molecule and having at least one functional feature of the nucleic acid molecule (or the encoded protein has one functional feature of the protein encoded by the nucleic acid molecule); or a fragment of a protein or a polypeptide containing at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 90, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280, 300, 320, 340, 360, 400, 500, 600, 700, 800, 900, 1,000, 1,500, 2,000, 2,500, 3,000, 3,500, 4,000, 4,100, 4,200, 4,300, 4,350, 4,360, 4,370, 4,380 amino acid residues in length of the relevant protein or polypeptide and having at least one functional feature of the protein or polypeptide.

[0022] The term "3' region of the hSAR viral genome" refers to from about nucleotide position 18,000 to 29742 of SEQ ID NO:15.

[0023] The term "having a biological activity of the protein" or "having biological activities of the polypeptides of the invention" refers to the characteristics of the polypeptides or proteins having a common biological activity similar or identical structural domain and/or having sufficient amino acid identity to the polypeptide encoded by the nucleotide sequence of SEQ ID NO:1, 11, 13, 15, 16, 240, 737, 1108, 1590, 1965, 2471 or 2473. Such common biological activities of the polypeptides of the invention include antigenicity and immunogenicity.

[0024] The term "under stringent condition" refers to hybridization and washing conditions under which nucle-

otide sequences having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% identity to each other remain hybridized to each other. Such hybridization conditions are described in, for example but not limited to, Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6.; Basic Methods in Molecular Biology, Elsevier Science Publishing Co., Inc., N.Y. (1986), pp. 75-78, and 84-87; and Molecular Cloning, Cold Spring Harbor Laboratory, N.Y. (1982), pp. 387-389, and are well known to those skilled in the art. A preferred, non-limiting example of stringent hybridization conditions is hybridization in 6× sodium chloride/sodium citrate (SSC), 0.5% SDS at about 68° C. followed by one or more washes in 2×SSC, 0.5% SDS at room temperature. Another preferred, non-limiting example of stringent hybridization conditions is hybridization in 6×SSC at about 45° C. followed by one or more washes in 0.2×SSC, 0.1% SDS at about 50-65° C.

[0025] The term "variant" as used herein refers either to a naturally occurring genetic mutant of hSARS or a recombinantly prepared variation of hSARS each of which contain one or more mutations in its genome compared to the hSARS of CCTCC-V200303. The term "variant" may also refer either to a naturally occurring variation of a given peptide or a recombinantly prepared variation of a given peptide or protein in which one or more amino acid residues have been modified by amino acid substitution, addition, or deletion.

4. BRIEF DESCRIPTION OF THE FIGURES

[0026] FIG. 1 shows a partial DNA sequence (SEQ ID NO:1) and its deduced amino acid sequence (SEQ ID NO:2) obtained from the SARS virus that has 57% homology to the RNA-dependent RNA polymerase protein of known Coronaviruses.

[0027] FIG. 2 shows an electron micrograph of the novel hSARS virus that has similar morphological characteristics of coronaviruses.

[0028] FIG. 3 shows an immunofluorescent staining for IgG antibodies that are specifically bound to the FrHK-4 cells infected with the novel human respiratory virus of Coronaviridae.

[0029] FIG. 4 shows an electron micrograph of ultracentrifuged deposit of hSARS virus that was grown in the cell culture and negatively stained with 3% potassium phospho-tungstate at pH 7.0.

[0030] FIG. 5A shows a thin-section electron micrograph of lung biopsy of a patient with SARS; and FIG. 5B shows a thin section electron micrograph of hSARS-infected cells.

[0031] FIG. 6 shows the result of phylogenetic analysis for the partial protein sequence (215 amino acids; SEQ ID NO:2) of the hSARS virus (GenBank accession number AY268070). The phylogenetic tree is constructed by the neighbor-joining method. The horizontal-line distance represents the number of sites at which the two sequences compared are different. Bootstrap values are deducted from 500 replicates.

[0032] FIG. 7A shows an amplification plot of fluorescence intensity against the PCR cycle in a real-time quantitative PCR assay that can detect a hSARS virus in samples

quantitatively. The copy numbers of input plasmid DNA in the reactions are indicated. The X-axis denotes the cycle number of a quantitative PCR assay and the Y-axis denotes the fluorescence intensity (FI) over the background. **FIG. 7B** shows the result of a melting curve analysis of PCR products from clinical samples. Signals from positive (+ve) samples, negative (-ve) samples and water control (water) are indicated. The X-axis denotes the temperature ($^{\circ}$ C.) and the Y-axis denotes the fluorescence intensity (FI) over the background.

[0033] **FIG. 8** shows another partial DNA sequence (SEQ ID NO:11) and its deduced amino acid sequence (SEQ ID NO:12) obtained from the SARS virus.

[0034] **FIG. 9** shows yet another partial DNA sequence (SEQ ID NO:13) and its deduced amino acid sequence (SEQ ID NO:14) obtained from the SARS virus.

[0035] **FIG. 10** shows the entire genomic DNA sequence (SEQ ID NO:15) of the SARS virus.

[0036] **FIG. 11** shows the deduced amino acid sequences obtained from SEQ ID NO:15 in three frames (see SEQ ID NOS:16, 240 and 737). An asterisk (*) indicates a stop codon which marks the end of a peptide. The first-frame amino acid sequences: SEQ ID NOS:17-239; the second-frame amino acid sequences: SEQ ID NOS:241-736; and the third-frame amino acid sequences: SEQ ID NO:738-1107.

[0037] **FIG. 12** shows the deduced amino acid sequences obtained from the complement of SEQ ID NO:15 in three frames (see SEQ ID NOS:1108, 1590 and 1965). An asterisk (*) indicates a stop codon which marks the end of a peptide. The first-frame amino acid sequences: SEQ ID NOS:1109-1589; the second-frame amino acid sequences: SEQ ID NOS:1591-1964; and the third-frame amino acid sequences: SEQ ID NO:1966-2470.

[0038] **FIG. 13** shows the N-gene primer sequences (which amplifies nucleotides at position 29247-29410 of SEQ ID NO:2471). 150# (SEQ ID NO:2475); 200# (SEQ ID NO:2476); and S-gene primer sequences (which amplifies nucleotides at position 24751 to 25049 of SEQ ID NO:2473). 131# (SEQ ID NO:2477); 132# (SEQ ID NO:2478).

[0039] **FIG. 14A** shows the nucleic acid sequence of the N-gene (SEQ ID NO:2471). **FIG. 14B** shows the amino acid sequence of the N-gene (SEQ ID NO:2472).

[0040] **FIG. 15A** shows the nucleic acid sequence of the S-gene (SEQ ID NO:2473). **FIG. 15B** shows the amino acid sequence of the S-gene (SEQ ID NO:2474).

[0041] **FIG. 16** shows the genome organization and transcription strategy of SARS-CoV HK-39. Genomic and mRNA transcripts are capped (black circles), carry leader sequences (vertical lines) at 5' proximal and are polyadenylated (A^{15}). Arrows point the position of the intergenic sequence, 5'-CTAAACGAAC-3' (SEQ ID NO:2479). After release of the positive-sense genomic RNA in the cytoplasm of host cell, the viral RNA-dependent RNA polymerase, encoded from ORF 1a and 1b, is synthesized. It carries out transcription of a full-length complementary (negative-sense) RNA, from which new genomic RNA, an overlapping set of subgenomic mRNA transcripts, and leader RNA are synthesized. Note that all transcripts are preceded with common 5' leader sequences and common 3' ends. ORF1a

and 1b—RNA-dependent RNA polymerase; S—the major peplomer glycoprotein; M—transmembrane glycoprotein; N—nucleocapsid; X1, X2, X3—putative proteins.

[0042] **FIG. 17** shows a construct map of pSARSCoV-ORF 1b-N. PCR products amplified from ORF1b (1b) and N gene of SARS-CoV were co-ligated into a cloning vector pCR2.1-TOPO (Invitrogen). The nucleotide (nt) numbers corresponds to the positions in the sequence of HK-39 strain SARS-CoV (AY278491). Shaded areas indicate the amplicons by the primers used in diagnostic test (i.e., SEQ ID NOS:2480 and 2481).

[0043] **FIG. 18** shows a photo of an agarose gel after electrophoresis of total RNA extracted from SARS patients using SV Total RNA isolation system. The extracted RNA was then subjected to a reverse-transcription polymerase chain reaction (RT-PCR) assay for the detection of *coronavirus* in the patients.

[0044] **FIG. 19** shows the effect of potential inhibitors in Reverse Transcription Polymerase Chain Reaction (RT-PCR). To remove potential inhibitors, total RNA eluted from SV96 Binding Plate was precipitated with 95% ethanol and 3 M sodium acetate and resuspended in 12 μ l of nuclease-free water. RT-PCR was performed with actin-F (SEQ ID NO:2482) and actin-R (SEQ ID NO:2483) primers. Numbers indicated were the number of pig kidney epithelial (PK-15) cell added in the sample as an internal control. There was no DNA fragment amplified with untreated RNA samples.

[0045] **FIG. 20** shows the primers used for amplifying various genes. SRS251 (SEQ ID NO:2480) and SRS252 (SEQ ID NO:2481) amplified a 225 base pair fragment from the region of N-gene that showed no homology to other *coronavirus*. *coro3* (SEQ ID NO:3) and *coro4* (SEQ ID NO:4) amplified RNA-dependent RNA polymerase (1b gene) as a control. Actin-F (SEQ ID NO:2482) and actin-R (SEQ ID NO:2483) amplified a 745 base pair fragment from P-actin gene as internal control for PCR assays.

[0046] **FIG. 21A** shows Amplification plot of fluorescence Intensity against the number of PCR cycles. Black lines show the dynamic range of N-gene specific PCR with serially diluted plasmid construct from 10^1 to 10^6 copies. NPA samples from non-SARS patients, including patients suffering from adenovirus (n=5), respiratory syncytial virus (n=5), human metapneumovirus (n=5), influenza A virus (n=5), or influenza B virus (n=5) infection, are shown in gray lines. Lines with triangles denotes the SARS-CoV positive NPA samples; NTC represents no template control; X-axis indicates the cycle number of quantitative PCR performed, while Y-axis represents the fluorescence intensity (FAM-400) over background signal (Delta Rn). Inlet shows the melting curve analysis of the PCR products. Signals from positive (+ve), negative (-ve) samples and no template control are indicated. X-axis indicates the temperature ($^{\circ}$ C.), while Y-axis represents the fluorescence intensity (Delta Rn). **FIG. 21B** shows comparison of dynamic ranges of N-gene and 1b-gene specific PCRs. Dynamic ranges of both N-gene and 1b-gene PCR were obtained with same plasmid construct in which 1:1 ratio of corresponding amplicons were subcloned. Serially diluted plasmid with copy number ranged from 10^{-1} to 10^5 copies was used as template in both PCRs. Lines with triangles denotes N-gene specific PCR while the gray lines indicates 1b-gene specific PCR.

Inlet shows Ct values \pm standard deviation in triplicate set of experiment of both PCRs with different copy numbers of template used. NTC represents no template control; X-axis indicated the cycle number of quantitative PCR performed, while Y-axis represents fluorescence intensity.

[0047] FIGS. 22A and 22B show an amplification curve and a melting curve, respectively, of real-time quantitative PCR specific to 1b (using the primers having SEQ ID NOS:3 and 4) and N gene (using the primers having SEQ ID NOS:2480 and 2481) of SARS CoV. FIG. 22A: Amplification plot of fluorescence intensity against the number of PCR cycles. One (1) μ l of cDNA from a NPA, tracheal dispersion and lung biopsy of patients with clinical symptoms were used as template in each PCR. Fifty (50) cycles of PCR were performed to achieve the saturation phase of the reaction. X-axis indicates the cycle number of quantitative PCR performed, while y-axis represents the fluorescence intensity (FAM-490) over background signal. Horizontal gray line indicates the calculated threshold value by maximum curvature approach, and the baseline cycle Ct was calculated automatically. Inlet shows half-maximal fluorescence value ($\frac{1}{2}$ max) and Ct of both PCR with cDNA from various tissue isolated from a key patient (patient A indicated in *New Engl. J. Med.* 348:1967-76 (by Drosten et al., 2003) in three different time points. NPA=nasopharyngeal aspirate; TW=tracheal wash; LW=lung wash. FIG. 22B: Melting curves of PCR products. Melting curve analysis was carried out after 10-minute further-extension step of the reaction. The temperature was raised from 56° C. to 94° C. by 76 increments of 0.5° C. each, while each set-point temperature had been held for 7 seconds for data collection and analysis. Melting temperature of 1b- and N-gene specific PCR products was 80.5° C. and 85.5° C. respectively. X-axis indicates the temperature in degree Celsius while Y-axis represents the fluorescence intensity (FAM-490) over background signal. One (1) μ l of water was used as no template control in the reaction.

[0048] FIG. 23 shows the diagnostic result of 48 clinical samples using the primers having SEQ ID NOS:2480 and 2481, respectively, with β -actin PCR as an internal control. Upper bands in each row showed a 745 bp DNA fragment amplified with actin-F and actin-R, while lower bands were the amplicons by primers specific for N-gene of SARS coronavirus (225 bp). -ve control (water) and +ve control (cDNA from SARS coronavirus infected vero cell) of the assay were indicated. Five (5) μ l of PCR products of both reactions were mixed and loaded into the sample well in a 2% agarose gel. M=1 kb plus molecular marker (Invitrogen).

[0049] FIG. 24 shows Northern Blot analysis of SARS-CoV total RNA. Total RNA of SARS-CoV was extracted from SARS-CoV infected Vero E6 cell. RNA was separated in a 1% denaturing gel containing 6.29% formaldehyde. Afterwards RNA was transferred to positively charged nylon membrane and hybridized with digoxigenin-labelled PCR fragments specific to 1b, S, M and N genes, respectively. Lane 1—1b; lane 2—S; lane 3—M; lane 4—N. Vertical bar showed the molecular size reference. Arrows indicates the transcripts hybridized with N probe. Signals were analyzed by chemiluminescence.

[0050] FIG. 25 shows the DNA probes used in Northern blot analysis. The probes for 1b gene (nt 18057-18222; SEQ ID NO:2484), S gene (nt 21920-22107; SEQ ID NO:2485),

M gene (nt 25867-26996; SEQ ID NO:2486), and N gene (nt 28658-28883; SEQ ID NO:2487) are shown.

5. DETAILED DESCRIPTION OF THE INVENTION

[0051] The present inventors developed a rapid, high-throughput reverse transcription-PCR diagnostic test for SARS associated coronavirus (SARS-CoV). 3' region of the hSARS virus genome including the Nucleocapsid gene (N-gene) represents a sensitive molecular marker which can be used in addition to 1b gene to increase the sensitivity of the test. An internal control using PK-15 cells may be employed to ensure the integrity of RNA during its extraction process and cDNA synthesis, thus eliminating false negative results.

[0052] In mouse hepatitis virus (MHV), a typical member of the genus *Coronavirus*, both genomic RNA and mRNA transcripts are capped and with common 3' ends and common leader sequences on their 5' ends. With this unique transcription strategy, the copy numbers of different viral genes during proliferation of virus in its host are different (FIG. 19). N gene that encodes for the nucleocapsid has the most abundant copy number during virus replication as all transcripts may carry nucleotide sequence from N gene, although they are not all in-frame for translation for this gene product. The present inventors have discovered a diagnostic assay that is based on the 3' region, including the N-gene, of the viral genome provide a more sensitive assay than the rest of the viral genome. Accordingly, in preferred embodiments, nucleic acid molecules that may be used for a diagnostic assay comprise nucleic acid sequence of nucleotide position 18000 to 29742 of SEQ ID NO:15, or portions thereof. The portions may comprise 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150, 1200 of nucleotides having nucleic acid sequence from nucleotide position 18000 to 29742 of SEQ ID NO:15. In other preferred embodiments, nucleic acid molecules that may be used for a diagnostic assay comprising nucleic acid sequence of nucleotide position 28658 to 28883 or 29247-29410 of SEQ ID NO:15.

[0053] Nasopharyngeal aspirate (NPA) and stool samples were obtained from SARS suspected patients with major clinical symptoms and significant history of close contact with infected patients. Total RNA was extracted from the subject samples, together with PK-15 cell as an internal control. Samples were analyzed by the reverse-transcription-PCR assay. Northern blot analysis was performed to show different subgenomic transcripts of the virus. Real-time quantitative PCR was employed to compare the sensitivity of two loci used in this diagnostic assay. In specific embodiments, PCR inhibitor was removed with ethanol precipitation after RNA extraction process.

[0054] In preferred embodiments, the present invention provides a method for detecting the presence or absence of nucleic acid of the N-gene in a biological sample. The method involves obtaining a biological sample from various sources and contacting the sample with a compound or an agent capable of detecting a nucleic acid (e.g., mRNA, genomic RNA) of the N-gene of the hSARS virus such that the presence of the N-gene is detected in the sample. In preferred embodiments, the N-gene may be detected using a

labeled nucleic acid probe comprising of the nucleotide sequence of SEQ ID NO:2471, complement thereof, or a portion thereof. The portion may be 10, 20, 30, 40, 50, 100, 200, 400, 500, 600, 800, 1000, 1200 nucleotides in length. In preferred embodiments, primers comprising nucleotide sequence of SEQ ID NOS:2475 and/or 2476 or SEQ ID NOS:2480 and/or 2481 may be used to amplify a portion of the N-gene for detection.

[0055] A preferred agent for detecting hSARS mRNA or genomic RNA of the invention is a labeled nucleic acid probe capable of hybridizing to mRNA or genomic RNA encoding a polypeptide of the invention. The nucleic acid probe can be, for example, a nucleic acid molecule comprising or consisting of the nucleotide sequence or SEQ ID NO:1, 11, 13, 15, 2471 or 2473, complement thereof, or a portion thereof, such as an oligonucleotide of at least 15, 20, 25, 30, 50, 100, 250, 500, 750, 1,000 or more contiguous nucleotides in length and sufficient to specifically hybridize under stringent conditions to a hSARS mRNA or genomic RNA.

[0056] In another preferred specific embodiment, the presence of N-gene is detected in the sample by an reverse transcription polymerase chain reaction (RT-PCR) using the primers that are constructed based on a partial nucleotide sequence of the N-gene or a genomic nucleic acid sequence of SEQ ID NO:15, or based on a nucleotide sequence of SEQ ID NO:1, 11, 13, 15, 2471, or 2473. In a non-limiting specific embodiment, preferred primers to be used in a RT-PCR method are: 5'-TACACACCTCAGC-GTTG-3' (SEQ ID NO:3) and/or 5'-CACGAACGTGACG-AAT-3' (SEQ ID NO:4), in the presence of 2.5 mM MgCl₂, and the thermal cycles are, for example, but not limited to, 94° C. for 8 min followed by 40 cycles of 94° C. for 1 min, 50° C. for 1 min, 72° C. for 1 min (also see Sections 6.7 and 6.8 infra). In preferred embodiments, the primers comprise nucleic acid sequence of SEQ ID NOS:2475 and 2476. In another preferred embodiment, the primers comprise nucleic acid sequence of SEQ ID NOS:2480 and 2481. In preferred embodiments, the thermal cycles are 94° C. for 10 min followed by 40 cycles of 94° C. for 30 seconds, 56° C. for 30 seconds, 72° C. for 30 seconds, 72° C. for 10 minutes. In another preferred embodiment, the thermal cycles are 94° C. for 3 min followed by 40 cycles of 94° C. for 30 seconds, 56° C. for 30 seconds, 72° C. for 30 seconds, 72° C. for 10 minutes. In more preferred specific embodiment, the present invention provides a real-time quantitative PCR assay to detect the presence of hSARS virus in a biological sample by subjecting the cDNA obtained by reverse transcription of the extracted total RNA from the sample to PCR reactions using the specific primers, such as those having nucleotide sequences of SEQ ID NOS:3 and 4, and a fluorescence dye, such as SYBR® Green I, which fluoresces when bound non-specifically to double-stranded DNA. The fluorescence signals from these reactions are captured at the end of extension steps as PCR product is generated over a range of the thermal cycles, thereby allowing the quantitative determination of the viral load in the sample based on an amplification plot (see Section 6.7, infra).

[0057] In the preferred embodiment, the present invention provides a method for detecting the presence or absence of nucleic acid of the S-gene in a biological sample. The method involves obtaining a biological sample from various sources and contacting the sample with a compound or an

agent capable of detecting a nucleic acid (e.g., mRNA, genomic RNA) of the S-gene of the hSARS virus such that the presence of the S-gene is detected in the sample. A preferred agent for detecting hSARS mRNA or genomic RNA of the invention is a labeled nucleic acid probe capable of hybridizing to mRNA or genomic RNA encoding a polypeptide of the invention. The nucleic acid probe can be, for example, a nucleic acid molecule comprising or consisting of the nucleotide sequence or SEQ ID NO:1, 11, 13, 15, 2471, or 2473, or a portion thereof, such as an oligonucleotide of at least 15, 20, 25, 30, 50, 100, 250, 500, 750, 1,000 or more contiguous nucleotides in length and sufficient to specifically hybridize under stringent conditions to a hSARS mRNA or genomic RNA.

[0058] In another preferred specific embodiment, the presence of S-gene is detected in the sample by an reverse transcription polymerase chain reaction (RT-PCR) using the primers that are constructed based on a partial nucleotide sequence of the S-gene (SEQ ID NO:2473).

[0059] In vitro techniques for detection of mRNA include northern hybridizations, in situ hybridizations, RT-PCR, and RNase protection. In vitro techniques for detection of genomic RNA include northern hybridizations, RT-PCR, and RNase protection.

[0060] The polynucleotides encoding the N-gene may be amplified before they are detected. The term "amplified" refers to the process of making multiple copies of the nucleic acid from a single polynucleotide molecule. The amplification of polynucleotides can be carried out in vitro by biochemical processes known to those of skill in the art. The amplification agent may be any compound or system that will function to accomplish the synthesis of primer extension products, including enzymes. Suitable enzymes for this purpose include, for example, *E. coli* DNA polymerase I, Taq polymerase, Klenow fragment of *E. coli* DNA polymerase I, T4 DNA polymerase, other available DNA polymerases, polymerase muteins, reverse transcriptase, ligase, and other enzymes, including heat-stable enzymes (i.e., those enzymes that perform primer extension after being subjected to temperatures sufficiently elevated to cause denaturation). Suitable enzymes will facilitate combination of the nucleotides in the proper manner to form the primer extension products that are complementary to each mutant nucleotide strand. Generally, the synthesis will be initiated at the 3'-end of each primer and proceed in the 5'-direction along the template strand, until synthesis terminates, producing molecules of different lengths. There may be amplification agents, however, that initiate synthesis at the 5'-end and proceed in the other direction, using the same process as described above. In any event, the method of the invention is not to be limited to the embodiments of amplification described herein.

[0061] One method of in vitro amplification, which can be used according to this invention, is the polymerase chain reaction (PCR) described in U.S. Pat. Nos. 4,683,202 and 4,683,195. The term "polymerase chain reaction" refers to a method for amplifying a DNA base sequence using a heat-stable DNA polymerase and two oligonucleotide primers, one complementary to the (+)-strand at one end of the sequence to be amplified and the other complementary to the (-)-strand at the other end. Because the newly synthesized DNA strands can subsequently serve as additional templates

for the same primer sequences, successive rounds of primer annealing, strand elongation, and dissociation produce rapid and highly specific amplification of the desired sequence. The polymerase chain reaction is used to detect the presence of polynucleotides encoding cytokines in the sample. Many polymerase chain methods are known to those of skill in the art and may be used in the method of the invention. For example, DNA can be subjected to 30 to 35 cycles of amplification in a thermocycler as follows: 95° C. for 30 sec, 52° to 60° C. for 1 min, and 72° C. for 1 min, with a final extension step of 72° C. for 5 min. For another example, DNA can be subjected to 35 polymerase chain reaction cycles in a thermocycler at a denaturing temperature of 95° C. for 30 sec, followed by varying annealing temperatures ranging from 54-58° C. for 1 min, an extension step at 70° C. for 1 min and a final extension step at 70° C.

[0062] The primers for use in amplifying the N-gene or S-gene of the invention may be prepared using any suitable method, such as conventional phosphotriester and phosphodiester methods or automated embodiments thereof so long as the primers are capable of hybridizing to the polynucleotides of interest. One method for synthesizing oligonucleotides on a modified solid support is described in U.S. Pat. No. 4,458,066. The exact length of primer will depend on many factors, including temperature, buffer, and nucleotide composition. The primer must prime the synthesis of extension products in the presence of the inducing agent for amplification.

[0063] Primers used according to the method of the invention are complementary to each strand of nucleotide sequence to be amplified. The term "complementary" means that the primers must hybridize with their respective strands under conditions, which allow the agent for polymerization to function. In other words, the primers that are complementary to the flanking sequences hybridize with the flanking sequences and permit amplification of the nucleotide sequence. Preferably, the 3' terminus of the primer that is extended has perfectly base paired complementarity with the complementary flanking strand. Primers and probes for polynucleotides encoding N-gene or S-gene of the present invention can be developed using known methods combined with the present disclosure.

[0064] Those of ordinary skill in the art will know of various amplification methodologies that can also be utilized to increase the copy number of target nucleic acid. The polynucleotides detected in the method of the invention can be further evaluated, detected, cloned, sequenced, and the like, either in solution or after binding to a solid support, by any method usually applied to the detection of a specific nucleic acid sequence such as another polymerase chain reaction, oligomer restriction (Saiki et al., *Bio/Technology* 3:1008-1012 (1985)), allele-specific oligonucleotide (ASO) probe analysis (Conner et al., *Proc. Natl. Acad. Sci. USA* 80: 278 (1983)), oligonucleotide ligation assays (OLAs) (Landegren et al., *Science* 241:1077 (1988)), RNase Protection Assay and the like. Molecular techniques for DNA analysis have been reviewed (Landegren et al., *Science* 242: 229-237 (1988)). Following DNA amplification, the reaction product may be detected by Southern blot analysis, without using radioactive probes. In such a process, for example, a small sample of DNA containing the polynucleotides obtained from the tissue or subject are amplified, and analyzed via a Southern blotting technique. The use of non-radioactive

probes or labels is facilitated by the high level of the amplified signal. In one embodiment of the invention, one nucleoside triphosphate is radioactively labeled, thereby allowing direct visualization of the amplification product by autoradiography. In another embodiment, amplification primers are fluorescently labeled and run through an electrophoresis system. Visualization of amplified products is by laser detection followed by computer assisted graphic display, without a radioactive signal.

[0065] The methods of the present invention can involve a real-time quantitative PCR assay, such as a Taqman assay (Holland et al., *Proc Natl Acad Sci USA*, 88(16):7276 (1991); also see U.S. patent application of Attorney Docket No. V9661.0078 filed Mar. 24, 2004, which is incorporated by reference in its entirety). The assays can be performed on an instrument designed to perform such assays, for example those available from Applied Biosystems (Foster City, Calif.). Primers and probes for such an assay can be designed according to known procedures in the art.

[0066] The size of the primers used to amplify a portion of the N-gene or S-gene is at least 10, 15, 20, 25, 30 nucleotide in length. In particular, primers that amplify the N-gene or S-gene is most preferred. Preferably, the GC ratio should be above 30, 35, 40, 45, 50, 55, 60% so as to prevent hair-pin structure on the primer. Furthermore, the amplicon should be sufficiently long enough to be detected by standard molecular biology methodologies.

[0067] Preferably, the amplicon is at least 40, 60, 100, 200, 300, 400, 500, 600, 800, 1000 base pair in length.

[0068] In a specific embodiment, the methods further involve obtaining a control sample from a control subject, contacting the control sample with a compound or agent capable of detecting N-gene or S-gene, such that the presence of mRNA or genomic RNA encoding the N-gene or S-gene is detected in the sample, and comparing the presence (or absence) of N-gene or S-gene, or mRNA or genomic RNA encoding the polypeptide in the control sample with the presence of N-gene or S-gene, or mRNA or genomic DNA encoding the polypeptide in the test sample.

[0069] The invention also encompasses kits for detecting the presence of N-gene nucleic acid in a test sample. The kit, for example, can comprise a labeled compound or agent capable of detecting a nucleic acid molecule encoding the polypeptide in a test sample and, in certain embodiments, a means for determining the amount of mRNA in the sample (an oligonucleotide probe which binds to DNA or mRNA encoding the polypeptide).

[0070] For oligonucleotide-based kits, the kit can comprise, for example: (1) an oligonucleotide, e.g., a detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a polypeptide of the invention or to a sequence within the N-gene; (2) a pair of primers useful for amplifying a nucleic acid molecule containing the N-gene sequence. The kit can also comprise, e.g., a buffering agent, a preservative, or a protein stabilizing agent. The kit can also comprise components necessary for detecting the detectable agent (e.g., an enzyme or a substrate). The kit can also contain a control sample or a series of control samples which can be assayed and compared to the test sample contained. Each component of the kit is usually enclosed within an individual container and all of the various containers are within a single package along with instructions for use.

[0071] The present invention relates to the isolated N-gene and S-gene of the hSARS virus. In a specific embodiment, the virus comprises a nucleotide sequence of SEQ ID NO:1, 11, 13, 15, 2471, and/or 2473. In a specific embodiment, the present invention provides isolated nucleic acid molecules of the hSARS virus, comprising, or, alternatively, consisting of the nucleotide sequence of SEQ ID NO:1, 11, 13, 15, 2471, and/or, 2473, a complement thereof or a portion thereof. In another specific embodiment, the invention provides isolated nucleic acid molecules which hybridize under stringent conditions, as defined herein, to a nucleic acid molecule having the sequence of SEQ ID NO:1, 11, 13, 15, 2471, and/or 2473, or specific genes of known member of Coronaviridae, or a complement thereof. In another specific embodiment, the invention provides isolated polypeptides or proteins that are encoded by a nucleic acid molecule comprising a nucleotide sequence that is at least about 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:1, or a complement thereof. In another specific embodiment, the invention provides isolated polypeptides or proteins that are encoded by a nucleic acid molecule comprising a nucleotide sequence that is at least about 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1,000, 1,050, 1,100, 1,150, 1,200, or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:11, or a complement thereof. In yet another specific embodiment, the invention provides isolated polypeptides or proteins that are encoded by a nucleic acid molecule comprising a nucleotide sequence that is at least about 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, 650, 700, or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:13, or a complement thereof. In yet another specific embodiment, the invention provides isolated polypeptides or proteins that are encoded by a nucleic acid molecule comprising or, alternatively consisting of a nucleotide sequence that is at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1,000, 1,050, 1,100, 1,150, 1,200 or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:2471, or a complement thereof. In yet another specific embodiment, the invention provides isolated polypeptides or proteins that are encoded by a nucleic acid molecule comprising or, alternatively consisting of a nucleotide sequence that is at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1,000, 1,050, 1,100, 1,150, 1,200, 2,000, 3,000, or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:2473, or a complement thereof. In yet another specific embodiment, the invention provides isolated polypeptides or proteins that are encoded by a nucleic acid molecule comprising or, alternatively consisting of a nucleotide sequence that is at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 100, 150, 200, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1,000, 1,050, 1,100, 1,150, 1,200, 2,000, 3,000, 4,000, 5,000, 6,000, 7,000, 8,000, 9,000, 10,000, 11,000, 12,000, 13,000, 14,000, 15,000, 16,000, 17,000, 18,000, 19,000, 20,000, 21,000, 22,000, 23,000, 24,000, 25,000, 26,000, 27,000, 28,000, 29,000 or more contiguous nucleotides of the nucleotide sequence of SEQ ID NO:15, or a complement thereof. The polypeptides includes those shown in FIGS. 11 (SEQ ID NOS:17-239, 241-736 and 738-1107) and 12 (SEQ

ID NOS: 1109-1589, 1591-1964 and 1966-2470) or having an amino acid sequence of SEQ ID NO:2472 or 2474. The polypeptides or the proteins of the present invention preferably have one or more biological activities of the proteins encoded by the sequence of SEQ ID NO:1, 11, 13, 15, 2471 or 2473, or the polypeptides shown in FIGS. 11 and 12, or the native viral proteins containing the amino acid sequences encoded by the sequence of SEQ ID NO:1, 11, 13, 15, 2471 or 2473.

[0072] The present invention also relates to a method for propagating the hSARS virus in host cells.

[0073] The invention further relates to the use of the sequence information of the isolated virus for diagnostic and therapeutic methods. In a specific embodiment, the invention provides the entire nucleotide sequence of hSARS virus, CCTCC-V200303, SEQ ID NO:15, or fragments, or complement thereof. Furthermore, the present invention relates to a nucleic acid molecule that hybridizes any portion of the genome of the hSARS virus, CCTCC-V200303, or SEQ ID NO:15, under the stringent conditions. In a specific embodiment, the invention provides nucleic acid molecules which are suitable for use as primers consisting of or comprising the nucleotide sequence of SEQ ID NO:1, 11, 13, 15, 2471 or 2473, or a complement thereof, or a portion thereof. In specific embodiments, the primers comprise nucleotide sequence of SEQ ID NO: 2475, 2476, 2477, 2478, 2480 or 2481. In another specific embodiment, the invention provides nucleic acid molecules which are suitable for use as hybridization probes for the detection of nucleic acids encoding a polypeptide of the invention, consisting of or comprising the nucleotide sequence of SEQ ID NO:1, 11, 13, 15, 2471 or 2473, a complement thereof, or a portion thereof. The invention further relates to a kit comprising primers having nucleic acid sequence of SEQ ID NOS:2475 and 2476; and SEQ ID NOS:2480 and 2481, for the detection of N-gene. In another embodiment, the invention relates to a kit comprising primers having nucleic acid sequence of SEQ ID NOS:2477 and/or 2478 for the detection of S-gene. In a preferred embodiment, the kit further comprises reagents for the detection of genes not found in hSARS virus as a negative control. The invention further encompasses chimeric or recombinant viruses or viral proteins encoded by said nucleotide sequences.

[0074] The invention further provides antibodies that specifically bind a polypeptide of the invention encoded by the nucleotide sequence of SEQ ID NO:1, 11, 13, 2471 or 2473, or a fragment thereof, or any hSARS epitope. The invention further provides antibodies that specifically bind a polypeptide having amino acid sequence of SEQ ID NO: 2472 or 2474. The invention further provides antibodies that specifically bind the polypeptides of the invention encoded by the nucleotide sequence of SEQ ID NO:15, or the polypeptides shown in FIGS. 11 and 12, or a fragment thereof, or any hSARS epitope. Such antibodies include, but are not limited to polyclonal, monoclonal, bi-specific, multi-specific, human, humanized, chimeric antibodies, single chain antibodies, Fab fragments, F(ab)₂ fragments, disulfide-linked Fvs, intrabodies and fragments containing either a VL or VH domain or even a complementary determining region (CDR) that specifically binds to a polypeptide of the invention.

[0075] In one embodiment, the invention provides methods for detecting the presence, activity or expression of the

hSARS virus of the invention in a biological material, such as cells, blood, saliva, urine, sputum, nasopharyngeal aspirates, and so forth. The presence of the hSARS virus in a sample can be determined by contacting the biological material with an agent which can detect directly or indirectly the presence of the hSARS virus. In a specific embodiment, the detection agents are the antibodies of the present invention. In another embodiment, the detection agent is a nucleic acid of the present invention.

[0076] In another embodiment, the invention provides vaccine preparations comprising the hSARS virus, including recombinant and chimeric forms of said virus, or subunits of the virus. In a specific embodiment, the vaccine preparations comprise live but attenuated hSARS virus with or without pharmaceutically acceptable excipients, including adjuvants. In another specific embodiment, the vaccine preparations comprise an inactivated or killed hSARS virus with or without pharmaceutically acceptable excipients, including adjuvants. The vaccine preparations of the present invention may further comprise with adjuvants or Accordingly, the present invention further provides methods of preparing recombinant or chimeric forms of hSARS. In another specific invention, the vaccine preparations of the present invention comprise one or more nucleic acid molecules comprising or consisting of the sequence of SEQ ID NO. 1, 11, 13, 15, 2471 and/or 2473, or a fragment thereof. In another embodiment, the invention provides vaccine preparations comprising one or more polypeptides of the invention encoded by a nucleotide sequence comprising or consisting of the nucleotide sequence of SEQ ID NO:1, 11, 13, 2471 and/or 2473, or the polypeptides shown in **FIGS. 11 and 12**, or a fragment thereof. In another embodiment, the invention provides vaccine preparations comprising one or more polypeptides of the invention encoded by a nucleotide sequence comprising or consisting of the nucleotide sequence of SEQ ID NO:15, or a fragment thereof. Furthermore, the present invention provides methods for treating, ameliorating, managing, or preventing SARS by administering the vaccine preparations or antibodies of the present invention alone or in combination with antivirals [e.g., amantadine, rimantadine, gancyclovir, acyclovir, ribavirin, penciclovir, oseltamivir, foscarnet, zidovudine (AZT), didanosine (ddI), lamivudine (3TC), zalcitabine (ddC), stavudine (d4T), nevirapine, delavirdine, indinavir, ritonavir, zalcitabine, nelfinavir, saquinavir, relenza, tamiflu, pleconaril, interferons, etc.], steroids and corticosteroids such as prednisone, cortisone, fluticasone and glucocorticoid, antibiotics, analgesics, bronchodilators, or other treatments for respiratory and/or viral infections.

[0077] Furthermore, the present invention provides pharmaceutical compositions comprising anti-viral agents of the present invention and a pharmaceutically acceptable carrier. The present invention also provides kits comprising pharmaceutical compositions of the present invention.

[0078] In another aspect, the present invention provides methods for screening anti-viral agents that inhibit the infectivity or replication of hSARS virus or variants thereof.

[0079] 5.1 Recombinant and Chimeric hSARS Viruses

[0080] The present invention encompasses recombinant or chimeric viruses encoded by viral vectors derived from the genome of hSARS virus or natural variants thereof. In a specific embodiment, a recombinant virus is one derived

from the hSARS virus of deposit accession no. CCTCC-V200303. In a specific embodiment, the virus has a nucleotide sequence of SEQ ID NO:15. In another specific embodiment, a recombinant virus is one derived from a natural variant of hSARS virus. A natural variant of hSARS has a sequence that is different from the genomic sequence (SEQ ID NO:15) of the hSARS virus, CCTCC-V200303, due to one or more naturally occurred mutations, including, but not limited to, point mutations, rearrangements, insertions, deletions etc., to the genomic sequence that may or may not result in a phenotypic change. In accordance with the present invention, a viral vector which is derived from the genome of the hSARS virus, CCTCC-V200303, is one that contains a nucleic acid sequence that encodes at least a part of one ORF of the hSARS virus. In a specific embodiment, the ORF comprises or consists of a nucleotide sequence of SEQ ID NO:1, 11, 13, 2471, 2473, or a fragment thereof. In a specific embodiment, there are more than one ORF within the nucleotide sequence of SEQ ID NO:15, as shown in **FIGS. 11** (SEQ ID NOS:16, 240 and 737) and **12** (SEQ ID NOS:1108, 1590 and 1965), or a fragment thereof. In another embodiment, the polypeptide encoded by the ORF comprises or consists of an amino acid sequence of SEQ ID NO:2, 12, 14, 2472, 2474, or a fragment thereof, or shown in **FIGS. 11** (SEQ ID NOS: 17-239, 241-736 and 738-1107) and **12** (SEQ ID NOS:1 109-1589, 1591-1964 and 1966-2470), or a fragment thereof. In accordance with the present invention these viral vectors may or may not include nucleic acids that are non-native to the viral genome.

[0081] In another specific embodiment, a chimeric virus of the invention is a recombinant hSARS virus which further comprises a heterologous nucleotide sequence. In accordance with the invention, a chimeric virus may be encoded by a nucleotide sequence in which heterologous nucleotide sequences have been added to the genome or in which endogenous or native nucleotide sequences have been replaced with heterologous nucleotide sequences.

[0082] According to the present invention, the chimeric viruses are encoded by the viral vectors of the invention which further comprise a heterologous nucleotide sequence. In accordance with the present invention a chimeric virus is encoded by a viral vector that may or may not include nucleic acids that are non-native to the viral genome. In accordance with the invention a chimeric virus is encoded by a viral vector to which heterologous nucleotide sequences have been added, inserted or substituted for native or non-native sequences. In accordance with the present invention, the chimeric virus may be encoded by nucleotide sequences derived from different strains or variants of hSARS virus. In particular, the chimeric virus is encoded by nucleotide sequences that encode antigenic polypeptides derived from different strains or variants of hSARS virus.

[0083] A chimeric virus may be of particular use for the generation of recombinant vaccines protecting against two or more viruses (Tao et al., *J. Virol.* 72, 2955-2961; Durbin et al., 2000, *J. Virol.* 74, 6821-6831; Skiadopoulou et al., 1998, *J. Virol.* 72, 1762-1768 (1998); Teng et al., 2000, *J. Virol.* 74, 9317-9321). For example, it can be envisaged that a virus vector derived from the hSARS virus expressing one or more proteins of variants of hSARS virus, or vice versa, will protect a subject vaccinated with such vector against infections by both the native hSARS and the variant. Attenuated and replication-defective viruses may be of use for

vaccination purposes with live vaccines as has been suggested for other viruses. (See, PCT WO 02/057302, at pp. 6 and 23, incorporated by reference herein).

[0084] In accordance with the present invention the heterologous sequence to be incorporated into the viral vectors encoding the recombinant or chimeric viruses of the invention include sequences obtained or derived from different strains or variants of hSARS.

[0085] In certain embodiments, the chimeric or recombinant viruses of the invention are encoded by viral vectors derived from viral genomes wherein one or more sequences, intergenic regions, termini sequences, or portions or entire ORF have been substituted with a heterologous or non-native sequence. In certain embodiments of the invention, the chimeric viruses of the invention are encoded by viral vectors derived from viral genomes wherein one or more heterologous sequences have been inserted or added to the vector.

[0086] The selection of the viral vector may depend on the species of the subject that is to be treated or protected from a viral infection. If the subject is human, then an attenuated hSARS virus can be used to provide the antigenic sequences.

[0087] In accordance with the present invention, the viral vectors can be engineered to provide antigenic sequences which confer protection against infection by the hSARS and natural variants thereof. The viral vectors may be engineered to provide one, two, three or more antigenic sequences. In accordance with the present invention the antigenic sequences may be derived from the same virus, from different strains or variants of the same type of virus, or from different viruses.

[0088] The expression products and/or recombinant or chimeric virions obtained in accordance with the invention may advantageously be utilized in vaccine formulations. The expression products and chimeric virions of the present invention may be engineered to create vaccines against a broad range of pathogens, including viral and bacterial antigens, tumor antigens, allergen antigens, and auto antigens involved in autoimmune disorders. In particular, the chimeric virions of the present invention may be engineered to create vaccines for the protection of a subject from infections with hSARS virus and variants thereof.

[0089] In certain embodiments, the expression products and recombinant or chimeric virions of the present invention may be engineered to create vaccines against a broad range of pathogens, including viral antigens, tumor antigens and autoantigens involved in autoimmune disorders. One way to achieve this goal involves modifying existing hSARS genes to contain foreign sequences in their respective external domains. Where the heterologous sequences are epitopes or antigens of pathogens, these chimeric viruses may be used to induce a protective immune response against the disease agent from which these determinants are derived.

[0090] Thus, the present invention relates to the use of viral vectors and recombinant or chimeric viruses to formulate vaccines against a broad range of viruses and/or antigens. The present invention also encompasses recombinant viruses comprising a viral vector derived from the hSARS or variants thereof which contains sequences which result in a virus having a phenotype more suitable for use in vaccine formulations, e.g., attenuated phenotype or enhanced anti-

genicity. The mutations and modifications can be in coding regions, in intergenic regions and in the leader and trailer sequences of the virus.

[0091] The invention provides a host cell comprising a nucleic acid or a vector according to the invention. Plasmid or viral vectors containing the polymerase components of hSARS virus are generated in prokaryotic cells for the expression of the components in relevant cell types (bacteria, insect cells, eukaryotic cells). Plasmid or viral vectors containing full-length or partial copies of the hSARS genome will be generated in prokaryotic cells for the expression of viral nucleic acids in-vitro or in-vivo. The latter vectors may contain other viral sequences for the generation of chimeric viruses or chimeric virus proteins, may lack parts of the viral genome for the generation of replication defective virus, and may contain mutations, deletions or insertions for the generation of attenuated viruses. In addition, the present invention provides a host cell infected with hSARS virus, for example, of deposit no. CCTCC-V200303.

[0092] Infectious copies of hSARS (being wild type, attenuated, replication-defective or chimeric) can be produced upon co-expression of the polymerase components according to the state-of-the-art technologies described above.

[0093] In addition, eukaryotic cells, transiently or stably expressing one or more full-length or partial hSARS proteins can be used. Such cells can be made by transfection (proteins or nucleic acid vectors), infection (viral vectors) or transduction (viral vectors) and may be useful for complementation of mentioned wild type, attenuated, replication-defective or chimeric viruses.

[0094] The viral vectors and chimeric viruses of the present invention may be used to modulate a subject's immune system by stimulating a humoral immune response, a cellular immune response or by stimulating tolerance to an antigen. As used herein, a subject means: humans, primates, horses, cows, sheep, pigs, goats, dogs, cats, avian species and rodents.

[0095] 5.2 Formulation of Vaccines and Antivirals

[0096] In a preferred embodiment, the invention provides a proteinaceous molecule or hSARS virus specific viral protein or functional fragment thereof encoded by a nucleic acid according to the invention. Useful proteinaceous molecules are for example derived from any of the genes or genomic fragments derivable from the virus according to the invention, including envelop protein (E protein), integral membrane protein (M protein), spike protein (S protein), nucleocapsid protein (N protein), hemagglutinin esterase (HE protein), and RNA-dependent RNA polymerase. Such molecules, or antigenic fragments thereof, as provided herein, are for example useful in diagnostic methods or kits and in pharmaceutical compositions such as subunit vaccines. Particularly useful are polypeptides encoded by the nucleotide sequence of SEQ ID NO:1, 11, 13, 15, 2471, 2473, or as shown in FIG. 11 (SEQ ID NOS:17-239, 241-736 and 738-1107) and FIG. 12 (SEQ ID NOS:1109-1589, 1591-1964 and 1966-2470), or having the amino acid sequence of SEQ ID NO:2472 or 2474, or antigenic fragments thereof for inclusion as antigen or subunit immunogen, but inactivated whole virus can also be used. Particularly useful are

also those proteinaceous substances that are encoded by recombinant nucleic acid fragments of the hSARS genome, of course preferred are those that are within the preferred bounds and metes of ORFs, in particular, for eliciting hSARS specific antibody or T cell responses, whether in vivo (e.g. for protective or therapeutic purposes or for providing diagnostic antibodies) or in vitro (e.g. by phage display technology or another technique useful for generating synthetic antibodies).

[0097] The invention provides vaccine formulations for the prevention and treatment of infections with hSARS virus. In certain embodiments, the vaccine of the invention comprises recombinant and chimeric viruses of the hSARS virus. In certain embodiments, the virus is attenuated.

[0098] In another embodiment of this aspect of the invention, inactivated vaccine formulations may be prepared using conventional techniques to "kill" the chimeric viruses. Inactivated vaccines are "dead" in the sense that their infectivity has been destroyed. Ideally, the infectivity of the virus is destroyed without affecting its immunogenicity. In order to prepare inactivated vaccines, the chimeric virus may be grown in cell culture or in the allantois of the chick embryo, purified by zonal ultracentrifugation, inactivated by formaldehyde or β -propiolactone, and pooled. The resulting vaccine is usually inoculated intramuscularly.

[0099] Inactivated viruses may be formulated with a suitable adjuvant in order to enhance the immunological response. Such adjuvants may include but are not limited to mineral gels, e.g., aluminum hydroxide; surface active substances such as lysolecithin, pluronic polyols, polyanions; peptides; oil emulsions; and potentially useful human adjuvants such as BCG and *Corynebacterium parvum*.

[0100] In another aspect, the present invention also provides DNA vaccine formulations comprising a nucleic acid or fragment of the hSARS virus, e.g., the virus having accession no. CCTCC-V200303, or nucleic acid molecules having the sequence of SEQ ID NO:1, 11, 13, 15, 2471, 2473, or a fragment thereof. In another specific embodiment, the DNA vaccine formulations of the present invention comprises a nucleic acid or fragment thereof encoding the antibodies which immunospecifically binds hSARS viruses. In DNA vaccine formulations, a vaccine DNA comprises a viral vector, such as that derived from the hSARS virus, bacterial plasmid, or other expression vector, bearing an insert comprising a nucleic acid molecule of the present invention operably linked to one or more control elements, thereby allowing expression of the vaccinating proteins encoded by said nucleic acid molecule in a vaccinated subject. Such vectors can be prepared by recombinant DNA technology as recombinant or chimeric viral vectors carrying a nucleic acid molecule of the present invention (see also Section 5.1, supra).

[0101] Various heterologous vectors are described for DNA vaccinations against viral infections. For example, the vectors described in the following references may be used to express hSARS sequences instead of the sequences of the viruses or other pathogens described; in particular, vectors described for hepatitis B virus (Michel, M. L. et al., 1995, DAN-mediated immunization to the hepatitis B surface antigen in mice: Aspects of the humoral response mimic hepatitis B viral infection in humans, *Proc. Natl. Acad. Sci. USA* 92:5307-5311; Davis, H. L. et al., 1993, DNA-based

immunization induces continuous secretion of hepatitis B surface antigen and high levels of circulating antibody, *Human Molec. Genetics* 2:1847-1851), HIV virus (Wang, B. et al., 1993, Gene inoculation generates immune responses against human immunodeficiency virus type 1, *Proc. Natl. Acad. Sci. USA* 90:4156-4160; Lu, S. et al., 1996, Simian immunodeficiency virus DNA vaccine trial in macaques, *J. Virol.* 70:3978-3991; Letvin, N. L. et al., 1997, Potent, protective anti-HIV immune responses generated by bimodal HIV envelope DNA plus protein vaccination, *Proc Natl Acad Sci USA*. 94(17):9378-83), and influenza viruses (Robinson, H I et al., 1993, Protection against a lethal influenza virus challenge by immunization with a haemagglutinin-expressing plasmid DNA, *Vaccine* 11:957-960; Ulmer, J. B. et al., Heterologous protection against influenza by injection of DNA encoding a viral protein, *Science* 259:1745-1749), as well as bacterial infections, such as tuberculosis (Tascon, R. E. et al., 1996, Vaccination against tuberculosis by DNA injection, *Nature Med.* 2:888-892; Huygen, K. et al., 1996, Immunogenicity and protective efficacy of a tuberculosis DNA vaccine, *Nature Med.*, 2:893-898), and parasitic infection, such as malaria (Sedegah, M., 1994, Protection against malaria by immunization with plasmid DNA encoding circumsporozoite protein, *Proc. Natl. Acad. Sci. USA* 91:9866-9870; Doolan, D. L. et al., 1996, Circumventing genetic restriction of protection against malaria with multigene DNA immunization: CD8+ T cell-interferon δ , and nitric oxide-dependent immunity, *J. Exper. Med.*, 1183:1739-1746).

[0102] Many methods may be used to introduce the vaccine formulations described above. These include, but are not limited to, oral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, and intranasal routes. Alternatively, it may be preferable to introduce the chimeric virus vaccine formulation via the natural route of infection of the pathogen for which the vaccine is designed. The DNA vaccines of the present invention may be administered in saline solutions by injections into muscle or skin using a syringe and needle (Wolff J. A. et al., 1990, Direct gene transfer into mouse muscle in vivo, *Science* 247:1465-1468; Raz, E., 1994, Intradermal gene immunization: The possible role of DNA uptake in the induction of cellular immunity to viruses, *Proc. Natl. Acad. Sci. USA* 91:9519-9523). Another way to administer DNA vaccines is called "gene gun" method, whereby microscopic gold beads coated with the DNA molecules of interest is fired into the cells (Tang, D. et al., 1992, Genetic immunization is a simple method for eliciting an immune response, *Nature* 356:152-154). For general reviews of the methods for DNA vaccines, see Robinson, H. L., 1999, DNA vaccines: basic mechanism and immune responses (Review), *Int. J. Mol. Med.* 4(5):549-555; Barber, B., 1997, Introduction: Emerging vaccine strategies, *Seminars in Immunology* 9(5):269-270; and Robinson, H. L. et al., 1997, DNA vaccines, *Seminars in Immunology* 9(5):271-283.

[0103] **5.3 Attenuation of hSARS Virus or Variants Thereof**

[0104] The hSARS virus or variants thereof of the invention can be genetically engineered to exhibit an attenuated phenotype. In particular, the viruses of the invention exhibit an attenuated phenotype in a subject to which the virus is administered as a vaccine. Attenuation can be achieved by any method known to a skilled artisan. Without being bound

by theory, the attenuated phenotype of the viruses of the invention can be caused, e.g., by using a virus that naturally does not replicate well in an intended host species, for example, by reduced replication of the viral genome, by reduced ability of the virus to infect a host cell, or by reduced ability of the viral proteins to assemble to an infectious viral particle relative to the wild type strain of the virus.

[0105] The attenuated phenotypes of hSARS virus or variants thereof can be tested by any method known to the artisan. A candidate virus can, for example, be tested for its ability to infect a host or for the rate of replication in a cell culture system. In certain embodiments, growth curves at different temperatures are used to test the attenuated phenotype of the virus. For example, an attenuated virus is able to grow at 35° C., but not at 39° C. or 40° C. In certain embodiments, different cell lines can be used to evaluate the attenuated phenotype of the virus. For example, an attenuated virus may only be able to grow in monkey cell lines but not the human cell lines, or the achievable virus titers in different cell lines are different for the attenuated virus. In certain embodiments, viral replication in the respiratory tract of a small animal model, including but not limited to, hamsters, cotton rats, mice and guinea pigs, is used to evaluate the attenuated phenotypes of the virus. In other embodiments, the immune response induced by the virus, including but not limited to, the antibody titers (e.g., assayed by plaque reduction neutralization assay or ELISA) is used to evaluate the attenuated phenotypes of the virus. In a specific embodiment, the plaque reduction neutralization assay or ELISA is carried out at a low dose. In certain embodiments, the ability of the hSARS virus to elicit pathological symptoms in an animal model can be tested. A reduced ability of the virus to elicit pathological symptoms in an animal model system is indicative of its attenuated phenotype. In a specific embodiment, the candidate viruses are tested in a monkey model for nasal infection, indicated by mucous production.

[0106] The viruses of the invention can be attenuated such that one or more of the functional characteristics of the virus are impaired. In certain embodiments, attenuation is measured in comparison to the wild type strain of the virus from which the attenuated virus is derived. In other embodiments, attenuation is determined by comparing the growth of an attenuated virus in different host systems. Thus, for a non-limiting example, hSARS virus or a variant thereof is said to be attenuated when grown in a human host if the growth of the hSARS or variant thereof in the human host is reduced compared to the non-attenuated hSARS or variant thereof.

[0107] In certain embodiments, the attenuated virus of the invention is capable of infecting a host, is capable of replicating in a host such that infectious viral particles are produced. In comparison to the wild type strain, however, the attenuated strain grows to lower titers or grows more slowly. Any technique known to the skilled artisan can be used to determine the growth curve of the attenuated virus and compare it to the growth curve of the wild type virus.

[0108] In certain embodiments, the attenuated virus of the invention (e.g., a recombinant or chimeric hSARS) cannot replicate in human cells as well as the wild type virus (e.g., wild type hSARS) does. However, the attenuated virus can replicate well in a cell line that lack interferon functions, such as Vero cells.

[0109] In other embodiments, the attenuated virus of the invention is capable of infecting a host, of replicating in the host, and of causing proteins of the virus of the invention to be inserted into the cytoplasmic membrane, but the attenuated virus does not cause the host to produce new infectious viral particles. In certain embodiments, the attenuated virus infects the host, replicates in the host, and causes viral proteins to be inserted in the cytoplasmic membrane of the host with the same efficiency as the wild type hSARS. In other embodiments, the ability of the attenuated virus to cause viral proteins to be inserted into the cytoplasmic membrane into the host cell is reduced compared to the wild type virus. In certain embodiments, the ability of the attenuated hSARS virus to replicate in the host is reduced compared to the wild type virus. Any technique known to the skilled artisan can be used to determine whether a virus is capable of infecting a mammalian cell, of replicating within the host, and of causing viral proteins to be inserted into the cytoplasmic membrane of the host.

[0110] In certain embodiments, the attenuated virus of the invention is capable of infecting a host. In contrast to the wild type hSARS, however, the attenuated hSARS cannot be replicated in the host. In a specific embodiment, the attenuated hSARS virus can infect a host and can cause the host to insert viral proteins in its cytoplasmic membranes, but the attenuated virus is incapable of being replicated in the host. Any method known to the skilled artisan can be used to test whether the attenuated hSARS has infected the host and has caused the host to insert viral proteins in its cytoplasmic membranes.

[0111] In certain embodiments, the ability of the attenuated virus to infect a host is reduced compared to the ability of the wild type virus to infect the same host. Any technique known to the skilled artisan can be used to determine whether a virus is capable of infecting a host.

[0112] In certain embodiments, mutations (e.g., missense mutations) are introduced into the genome of the virus, for example, into the sequence of SEQ ID NO:1, 11, 13, 15, 2471 or 2473, or to generate a virus with an attenuated phenotype. Mutations (e.g., missense mutations) can be introduced into the structural genes and/or regulatory genes of the hSARS. Mutations can be additions, substitutions, deletions, or combinations thereof. Such variant of hSARS can be screened for a predicted functionality, such as infectivity, replication ability, protein synthesis ability, assembling ability, as well as cytopathic effect in cell cultures. In a specific embodiment, the missense mutation is a cold-sensitive mutation. In another embodiment, the missense mutation is a heat-sensitive mutation. In another embodiment, the missense mutation prevents a normal processing or cleavage of the viral proteins.

[0113] In other embodiments, deletions are introduced into the genome of the hSARS virus, which result in the attenuation of the virus.

[0114] In certain embodiments, attenuation of the virus is achieved by replacing a gene of the wild type virus with a gene of a virus of a different species, of a different subgroup, or of a different variant. In another aspect, attenuation of the virus is achieved by replacing one or more specific domains of a protein of the wild type virus with domains derived from the corresponding protein of a virus of a different species. In certain other embodiments, attenuation of the virus is

achieved by deleting one or more specific domains of a protein of the wild type virus.

[0115] When a live attenuated vaccine is used, its safety must also be considered. The vaccine must not cause disease. Any techniques known in the art that can make a vaccine safe may be used in the present invention. In addition to attenuation techniques, other techniques may be used. One non-limiting example is to use a soluble heterologous gene that cannot be incorporated into the virion membrane. For example, a single copy of the soluble version of a viral transmembrane protein lacking the transmembrane and cytosolic domains thereof, can be used.

[0116] Various assays can be used to test the safety of a vaccine. For example, sucrose gradients and neutralization assays can be used to test the safety. A sucrose gradient assay can be used to determine whether a heterologous protein is inserted in a virion. If the heterologous protein is inserted in the virion, the virion should be tested for its ability to cause symptoms in an appropriate animal model since the virus may have acquired new, possibly pathological, properties.

[0117] 5.4 Adjuvants and Carrier Molecules

[0118] hSARS-associated antigens are administered with one or more adjuvants. In one embodiment, the hSARS-associated antigen is administered together with a mineral salt adjuvants or mineral salt gel adjuvant. Such mineral salt and mineral salt gel adjuvants include, but are not limited to, aluminum hydroxide (ALHYDROGEL, REHYDRAGEL), aluminum phosphate gel, aluminum hydroxyphosphate (ADJU-PHOS), and calcium phosphate.

[0119] In another embodiment, hSARS-associated antigen is administered with an immunostimulatory adjuvant. Such class of adjuvants, include, but are not limited to, cytokines (e.g., interleukin-2, interleukin-7, interleukin-12, granulocyte-macrophage colony stimulating factor (GM-CSF), interferon- γ -interleukin-1 β (IL-1 β), and IL-1 β peptide or Sclavo Peptide), cytokine-containing liposomes, triterpenoid glycosides or saponins (e.g., QuilA and QS-21, also sold under the trademark STIMULON, ISCOPREP), Muramyl Dipeptide (MDP) derivatives, such as N-acetylmuramyl-L-threonyl-D-isoglutamine (Threonyl-MDP, sold under the trademark TERMURTIDE), GMDP, N-acetylnor-muramyl-L-alanyl-D-isoglutamine, N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-sn-glycero-3-hydroxy phosphoryloxy)-ethylamine, muramyl tripeptide phosphatidylethanolamine (MTP-PE), unmethylated CpG dinucleotides and oligonucleotides, such as bacterial DNA and fragments thereof, LPS, monophosphoryl Lipid A (3D-MLA sold under the trademark MPL), and polyphosphazenes.

[0120] In another embodiment, the adjuvant used is a particular adjuvant, including, but not limited to, emulsions, e.g., Freund's Complete Adjuvant, Freund's Incomplete Adjuvant, squalene or squalene oil-in-water adjuvant formulations, such as SAF and MF59, e.g., prepared with block-copolymers, such as L-121 (polyoxypropylene/polyoxyethylene) sold under the trademark PLURONIC L-121, Liposomes, Virosomes, cochleates, and immune stimulating complex, which is sold under the trademark ISCOM.

[0121] In another embodiment, a microparticulate adjuvant is used. Microparticulate adjuvants include, but are not limited to biodegradable and biocompatible polyesters,

homo- and copolymers of lactic acid (PLA) and glycolic acid (PGA), poly(lactide-co-glycolides) (PLGA) microparticles, polymers that self-associate into particulates (poloxamer particles), soluble polymers (polyphosphazenes), and virus-like particles (VLPs) such as recombinant protein particulates, e.g., hepatitis B surface antigen (HbsAg).

[0122] Yet another class of adjuvants that may be used include mucosal adjuvants, including but not limited to heat-labile enterotoxin from *Escherichia coli* (LT), cholera holotoxin (CT) and cholera Toxin B Subunit (CTB) from *Vibrio cholerae*, mutant toxins (e.g., LTK63 and LTR72), microparticles, and polymerized liposomes.

[0123] In other embodiments, any of the above classes of adjuvants may be used in combination with each other or with other adjuvants. For example, non-limiting examples of combination adjuvant preparations that can be used to administer the hSARS-associated antigens of the invention include liposomes containing immunostimulatory protein, cytokines, or T-cell and/or B-cell peptides, or microbes with or without entrapped IL-2 or microparticles containing enterotoxin. Other adjuvants known in the art are also included within the scope of the invention (see *Vaccine Design: The Subunit and Adjuvant Approach*, Chap. 7, Michael F. Powell and Mark J. Newman (eds.), Plenum Press, New York, 1995, which is incorporated herein in its entirety).

[0124] The effectiveness of an adjuvant may be determined by measuring the induction of antibodies directed against an immunogenic polypeptide containing a hSARS polypeptide epitope, the antibodies resulting from administration of this polypeptide in vaccines which are also comprised of the various adjuvants.

[0125] The polypeptides may be formulated into the vaccine as neutral or salt forms. Pharmaceutically acceptable salts include the acid additional salts (formed with free amino groups of the peptide) and which are formed with inorganic acids, such as, for example, hydrochloric or phosphoric acids, or organic acids such as acetic, oxalic, tartaric, maleic, and the like. Salts formed with free carboxyl groups may also be derived from inorganic bases, such as, for example, sodium potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine and the like.

[0126] The vaccines of the invention may be multivalent or univalent. Multivalent vaccines are made from recombinant viruses that direct the expression of more than one antigen.

[0127] Many methods may be used to introduce the vaccine formulations of the invention; these include but are not limited to oral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal routes, and via scarification (scratching through the top layers of skin, e.g., using a bifurcated needle).

[0128] The patient to which the vaccine is administered is preferably a mammal, most preferably a human, but can also be a non-human animal including but not limited to cows, horses, sheep, pigs, fowl (e.g., chickens), goats, cats, dogs, hamsters, mice and rats.

[0129] 5.5 Preparation of Antibodies

[0130] Antibodies which specifically recognize a polypeptide of the invention, such as, but not limited to, polypeptides comprising the sequence of SEQ ID NO:2, 12, 14, 2472, 2474, and polypeptides as shown in FIGS. 11 (SEQ ID NOS:17-239, 241-736 and 738-1107) and 12 (SEQ ID NOS:1109-1589, 1591-1964 and 1966-2470), or hSARS epitope or antigen-binding fragments thereof can be used for detecting, screening, and isolating the polypeptide of the invention or fragments thereof, or similar sequences that might encode similar enzymes from the other organisms. For example, in one specific embodiment, an antibody which immunospecifically binds hSARS epitope, or a fragment thereof, can be used for various in vitro detection assays, including enzyme-linked immunosorbent assays (ELISA), radioimmunoassays, Western blot, etc., for the detection of a polypeptide of the invention or, preferably, hSARS, in samples, for example, a biological material, including cells, cell culture media (e.g., bacterial cell culture media, mammalian cell culture media, insect cell culture media, yeast cell culture media, etc.), blood, plasma, serum, tissues, sputum, nasopharyngeal aspirates, etc.

[0131] Antibodies specific for a polypeptide of the invention or any epitope of hSARS may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of-interest, for example, the hSARS virus from deposit no. CCTCC-V200303, or comprises a nucleotide sequence of SEQ ID NO:15, can be produced by various procedures well known in the art. For example, an antigen can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc., to induce the production of antisera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete) adjuvant, mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful adjuvants for humans such as BCG (*Bacille Calmette-Guerin*) and *Corynebacterium parvum*. Such adjuvants are also well known in the art.

[0132] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: *Monoclonal Antibodies and T-Cell Hybridomas*, pp. 563-681 (Elsevier, N.Y., 1981) (both of which are incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

[0133] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art. In a non-limiting example, mice can be

immunized with an antigen of interest or a cell expressing such an antigen. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells. Hybridomas are selected and cloned by limiting dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding the antigen. Ascites fluid, which generally contains high levels of antibodies, can be generated by inoculating mice intraperitoneally with positive hybridoma clones.

[0134] Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')₂ fragments may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments). F(ab')₂ fragments contain the complete light chain, and the variable region, the CH1 region and the hinge region of the heavy chain.

[0135] The antibodies of the invention or fragments thereof can be also produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

[0136] The nucleotide sequence encoding an antibody may be obtained from any information available to those skilled in the art (i.e., from Genbank, the literature, or by routine cloning and sequence analysis). If a clone containing a nucleic acid encoding a particular antibody or an epitope-binding fragment thereof is not available, but the sequence of the antibody molecule or epitope-binding fragment thereof is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

[0137] Once the nucleotide sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., *supra*; and Ausubel et al., eds., 1998, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence by, for example, introducing amino acid substitutions, deletions, and/or insertions into the epitope-binding domain regions of the antibodies or any portion of antibodies which may enhance or reduce biological activities of the antibodies.

[0138] Recombinant expression of an antibody requires construction of an expression vector containing a nucleotide

sequence that encodes the antibody. Once a nucleotide sequence encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art as discussed in the previous sections. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The nucleotide sequence encoding the heavy-chain variable region, light-chain variable region, both the heavy-chain and light-chain variable regions, an epitope-binding fragment of the heavy- and/or light-chain variable region, or one or more complementarity determining regions (CDRs) of an antibody may be cloned into such a vector for expression. Thus-prepared expression vector can be then introduced into appropriate host cells for the expression of the antibody. Accordingly, the invention includes host cells containing a polynucleotide encoding an antibody specific for the polypeptides of the invention or fragments thereof.

[0139] The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides or different selectable markers to ensure maintenance of both plasmids. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, *Nature*, 322:52, 1986; and Kohler, *Proc. Natl. Acad. Sci. USA*, 77:2 197, 1980). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[0140] In another embodiment, antibodies can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains, such as Fab and Fv or disulfide-bond stabilized Fv, expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage, including fd and M13. The antigen binding domains are expressed as a recombinantly fused protein to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the immunoglobulins, or fragments thereof, of the present invention include those disclosed in Brinkman et al., *J. Immunol. Methods*, 182:41-50, 1995; Ames et al., *J. Immunol. Methods*, 184:177-186, 1995; Kettleborough et al., *Eur. J. Immunol.*, 24:952-958, 1994; Persic et al., *Gene*, 187:9-18, 1997; Burton et al., *Advances in Immunology*, 57:191-280, 1994; PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and

U.S. Pat. Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

[0141] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired fragments, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab)₂ fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., *BioTechniques*, 12(6):864-869, 1992; and Sawai et al., *AJRI*, 34:26-34, 1995; and Better et al., *Science*, 240:1041-1043, 1988 (each of which is incorporated by reference in its entirety). Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Pat. Nos. 4,946,778 and 5,258,498; Huston et al., *Methods in Enzymology*, 203:46-88, 1991; Shu et al., *PNAS*, 90:7995-7999, 1993; and Skerra et al., *Science*, 240:1038-1040, 1988.

[0142] Once an antibody molecule of the invention has been produced by any methods described above, it may then be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A or Protein G purification, and sizing column chromatography), centrifugation, differential solubility, or by any other standard techniques for the purification of proteins. Further, the antibodies of the present invention or fragments thereof may be fused to heterologous polypeptide sequences described herein or otherwise known in the art to facilitate purification.

[0143] For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a constant region derived from a human immunoglobulin. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, *Science*, 229:1202, 1985; Oi et al., *BioTechniques*, 4:214 1986; Gillies et al., *J. Immunol. Methods*, 125:191-202, 1989; U.S. Pat. Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entireties. Humanized antibodies are antibody molecules from non-human species that bind the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. See, e.g., Queen et al., U.S. Pat. No. 5,585,089; Riechmann et al.,

Nature, 332:323, 1988, which are incorporated herein by reference in their entireties. Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Pat. Nos. 5,225,539; 5,530,101 and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, *Molecular Immunology*, 28(4/5):489-498, 1991; Studnicka et al., *Protein Engineering*, 7(6):805-814, 1994; Roguska et al., *Proc Natl. Acad. Sci. USA*, 91:969-973, 1994), and chain shuffling (U.S. Pat. No. 5,565,332), all of which are hereby incorporated by reference in their entireties.

[0144] Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See U.S. Pat. Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645; WO 98/50433; WO 98/24893; WO 98/16654; WO 96/34096; WO 96/33735; and WO 91/10741, each of which is incorporated herein by reference in its entirety.

[0145] Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, *Int. Rev. Immunol.*, 13:65-93, 1995. For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Pat. Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598, which are incorporated by reference herein in their entireties. In addition, companies such as Abgenix, Inc. (Fremont, Calif.), Medarex (NJ) and Genpharm (San Jose, Calif.) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[0146] Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespersen et al., *Bio/technology*, 12:899-903, 1988).

[0147] Antibodies fused or conjugated to heterologous polypeptides may be used in *in vitro* immunoassays and in purification methods (e.g., affinity chromatography) well known in the art. See e.g., PCT publication Number WO 93/21232; EP 439,095; Naramura et al., *Immunol. Lett.*, 39:91-99, 1994; U.S. Pat. No. 5,474,981; Gillies et al., *PNAS*, 89:1428-1432, 1992; and Fell et al., *J. Immunol.*, 146:2446-2452, 1991, which are incorporated herein by reference in their entireties.

[0148] Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the polypeptides of the invention or fragments, derivatives, analogs, or variants thereof, or similar molecules having the similar enzymatic activities as the

polypeptide of the invention. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[0149] 5.6 Pharmaceutical Compositions and Kits

[0150] The present invention encompasses pharmaceutical compositions comprising anti-viral agents of the present invention. In a specific embodiment, the anti-viral agent is an antibody which immunospecifically binds and neutralize the hSARS virus or variants thereof, or any proteins derived therefrom. In another specific embodiment, the anti-viral agent is a polypeptide or nucleic acid molecule of the invention. The pharmaceutical compositions have utility as an anti-viral prophylactic agent and may be administered to a subject where the subject has been exposed or is expected to be exposed to a virus.

[0151] Various delivery systems are known and can be used to administer the pharmaceutical composition of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, e.g., Wu and Wu, 1987, *J. Biol. Chem.* 262:4429-4432). Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In a preferred embodiment, it may be desirable to introduce the pharmaceutical compositions of the invention into the lungs by any suitable route. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0152] In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. In one embodiment, administration can be by direct injection at the site (or former site) infected tissues.

[0153] In another embodiment, the pharmaceutical composition can be delivered in a vesicle, in particular a liposome (see Langer, 1990, *Science* 249:1527-1533; Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez Berestein and Fidler (eds.), Liss, N.Y., pp. 353-365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*).

[0154] In yet another embodiment, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:201; Buchwald et al., 1980, *Surgery* 88:507; and Saudek et al., 1989, *N. Engl. J. Med.* 321:574). In another embodiment, polymeric materials can be used (see *Medical Applications of Con-*

trolled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, N.Y. (1984); Ranger and Peppas, J. Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., 1985, Science 228:190; During et al., 1989, Ann. Neurol. 25:351; Howard et al., 1989, J. Neurosurg. 71:105). In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, i.e., the lung, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)).

[0155] Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

[0156] The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a live attenuated, inactivated or killed hSARS virus, or recombinant or chimeric hSARS virus, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the pharmaceutical composition is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin. The formulation should suit the mode of administration.

[0157] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be

administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0158] The pharmaceutical compositions of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2 ethylamino ethanol, histidine, procaine, etc.

[0159] The amount of the pharmaceutical composition of the invention which will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. However, suitable dosage ranges for intravenous administration are generally about 20 500 micrograms of active compound per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.01 pg/kg body weight to 1 mg/kg body weight. Effective doses may be extrapolated from dose response curves derived from *in vitro* or animal model test systems.

[0160] Suppositories generally contain active ingredient in the range of 0.5% to 10% by weight; oral formulations preferably contain 10% to 95% active ingredient.

[0161] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In a preferred embodiment, the kit contains an anti-viral agent of the invention, e.g., an antibody specific for the polypeptides encoded by a nucleotide sequence of SEQ ID NO:1, 11, 13, 15, 2471 or 2473, or as shown in FIGS. 11 (SEQ ID NOS: 17-239, 241-736 and 738-1107) and 12 (SEQ ID NOS: 1109-1589, 1591-1964 and 1966-2470), or any hSARS epitope, or a polypeptide or protein of the present invention, or a nucleic acid molecule of the invention, alone or in combination with adjuvants, antivirals, antibiotics, analgesic, bronchodilators, or other pharmaceutically acceptable excipients.

[0162] The present invention further encompasses kits comprising a container containing a pharmaceutical composition of the present invention and instructions to for use.

[0163] 5.7 Detection Assays

[0164] The present invention provides a method for detecting an antibody, which immunospecifically binds to the hSARS virus, in a biological sample, for example blood,

serum, plasma, saliva, urine, etc., from a patient suffering from SARS. In a specific embodiment, the method comprising contacting the sample with the hSARS virus, for example, of deposit no. CCTCC-V200303, or having a genomic nucleic acid sequence of SEQ ID NO:15, directly immobilized on a substrate and detecting the virus-bound antibody directly or indirectly by a labeled heterologous anti-isotype antibody. In another specific embodiment, the sample is contacted with a host cell which is infected by the hSARS virus, for example, of deposit no. CCTCC-V200303, or having a genomic nucleic acid sequence of SEQ ID NO:15, and the bound antibody can be detected by immunofluorescent assay as described in Section 6.5, *infra*.

[0165] An exemplary method for detecting the presence or absence of a polypeptide or nucleic acid of the invention in a biological sample involves obtaining a biological sample from various sources and contacting the sample with a compound or an agent capable of detecting an epitope or nucleic acid (e.g., mRNA, genomic RNA) of the hSARS virus such that the presence of the hSARS virus is detected in the sample. A preferred agent for detecting hSARS mRNA or genomic RNA of the invention is a labeled nucleic acid probe capable of hybridizing to mRNA or genomic RNA encoding a polypeptide of the invention. The nucleic acid probe can be, for example, a nucleic acid molecule comprising or consisting of the nucleotide sequence or SEQ ID NO:1, 11, 13, 15, 2471, or 2473, or a portion thereof, such as an oligonucleotide of at least 15, 20, 25, 30, 50, 100, 250, 500, 750, 1,000 or more contiguous nucleotides in length and sufficient to specifically hybridize under stringent conditions to a hSARS mRNA or genomic RNA.

[0166] In another preferred specific embodiment, the presence of hSARS virus is detected in the sample by a reverse transcription polymerase chain reaction (RT-PCR) using the primers that are constructed based on a partial nucleotide sequence of the genome of hSARS virus, for example, that of deposit accession no. CCTCC-V200303, or having a genomic nucleic acid sequence of SEQ ID NO:15, or based on a nucleotide sequence of SEQ ID NO:1, 11, 13, 2471 or 2473. In a non-limiting specific embodiment, preferred primers to be used in a RT-PCR method are: 5'-TACACAC-CTCAGC-GTTG-3' (SEQ ID NO:3) and 5'-CACGAACGT-GACG-AAT-3' (SEQ ID NO:4), in the presence of 2.5 mM MgCl₂ and the thermal cycles are, for example, but not limited to, 94° C. for 8 min followed by 40 cycles of 94° C. for 1 min, 50° C. for 1 min, 72° C. for 1 min (also see Sections 6.7 and 6.8 *infra*). In preferred embodiments, the primers comprise nucleic acid sequence of SEQ ID NOS:2475 and 2476, or SEQ ID NOS:2480 and 2481. In preferred embodiments, the thermal cycles are 94° C. for 10 min followed by 40 cycles of 94° C. for 30 seconds, 56° C. for 30 seconds, 72° C. for 30 seconds, 72° C. for 10 minutes. In preferred embodiments, the primers comprise nucleic acid sequence of SEQ ID NOS:2477 and 2478. In more preferred specific embodiment, the present invention provides a real-time quantitative PCR assay to detect the presence of hSARS virus in a biological sample by subjecting the cDNA obtained by reverse transcription of the extracted total RNA from the sample to PCR reactions using the specific primers, such as those having nucleotide sequences of SEQ ID NOS:3 and 4, and a fluorescence dye, such as SYBR® Green I, which fluoresces when bound non-specifically to double-stranded DNA. The fluorescence signals from these reactions are captured at the end of

extension steps as PCR product is generated over a range of the thermal cycles, thereby allowing the quantitative determination of the viral load in the sample based on an amplification plot (see Section 6.7, *infra*).

[0167] A preferred agent for detecting hSARS is an antibody that specifically binds a polypeptide of the invention or any hSARS epitope, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (e.g., Fab or F(ab')₂) can be used.

[0168] The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (i.e., physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin. The detection method of the invention can be used to detect mRNA, protein (or any epitope), or genomic RNA in a sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of mRNA include northern hybridizations, *in situ* hybridizations, RT-PCR, and RNase protection. *In vitro* techniques for detection of an epitope of hSARS include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of genomic RNA include northern hybridizations, RT-PCR, and RNase protection. Furthermore, *in vivo* techniques for detection of hSARS include introducing into a subject organism a labeled antibody directed against the polypeptide. For example, the antibody can be labeled with a radioactive marker whose presence and location in the subject organism can be detected by standard imaging techniques, including autoradiography.

[0169] In a specific embodiment, the methods further involve obtaining a control sample from a control subject, contacting the control sample with a compound or agent capable of detecting hSARS, e.g., a polypeptide of the invention or mRNA or genomic RNA encoding a polypeptide of the invention, such that the presence of hSARS or the polypeptide or mRNA or genomic RNA encoding the polypeptide is detected in the sample, and comparing the presence of hSARS or the polypeptide or mRNA or genomic RNA encoding the polypeptide in the control sample with the presence of hSARS, or the polypeptide or mRNA or genomic DNA encoding the polypeptide in the test sample.

[0170] The invention also encompasses kits for detecting the presence of hSARS or a polypeptide or nucleic acid of the invention in a test sample. The kit, for example, can comprise a labeled compound or agent capable of detecting hSARS or the polypeptide or a nucleic acid molecule encoding the polypeptide in a test sample and, in certain embodiments, a means for determining the amount of the polypeptide or mRNA in the sample (e.g., an antibody which binds the polypeptide or an oligonucleotide probe which binds to DNA or mRNA encoding the polypeptide). Kits can also include instructions for use.

[0171] For antibody-based kits, the kit can comprise, for example: (1) a first antibody (e.g., attached to a solid support) which binds to a polypeptide of the invention or

hSARS epitope; and, optionally, (2) a second, different antibody which binds to either the polypeptide or the first antibody and is conjugated to a detectable agent.

[0172] For oligonucleotide-based kits, the kit can comprise, for example: (1) an oligonucleotide, e.g., a detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a polypeptide of the invention or to a sequence within the hSARS genome or (2) a pair of primers useful for amplifying a nucleic acid molecule containing an hSARS sequence. The kit can also comprise, e.g., a buffering agent, a preservative, or a protein stabilizing agent. The kit can also comprise components necessary for detecting the detectable agent (e.g., an enzyme or a substrate). The kit can also contain a control sample or a series of control samples which can be assayed and compared to the test sample contained. Each component of the kit is usually enclosed within an individual container and all of the various containers are within a single package along with instructions for use.

[0173] 5.8 Screening Assays to Identify Anti-Viral Agents

[0174] The invention provides methods for the identification of a compound that inhibits the ability of hSARS virus to infect a host or a host cell. In certain embodiments, the invention provides methods for the identification of a compound that reduces the ability of hSARS virus to replicate in a host or a host cell. Any technique well-known to the skilled artisan can be used to screen for a compound that would abolish or reduce the ability of hSARS virus to infect a host and/or to replicate in a host or a host cell.

[0175] In certain embodiments, the invention provides methods for the identification of a compound that inhibits the ability of hSARS virus to replicate in a mammal or a mammalian cell. More specifically, the invention provides methods for the identification of a compound that inhibits the ability of hSARS virus to infect a mammal or a mammalian cell. In certain embodiments, the invention provides methods for the identification of a compound that inhibits the ability of hSARS virus to replicate in a mammalian cell. In a specific embodiment, the mammalian cell is a human cell.

[0176] In another embodiment, a cell is contacted with a test compound and infected with the hSARS virus. In certain embodiments, a control culture is infected with the hSARS virus in the absence of a test compound. The cell can be contacted with a test compound before, concurrently with, or subsequent to the infection with the hSARS virus. In a specific embodiment, the cell is a mammalian cell. In an even more specific embodiment, the cell is a human cell. In certain embodiments, the cell is incubated with the test compound for at least 1 minute, at least 5 minutes at least 15 minutes, at least 30 minutes, at least 1 hour, at least 2 hours, at least 5 hours, at least 12 hours, or at least 1 day. The titer of the virus can be measured at any time during the assay. In certain embodiments, a time course of viral growth in the culture is determined. If the viral growth is inhibited or reduced in the presence of the test compound, the test compound is identified as being effective in inhibiting or reducing the growth or infection of the hSARS virus. In a specific embodiment, the compound that inhibits or reduces the growth of the hSARS virus is tested for its ability to inhibit or reduce the growth rate of other viruses to test its specificity for the hSARS virus.

[0177] In one embodiment, a test compound is administered to a model animal and the model animal is infected with the hSARS virus. In certain embodiments, a control model animal is infected with the hSARS virus without the administration of a test compound. The test compound can be administered before, concurrently with, or subsequent to the infection with the hSARS virus. In a specific embodiment, the model animal is a mammal. In an even more specific embodiment, the model animal can be, but is not limited to, a cotton rat, a mouse, or a monkey. The titer of the virus in the model animal can be measured at any time during the assay. In certain embodiments, a time course of viral growth in the culture is determined. If the viral growth is inhibited or reduced in the presence of the test compound, the test compound is identified as being effective in inhibiting or reducing the growth or infection of the hSARS virus. In a specific embodiment, the compound that inhibits or reduces the growth of the hSARS in the model animal is tested for its ability to inhibit or reduce the growth rate of other viruses to test its specificity for the hSARS virus.

6. EXAMPLES

[0178] The following examples illustrate the isolation and identification of the novel hSARS virus. These examples should not be construed as limiting.

[0179] Methods and Results

[0180] As a general reference, Wiedbrauk D I & Johnston S L G. (Manual of Clinical Virology, Raven Press, New York, 1993) was used.

[0181] 6.1 Clinical Subjects

[0182] The study included all 50 patients who fitted a modified World Health Organization (WHO) definition of SARS and were admitted to 2 acute regional hospitals in Hong Kong Special Administrative Region (HKSAR) between Feb. 26 to Mar. 26, 2003 (WHO. Severe acute respiratory syndrome (SARS) *Weekly Epidemiol Rec.* 2003; 78: 81-83). A lung biopsy from an additional patient, who had typical SARS and was admitted to a third hospital, was also included in the study. Briefly, the case definition for SARS was: (i) fever of 38° C. or more; (ii) cough or shortness of breath; (iii) new pulmonary infiltrates on chest radiograph; and (iv) either a history of exposure to a patient with SARS or absence of response to empirical antimicrobial coverage for typical and atypical pneumonia (beta-lactams and macrolides, fluoroquinolones or tetracyclines).

[0183] Nasopharyngeal aspirates and serum samples were collected from all patients. Paired acute and convalescent sera and feces were available from some patients. Lung biopsy tissue from one patient was processed for a viral culture, RT-PCR, routine histopathological examination, and electron microscopy. Nasopharyngeal aspirates, feces and sera submitted for microbiological investigation of other diseases were included in the study under blinding and served as controls.

[0184] The medical records were reviewed retrospectively by the attending physicians and clinical microbiologists. Routine hematological, biochemical and microbiological examinations, including bacterial culture of blood and sputum, serological study and collection of nasopharyngeal aspirates for virological tests, were carried out.

[0185] 6.2 Cell Line

[0186] FRhK-4 (fetal rhesus monkey kidney) cells were maintained in minimal essential medium (MEM) with 1% fetal calf serum, 1% streptomycin and penicillin, 0.2% nystatin and 0.05% garamycin.

[0187] 6.3 Viral Infection

[0188] Two-hundred μ l of clinical (nasopharyngeal aspirates) samples, from two patients (see the Result section, infra), in virus transport medium were used to infect FRhK-4 cells. The inoculated cells were incubated at 37° C. for 1 hour. One ml of MEM containing 1 μ g trypsin was then added to the culture and the infected cells were incubated in a 37° C. incubator supplied with 5% carbon dioxide. Cytopathic effects were observed in the infected cells after 2 to 4 days of incubation. The infected cells were passaged into new FRhK-4 cells and cytopathic effects were observed within 1 day after the inoculation. The infected cells were tested by an immunofluorescent assay for influenza A, influenza B, respiratory syncytial virus, parainfluenza types 1, 2 and 3, adenovirus and human metapneumovirus (hMPV) and negative results were obtained for all cases. The infected cells were also tested by RT-PCR for influenza A and human metapneumovirus with negative results.

[0189] 6.4 Virus Morphology

[0190] The infected cells prepared as described above were harvested, pelleted by centrifugation and the cell pellets were processed for thin-section transmitted electron microscopic visualization. Viral particles were identified in the cells infected with both clinical specimens, but not in control cells which were not infected with the virus. Virions isolated from the infected cells were about 70-100 nanometers (**FIG. 2**). Viral capsids were found predominantly within the vesicles of the golgi and endoplasmic reticulum and were not free in the cytoplasm. Virus particles were also found at the cell membrane.

[0191] One virus isolate was ultracentrifuged and the cell pellet was negatively stained using phosphotungstic acid. Virus particles characteristic of Coronaviridae were thus visualized. Since the human Coronaviruses hitherto recognized are not known to cause a similar disease, the present inventors postulated that the virus isolates represent a novel virus that infects humans.

[0192] 6.5 Antibody Response to the Isolated Virus

[0193] To further confirm that this novel virus is responsible for causing SARS in the infected patients, blood serum samples from the patients who were suffering from SARS were obtained and a neutralization test was performed. Typically diluted serum ($\times 50$, $\times 200$, $\times 800$ and $\times 1600$) was incubated with acetone-fixed FRhK-4 cells infected with hSARS at 37° C. for 45 minutes. The incubated cells were then washed with phosphate-buffered saline and stained with anti-human IgG-FITC conjugated antibody. The cells were then washed and examined under a fluorescent microscope. In these experiments, positive signals were found in 8 patients who had SARS (**FIG. 3**), indicating that these patients had an IgG antibody response to this novel human respiratory virus of Coronaviridae. By contrast, no signal was detected in 4 negative-control paired sera. The serum titers of anti-hSARS antibodies of the tested patients are shown in Table 1.

TABLE 1

Name	Date	Lab No.	Anti-SARS
Patient A	25-Feb-03	S2728	<50
	6-Mar-03	S2728	1600
Patient B	26-Feb-03	S2441	50
	3-Mar-03	S2441	200
Patient C	4-Mar-03	S3279	200
	14-Mar-03	S3279	1600
Patient D	6-Mar-03	M41045	<50
	11-Mar-03	MB943703	800
Patient E	4-Mar-03	M38953	<50
	18-Mar-03	KWH03/3601	800
Control F	13-Feb-03	M27124	<50
	1-Mar-03	MB942968	<50
Patient G	3-Mar-03	M38685	<50
	7-Mar-03	KWH03/2900	Equivocal
Blinded samples:			
1a *		Acute	<50
1b		Convalescent	1600
2a *		Acute	50
2b		Convalescent	>1600
3a *		Acute	50
3b		Convalescent	>1600
4a *		Acute	<50
4b		Convalescent	<50
5a *		Acute	<50
5b		Convalescent	<50
6a *		Acute	<50
6b		Convalescent	<50

NB: * patients with SARS

These results indicated that this novel member of Coronaviridae is a key pathogen in SARS.

[0194] 6.6 Sequences of the hSARS Virus

[0195] Total RNA from infected or uninfected FRhK-4 cells was harvested two days post-infection. One-hundred ng of purified RNA was reverse transcribed using Superscript II 10 reverse transcriptase (Invitrogen) in a 20 μ l reaction mixture containing 10 pg of a degenerated primer (5'-GCCGGAGCTCTGCAGAAATTCNNNNNNN-3', N=A, T, G or C; SEQ ID NO:5) as recommended by the manufacturer. Reverse transcribed products were then purified by a QIAquick PCR purification kit as instructed by the manufacturer and eluted in 30 μ l of 10 mM Tris-HCl, pH 8.0. Three μ l of purified cDNA products were added in a 25 μ l reaction mixture containing 2.5 μ l of 10 \times PCR buffer, 4 μ l of 25 mM MgCl₂, 0.5 μ l of 10 mM dNTP, 0.25 μ l of AmpliTaq Gold® DNA polymerase (Applied Biosystems), 2.5 μ Ci of [α -³²P]CTP (Amersham), 2 μ l of 10 μ M primer (5'-GCCGGAGCTCTGCAGAAATTC-3'; SEQ ID NO:6). Reactions were thermal cycled through the following profile: 94° C. for 8 min followed by 2 cycles of 94° C. for 1 min, 40° C. for 1 min, 72° C. for 2 min. This temperature profile was followed by 35 cycles of 94° C. for 1 min, 60° C. for 1 min, 72° C. for 1 min. 6 μ l of the PCR products were analyzed in a 5% denaturing polyacrylamide gel electrophoresis. Gel was exposed to X-ray film and the film was developed after an over-night exposure. Unique PCR products which were only identified in infected cell samples were isolated from the gel and eluted in a 50 μ l of 1 \times TE buffer. Eluted PCR products were then re-amplified in 25 μ l of reaction mixture containing 2.5 μ l of 10 \times PCR buffer, 4 μ l of 25 mM MgCl₂, 0.5 μ l of 10 mM dNTP, 0.25 μ l of AmpliTaq Gold® DNA polymerase (Applied Biosystems), 1 μ l of 10 μ M primer (5'-GCCGGAGCTCTGCAGAAATTC-3'; SEQ ID NO:6).

Reaction mixtures were thermal cycled through the following profile: 94° C. for 8 min followed by 35 cycles of 94° C. for 1 min, 60° C. for 1 min, 72° C. for 1 min. PCR products were cloned using a TOPO TA cloning kit (Invitrogen) and ligated plasmids were transformed into TOP10 *E. coli* competent cells (Invitrogen). PCR inserts were sequenced by a BigDye cycle sequencing kit as recommended by the manufacturer (Applied Biosystems) and sequencing products were analyzed by an automatic sequencer (Applied Biosystems, model number 3770). The obtained sequence (SEQ ID NO:1) is shown in FIG. 1. The deduced amino acid sequence (SEQ ID NO:2) from the obtained DNA sequence showed 57% homology to the polymerase protein of identified coronaviruses.

[0196] Similarly, two other partial sequences (SEQ ID NOS:11 and 13) and deduced amino acid sequences (SEQ ID NOS:12 and 14, respectively) were obtained from the hSARS virus and are shown in FIGS. 8 (SEQ ID NOS:11 and 12) and 9 (SEQ ID NOS: 13 and 14).

[0197] The entire genomic sequence of hSARS virus is shown in FIG. 10 (SEQ ID NO:15). The deduced amino acid sequences of SEQ ID NO:15 in all three frames (SEQ ID NO:16, 240 and 737) are shown in FIG. 11 (SEQ ID NOS: 17-239, 241-736 and 738-1107). The deduced amino acid sequences of the complement of SEQ ID NO:15 in all three frames (SEQ ID NOS:1108, 1590 and 1965) are shown in FIG. 12 (SEQ ID NOS:1109-1589, 1591-1964 and 1966-2470).

[0198] 6.7 Detection of hSARS Virus in Nasopharyngeal Aspirates

[0199] First, the nasopharyngeal aspirates (NPA) were examined by rapid immunofluorescent antigen detection for influenza A and B, parainfluenza types 1, 2 and 3, respiratory syncytial virus and adenovirus (Chan K H, Maldeis N, Pope W, Yup A, Ozinskas A. Gill J, Seto W H, Shortridge K F, Peiris J S M. Evaluation of Directigen Fly A+B test for rapid diagnosis of influenza A and B virus infections. *J Clin Microbiol.* 2002; 40: 1675-1680) and were cultured for conventional respiratory pathogens on Mardin Darby Canine Kidney, LLC-Mk2, RDE, Hep-2 and MRC-5 cells (Wiedbrauk D L, Johnston S L G. *Manual of clinical virology.* Raven Press, New York. 1993). Subsequently, fetal rhesus kidney (FRhk-4) and A-549 cells were added to the panel of cell lines used. Reverse transcription polymerase chain reaction (RT-PCR) was performed directly on the clinical specimen for influenza A (Fouchier R A, Bestebroer T M, Herfst S, Van Der Kemp L, Rimmelzwan G F, Osterhaus A D. Detection of influenza A virus from different species by PCR amplification of conserved sequences in the matrix gene. *J Clin Microbiol.* 2000; 38: 4096-101) and human metapneumovirus (HMPV). The primers used for HMPV were: for first round, 5'-AARGTSAATGCAT-CAGC-3' (SEQ ID NO: 7) and 5'-CAKATTYTGCTTAT-GCTTTC-3' (SEQ ID NO:8); and nested primers: 5'-ACAC-CTGTTACAATACCAGC-3' (SEQ ID NO:9) and 5'-GACTTGAGTCCCAGCTCCA-3' (SEQ ID NO:10). The size of the nested PCR product was 201 bp. An ELISA for mycoplasma was used to screen cell cultures (Roche Diagnostics GmbH, Roche, Indianapolis, USA).

[0200] RT-PCR Assay

[0201] Subsequent to culturing and genetic sequencing of the hSARS virus from two patients (see Section 6.6, supra),

an RT-PCR was developed to detect the hSARS virus sequence from NPA samples. Total RNA from clinical samples was reverse transcribed using random hexamers and cDNA was amplified using primers 5'-TACACACCT-CAGC-GTTG-3' (SEQ ID NO:3) and 5'-CACGAACGT-GACGAAT-3' (SEQ ID NO:4), which are constructed based on the in the presence of 2.5 mM MgCl₂ (94° C. for 8 min followed by 40 cycles of 94° C. for 1 min, 50° C. for 1 min, 72° C. for 1 min).

[0202] The summary of a typical RT-PCR protocol is as follows:

[0203] 1. RNA Extraction

[0204] RNA from 140 µl of NPA samples is extracted by QIAquick viral RNA extraction kit and is eluted in 50 µl of elution buffer.

2. Reverse transcription

RNA	11.5 µl
0.1 M DTT	2 µl
5x buffer	4 µl
10 mM dNTP	1 µl
Superscript II, 200 U/µl (Invitrogen)	1 µl
Random hexamers, 0.3 µg/µl	0.5 µl
Reaction condition	42° C., 50 min 94° C., 3 min 4° C.

[0205] 3. PCR

[0206] cDNA generated by random primers is amplified in a 50 µl reaction as follows:

cDNA	2 µl
10 mM dNTP	0.5 µl
10x buffer	5 µl
25 mM MgCl ₂	5 µl
25 µM Forward primer	0.5 µl
25 µM Reverse primer	0.5 µl
AmpliTaq Gold polymerase, 5 U/µl (Applied Biosystems)	0.25 µl
Water	36.25 µl

[0207] Thermal-cycle condition: 95° C., 10 min, followed by 40 cycles of 95° C., 1 min; 50° C. 1 min; 72° C., 1 min.

[0208] 4. Primer Sequences

[0209] Primers were designed based on the RNA-dependent RNA polymerase encoding sequence (SEQ ID NO:1) of the hSARS virus.

Forward primer:
5' TACACACCTCAGCGTTG 3' (SEQ ID NO:3)

Reverse primer:
5' CACGAACGTGACGAAT 3' (SEQ ID NO:4)

[0210] Product size: 182 bps

[0211] Real-Time Quantitative PCR Assay

[0212] Total RNA from 140 µl of nasopharyngeal aspirate (NPA) was extracted by QIAamp® virus RNA mini kit

(Qiagen) as instructed by the manufacturer. Ten μl of eluted RNA samples were reverse transcribed by 200 U of Super-script II® reverse transcriptase (Invitrogen) in a 20 μl reaction mixture containing 0.15 μg of random hexamers, 10 mmol/l DTT, and 0.5 mmol/l dNTP, as instructed. Complementary DNA was then amplified in a SYBR® Green I fluorescence reaction (Roche) mixtures. Briefly, 20 μl reaction mixtures containing 2 μl of cDNA, 3.5 mmol/l MgCl_2 , 0.25 $\mu\text{mol/l}$ of forward primer (5'-TACACACCT-CAGCGTTG-3'; SEQ ID NO:3) and 0.25 $\mu\text{mol/l}$ reverse primer (5'-CACGAACGTGACGAAT-3'; SEQ ID NO:4) were thermal-cycled by a Light-Cycler (Roche) with the PCR program, [95° C., 10 min followed by 50 cycles of 95° C., 10 min; 57° C., 5 sec; 72° C. 9 sec]. Plasmids containing the target sequence were used as positive controls. Fluorescence signals from these reactions were captured at the end of extension step in each cycle. To determine the specificity of the assay, PCR products (184 base pairs) were subjected to a melting curve analysis at the end of the assay (65° C. to 95° C., 0.1° C. per second).

[0213] 6.8 Detection of N-Gene of hSARS Virus in Patients

[0214] 6.8.1 RT-PCR Diagnosis Protocol for *Coronavirus* in SARS Patients

[0215] Equipment required (for 96 samples):

[0216] 1×SV Total RNA Isolation system

[0217] 2×Mega titer plate

[0218] 3×96-well PCR plate

[0219] 1×0.5-10 μl multi-channel pipette

[0220] 1×10-100 μl multi-channel pipette

[0221] 1×20-200 μl multi-channel pipette

[0222] 1×vacuum pump

[0223] 1×swing-bucket rotor with microtest plate buckets

[0224] 2×PCR machine (96-well plate compatible)

[0225] 1×Gel electrophoresis apparatus

[0226] Station 1*—Clinical Samples Handling (1 Medical Officer/Clinical Technician)

[0227] Aliquot 500 μl sample in viral transport medium (containing, per liter, 2 g of sodium bicarbonate, 5 g of bovine serum albumin, 200 μg of vancomycin, 18 μg of amikacin, and 160 U of nystatin in Earle's balanced salt solution) from each individual vial into a well of 96-well mega titer plate containing 500 μl lysis buffer (1×) containing 100 μl PK-15 cell (ATCC CCL-33; 5.0×10^5 cell/ml) in complete minimum essential medium with Earle's salt (EMEM, Invitrogen) as internal control.**

[0228] Mix the lysate by pipetting up-and-down 3 times

[0229] Proceed to Station 2.

[0230] *Station 1 should be carried out inside Class III biological safety cabinet.

[0231] **At least two negative samples should be included in a 96-well platform as a negative control.

[0232] Station 2—Total RNA Extraction (1 Laboratory Technician)

[0233] Set up the Vacuum Manifold unit. Place the binding plate onto the Manifold Base.

[0234] Transfer the lysate from mega titer plate to each well of the SV 96 Binding Plate (binding plate).

[0235] Apply vacuum until the lysate passes through the binding plate. Release vacuum.

[0236] Add 500 μl of SV RNA Wash Solution (wash solution) to each well of binding plate.

[0237] Apply vacuum until the wash solution passes through binding plate. Release vacuum.

[0238] Prepare DNase incubation mix for an entire 96-well plate as below:

Yellow Core Buffer	2 ml
0.09 M MnCl_2	250 μl
DNase I	250 μl

[0239] Apply 25 μl freshly prepared DNase incubation mix directly to the membrane of the binding plate.

[0240] Incubate at 20-25° C. for 10 minutes.

[0241] Add 200 μl of SV DNase Stop Solution to each well of the binding plate.

[0242] Apply vacuum until the SV DNase Stop Solution passes through the binding plate. Release vacuum.

[0243] Add 500 μl wash solution to each well of the binding plate.

[0244] Apply vacuum until wash solution passes through the binding plate. Turn off vacuum.

[0245] Spin the binding plate at 3000×g for 30 seconds to remove residue wash solution.

[0246] Transfer the binding plate on top of a 96-well RT plate.

[0247] Add 50 μl nuclease-free water into each well of the binding plate to elute RNA.

[0248] Incubate at room temperature for 1 minute.

[0249] Spin the binding plate at 3000×g, 4° C. for 1 minute.

[0250] Collect eluted RNA in the 96-well RT plate.

[0251] Add 5 μl of 3 M sodium acetate and 200 μl of 95% ethanol into each well of the plate.

[0252] Place the RT plate on ice and incubate for 15 minutes.

[0253] Spin the plate at 3000×g, 4° C., 15 minutes.

[0254] Discard supernatant by inverting the plate and blotting on a clean paper towel.

[0255] Wash the pellet with 200 μl of 70% ethanol.

[0256] Spin the plate at 3000×g, 4° C., 10 minutes.

- [0257] Discard supernatant by inverting the plate and blotting on a clean paper towel.
 - [0258] Air-dry the pellet for 5 minutes.
 - [0259] Add 12 μ l of nuclease-free water into each well.
 - [0260] Vortex the plate briefly to dissolve the pellet (for an example result, see FIG. 18).
 - [0261] Proceed to Station 3.
- [0262] Station 3—Reverse Transcription (1 Laboratory Technician)
- [0263] Prepare RT master mix for an entire 96-well plate in a 1.5-ml tube as below (100 reactions):

	Per Reaction	$\times 100$
Random hexamers, 3 μ g/ μ l	0.05 μ l	5 μ l
DNTPs, 10 mM	1 μ l	100 μ l
First-strand buffer, 5x	4 μ l	400 μ l
DTT, 0.1 M	2 μ l	200 μ l
Superscript II, 200 U/ μ l	1 μ l	100 μ l
Total	8.05 μ l	805 μ l

- [0264] Aliquot 100 μ l RT mix into 8 wells of a clean 96-well master mix plate.
 - [0265] From this plate, transfer 8.05 μ l RT mix to each well of RT plate containing 12 μ l RNA, mix by pipetting up-and-down for 3 times with a multi channel pipette. REPLACE TIP AFTER EACH TRANSFER.
 - [0266] Incubate the samples at 42° C. for 50 minutes followed by 70° C. for 15 minutes.
 - [0267] Proceed to Station 4.
- [0268] Station 4—N-Gene Specific PCR (1 Laboratory Technician)
- [0269] Prepare PCR master mix for an entire 96-well plate in two 2059 culture tubes as below (100 reactions):

	N-specific PCR		Control PCR	
	Per 25 μ l Reaction	$\times 100$	Per 25 μ l Reaction	$\times 100$
mQH ₂ O	18.65 μ l	1865 μ l	17.65 μ l	1765 μ l
10x PCR buffer	2.5 μ l	250 μ l	2.5 μ l	250 μ l
25 mM MgCl ₂	1.5 μ l	150 μ l	2.5 μ l	250 μ l
10 mM dNTPs	0.25 μ l	25 μ l	0.25 μ l	25 μ l
Forward primer	0.5 μ l	50 μ l	0.5 μ l	50 μ l
10 μ M Reverse primer	0.5 μ l	50 μ l	0.5 μ l	50 μ l
10 μ M AmpliTaq Gold® 500 U	0.1 μ l	10 μ l	0.1 μ l	10 μ l
Template DNA	1 μ l	—	1 μ l	—
Total	25 μ l	2400 μ l	25 μ l	2400 μ l

- [0270] N-gene specific PCR and control PCR are performed in two individual PCR plates.
- [0271] Aliquot 290 μ l PCR master mix into the first column of a 96-well PCR plate.
- [0272] From the first column, aliquot 24 μ l of master mix into each well of PCR plate.
- [0273] Transfer 1 μ l of cDNA template (from station 4) into each well of PCR plate.
- [0274] Mix by pipetting up-and-down for 3 times with a multi-channel pipette. REPLACE TIP AFTER EACH TRANSFER.
- [0275] Seal the plate with sealing tape.
- [0276] Perform the following reaction in two 96-well PCR machines:

N-gene specific PCR		Control PCR	
94° C. 10 minutes	} 40 cycles	94° C. 10 minutes	} 35 cycles
94° C. 30 seconds		94° C. 30 seconds	
56° C. 30 seconds		55° C. 30 seconds	
72° C. 30 seconds		72° C. 45 seconds	
72° C. 10 minutes		72° C. 10 minutes	

- [0277] Station 5—Gel Electrophoresis (1 Laboratory Technician)
- [0278] Mix 5 μ l of N-gene specific PCR product and 5 μ l control PCR product with 1 μ l bromophenol blue loading dye
- [0279] Load the samples into the wells of a 2% agarose gel.
- [0280] Electrophoresize the PCR products at 140V, 250 mA for 30 minutes.
- [0281] Stain the gel with ethidium bromide.
- [0282] Visualize the products with UV and record the result.
- [0283] 6.8.2 Using Primers of SEQ ID NOS:2480 and 2481
- [0284] RT-PCR diagnostic protocol was performed as described in Section 6.8.1 with some modifications.

- [0285] RNA Isolation from Clinical Samples
- [0286] Clinical samples including nasopharyngeal aspirates (NPA) and stool specimens were provided by the Department of Microbiology, The University of Hong Kong. In addition, tracheal dispersion and lung biopsy from an index patient A described in *New Engl. J Med.* 348:1967-76 (by Drosten C. S., et al., 2003) at three time points was also collected. Sample collection was conducted from Apr. 1 to Apr. 28, 2003 in local hospitals. Method of sample collection was described in the previous section (also see, Poon et al., 2003, *Clinical Chemistry* 49:953-955). Total RNA extraction from clinical samples was carried out with SV96 Total RNA Isolation System (Promega, Wis., USA), with following modifications from manufacturer's protocol. Five-hundred (500) μ l of NPA/stool sample in viral transport medium (containing, per liter, 2 g of sodium bicarbonate, 5

g of bovine serum albumin, 200 μ g of vancomycin, 18 μ g of amikacin, and 160 U of nystatin in Earle's balanced salt solution) was mixed with equal volume of SV RNA Lysis Buffer containing 100 μ l of pig kidney epithelial (PK-15) cell (ATCC CCL-33; 5.0×10^5 cells/ml) in complete minimum essential medium with Earle's salt (EMEM, Invitrogen) as internal control. The mixture was transferred to the wells of the SV 96 Binding Plate. After washing with 500 μ l of SV RNA Wash Solution prior to elution step, the plate was spun at $3000 \times g$ for 30 seconds to remove residue wash solution. RNA was then eluted with 50 μ l of nuclease-free water, and was collected in a clean 96-well PCR plate by spinning the plate at $3000 \times g$ for 1 minute. Eluted RNA was then concentrated by incubating on ice for 15 minutes, in the presence of 5 μ l of 3 M sodium acetate and 200 μ l of 95% ethanol. After centrifugation at $3000 \times g$, 4° C. for 15 minutes, RNA pellet was washed with 200 μ l of 75% ethanol and dissolved with 12 μ l of nuclease-free water. Extracted RNA was immediately reverse-transcribed to first-strand cDNA.

[0287] First-Strand cDNA Synthesis

[0288] Reverse-transcription was performed with 200 U of Superscript® II reverse transcriptase (Invitrogen, USA) in a 20 μ l reaction containing 0.15 μ g of random hexamers, RT buffer (1 \times), 10 mM dithiothreitol (DTT) and 0.5 mM deoxynucleotide triphosphates (dNTPs). Reaction was carried out in Peltier Thermal Cycler (MJ Research) with the following conditions: 50 minutes at 42° C. followed by 15 minutes at 70° C.

[0289] Polymerase Chain Reaction (PCR)

[0290] Primers were designed according to complete SARS CoV genomic sequence of a local specimen HK-39 announced previously (accession no. AY278491). Forward primer (SRS251: 5'-GCAGTCAAGCCTCTCTCG-3'; SEQ ID NO:2480, corresponding to nt 28658-28676 of HK-39 SARS genome, i.e., CCTCC200303) and reverse primer (SRS252: 5'-GCCTCAGCAGCAGATTTC-3', SEQ ID NO:2481; corresponding to nt 28866-28883 of HK-39 SARS genome) amplified a 225 bp fragment from the region of N-gene that showed no homology to other *coronavirus*. Primers amplifying RNA-dependent RNA polymerase (1b gene) were used as parallel control (coro3: 5'-TACACACCTCAGCGTTG-3' (SEQ ID NO:3), corresponding to nt 18041-18057; and coro4: 5'-CACGAACGTGACGAAT-3' (SEQ ID NO:4), corresponding to nt 18207-18222, Department of Microbiology, the University of Hong Kong). Both amplicons were cloned into same pCR2.1 cloning vector (FIG. 17). Serially diluted plasmid was then used to determine the dynamic range and optimal condition of the PCRs (FIGS. 21A and 21B). Another set of primer that amplifying a 745 bp fragment from pig β -actin gene was employed as an internal control for the diagnostic PCR assay (actin-F: 5'-TGAGACCTTCAACACGCC-3' (SEQ ID NO:2482); and actin-R: 5'-ATCTGCTGGAAGGTGGAC-3' (SEQ ID NO:2483)).

[0291] Conventional PCR and gel electrophoresis was carried out as preliminary experiment. Briefly, 1 μ l of cDNA from clinical samples was amplified with 0.5 U Taq DNA polymerase recombinant (Invitrogen Life Technologies) in a 25- μ l reaction containing PCR buffer (1 \times), 1.5 mM $MgCl_2$, 0.1 mM dNTPs and 0.5 pmol of each forward and reverse primers. Reaction was performed in Peltier Thermal Cycler (MJ Research) with the following conditions: 3 minutes at

94° C., followed by 50 cycles of 94° C. for 10 seconds, 56° C. for 10 seconds, 72° C. for 10 seconds, and a 10-minute final extension step at 72° C. Amplicons were analyzed with 2% agarose gel electrophoresis (FIG. 23). Quantitative real-time PCR using SYBR® SYBR® green fluorophore was performed in diagnosis of clinical samples. In a 25 μ l reaction, 1 μ l cDNA template was mixed with 12.5 μ l (2 \times) Green PCR Master Mix (Applied Biosystems) and 0.5 pmol of each forward and reverse primer. Volume of the reaction was adjusted to 25 μ l with distilled water. Reactions were performed in the iCycler iQ Real-Time PCR Detection System (Bio-Rad) under the same condition as the conventional PCR. Fluorescence signals (FAM, excitation=490 nm, emission=530 nm) were collected at the end of each extension step during the PCR cycles (FIG. 22A). Threshold cycle (Ct) of each sample was determined using maximum curvature approach. Melting curve analysis was performed after 10 minutes final extension (FIG. 22B). cDNA from non-SARS patients, including patients suffering from adenovirus (n=5), respiratory syncytial virus (n=5), human metapneumovirus (n=5), influenza A virus (n=5), or influenza B virus (n=5) infection, were used as negative controls for the assay.

[0292] Northern Blot Analysis

[0293] SARS-CoV HK-39 strain infected Vero cell was provided by Department of Microbiology, the University of Hong Kong. Total RNA was extracted from the cell with TRIzol® reagent (Invitrogen Life Technologies) according to the manufacturer's protocol. Eight (8) μ g of total RNA was separated by electrophoresis on a 1% agarose gel containing 3.7% formaldehyde. RNA was transferred to a positively charged nylon membrane Roche Diagnostic Corporation) by capillary blotting and fixed by UV cross-linking. cDNA synthesized with the same RNA sample was used as template for probe synthesis. Four pairs of primers amplifying fragments from 1b (nt 18057-18222; SEQ ID NO:2484), S (nt 21920-22107; SEQ ID NO:2485), M (nt 26867-26996; SEQ ID NO:2486) and N (nt 28658-28883; SEQ ID NO:2487) gene were used in probe synthesis. DIG-labeling of probes, hybridization and detection of bands were performed with the digoxigenin system according to the manufacturer's procedures (Roche Molecular Biochemicals). Signals were then analysed with chemiluminescence (FIG. 24).

[0294] Results and Discussion

[0295] A large-scale RT-PCR assay provides a rapid means in monitoring and screening of SARS suspects. The result can be used to complement clinical diagnostic evaluation. In order to achieve a diagnostic purpose, the assay should be reliable and its accuracy should be assured so as to prevent occurrence of both false negative and false positive results. However, accuracy of the test may be influenced by several factors. A common technical problem with PCR is a failure of amplification due to the presence of PCR inhibitors (see FIG. 21).

[0296] These PCR inhibitors included heme compounds found in blood, aqueous and vitreous humors, heparin, EDTA, urine and polyamines (Fredricks et al., 1998, *J. Clin. Micro.* 36:2810-16). Currently, NPA or stool samples were collected into transport medium to maintain the viability of the viral particles. RT-PCR was inhibited when total RNA extracted was used directly for first-strand cDNA synthesis without any treatment (25 out of 27 samples) in preliminary

experiment. However, after a simple ethanol precipitation step, the amplification of DNA could be retained (FIG. 19). Same result was obtained by either using SV or SV96 total RNA Isolation System (data not shown). It demonstrated that some components either in the medium or NPA/stool samples would affect the downstream processes of the diagnosis test.

[0297] In addition, current sample collection procedure dilutes the virus titer in the samples, especially during early stage of infection, in which the virus titer is low in nasal and throat swab specimens (Drosten et al., 2003, *New England Journal of Medicine*, on-line at <http://content.nejm.org/cgi/reprint/NEJMoa030747v2>). It was suggested that the sensitivity of PCR tests for SARS depended on the quality of the specimen and the time of testing during the course of the illness. In order to increase sensitivity of the test, total RNA isolated from clinical samples was concentrated prior to 1st strand cDNA synthesis.

[0298] In order to avoid false negative PCR results due to failure in the process of RNA isolation and 1st strand cDNA synthesis, total RNA was extracted from clinical samples in parallel with PK-15 mammalian cells. FIG. 23 showed the RT-PCR screening result on 48 clinical samples, including both NPA and stool samples. Diagnostic PCR was performed in parallel with β -actin PCR. All samples were positive in β -actin PCR. The result indicated that RNA and cDNA could be extracted and synthesized successfully from the samples in a single-step protocol as disclosed herein. With this internal control, total RNA isolation and cDNA synthesis from the samples were ensured, which eliminated false negative that resulted from failure in either one of the above processes. Moreover, 96-well assay format currently developed can be adopted into a high-throughput screening protocol, with which we are able to obtain diagnostic result of more than 90 clinical samples in 3 hours with 1 clinical personnel, while the current existing protocol, in which samples are proceeded in individual tubes, can only handle about 30-50 samples a day per technician.

[0299] Real-time quantitative PCR assay is more sensitive than conventional agarose gel-electrophoresis-associated PCR assay (Poon et al., *J. Clin. Virol.* 28:233-8) and therefore employed for SARS-CoV diagnosis purpose. Positive signals were detected in 38 of 136 randomly selected clinical samples in both N-gene and 1b-gene specific PCR. Among these 38 positives, 3 were stool samples (2.2%) and 35 were NPA samples (25.7%). Detection rate of the assay

employing N-gene specific RT-PCR at different time points was shown in Table 2.

TABLE 2

Date of onset	No. of sample	No. of positive	Detection rate (%)
1-2	15	2	13.3
3-4	17	4	23.5
5-6	15	4	26.7
7-8	13	5	38.5
9-10	9	4	44.4
Negative control	19	All negative	—

[0300] Affirmative of these 38 positive cases was confirmed by melting curve analysis of PCR products. Specific melting temperature of N gene and 1b gene PCR products (85.5° C. and 80.5° C., respectively) indicated that the target fragments were amplified in the reaction. Specificity of the assay was also validated with non-SARS patients samples, including patients suffering from adenovirus (n=5), respiratory syncytial virus (n=5), human metapneumovirus (n=5), influenza A virus (n=5) and influenza B virus (n=5). The result shows that all of these samples were negative in the assay (Fig. ??). These results indicate that the N-gene specific RT-PCR assay is specific for SARS-CoV diagnosis.

[0301] Furthermore, we also demonstrated that the N-gene specific PCR was more sensitive than that of PCR amplifying 1b RNA polymerase gene. Amplification conditions for both PCR assays were optimized (see FIG. 22) first with the plasmid construct containing 1:1 ratio of 1b- and N-gene fragment (see FIG. 20). Dynamic range of N-gene specific PCR was obtained (Fig. ??) and it was found to be with lower Ct values than that of 1b-specific PCR. This revealed that N-gene specific PCR could achieve higher amplification efficiency than 1b-gene specific PCR when using same copy number of template. PCR with cDNA from clinical samples or virus infected Vero cells were then performed. FIG. 22A shows the Ct and half-maximal values of the fluorescent signal of N gene and 1b gene specific PCR generated from NPA, tracheal dispersion and lung biopsy from patient A. The results indicated that fluorescent signals given in N gene specific PCR are higher (26.0% in average, ranged from 6.3-60%) than that of 1b specific PCR in all positive samples. Furthermore, Ct values of N gene specific PCR are lower (0.1-4.6 cycles) than that of 1b specific PCR among most of the SARS-CoV positive samples (Table 3).

TABLE 3

S/N	N	1b	?Ct	S/N	N	1b	?Ct	S/N	N	1b	?Ct	S/N	N	1b	?Ct
56851	27.1	27.8	0.6	34862	31.9	33.2	1.3	67429	35.3	35.6	0.3	68796	32.4	34.5	2.1
55751	27.6	27.7	0.1	45971	43.6	48.2	4.6	67438	28.4	27.5	-0.9	68798	28.8	28.4	-0.4
62290	41.9	43.2	1.3	45972	43.6	46.5	2.9	68116	30.0	33.5	3.5	68800	34.6	38.3	3.7
55531	41.0	43.1	2.1	45973	42.1	43.2	1.1	68118	36.7	37.7	1.0	68801	31.9	32.8	0.9
55963	41.7	42.3	0.6	69145	27.2	27.7	0.5	68134	32.4	33.2	0.8	70562	40.2	43.3	3.1
65733	43.6	44.9	1.3	56386	32.8	33.8	1.0	68184	30.6	32.4	1.8	70589	35.5	38.2	2.7
34862	33.5	33.7	0.2	55527	37.3	39.4	2.1	68185	27.5	30.1	2.6	70591	36.0	38.2	2.2
32814	38.6	40.8	2.2	56851	23.9	26.1	2.2	68187	40.3	41.5	1.2	70059	41.4	43.1	1.7
33935	35.3	36.5	1.2	69073	24.3	26.1	1.3	68788	35.5	37.6	2.1				
34861	31.4	31.7	0.3	67423	28.7	29.4	0.7	68791	34.8	35.3	0.5				

$\Delta Ct = 1.49 \pm 0.47$,
95% confidence intervals = 0.74 to 2.23 (F-test)

[0302] Statistic analysis indicates that Ct of N-gene PCR assay is significantly lower than that of ab-gene assay (95% confidence interval=0.74 to 2.23, F-test). Stronger fluorescence signals and lower Ct values of N gene specific PCR provide a more sensitive diagnostic result and much target for the assay.

[0303] Using cDNA from SARS-CoV infected Vero cells, amplification curves shown in FIG. 21B show the differences between N gene and 1b gene specific PCR. Ct of the N gene and 1b gene specific PCR was 35.3 and 37.8, respectively. This phenomenon had two main causes: (1) Expression level of N gene was higher than that of 1b gene; and; (2) Copy number of N gene was much larger than that of 1b gene because each transcript preceded a copy of N gene, in SARS-CoV infected cells. Northern blot analysis supported this hypothesis (FIG. 24). When N-gene specific PCR product was used as a probe, at least five transcripts from the virus were hybridized and gave positive signals (FIG. 24). This result agreed with the findings in which five subgenomic mRNAs were detected by Northern hybridization of RNA from SARS-CoV infected cells using a probe derived from the 3' untranslated region (Rota et al., 2003, *Science* 300:1394-99). On the other hand, when 1b PCR product was used as a probe, only 2 transcripts with high molecular size were hybridized, demonstrating that the copy number of N gene was much higher than that of 1b gene, during transcription and gene expression in the host cells. The Northern hybridization result strongly supports the conclusion that PCR amplifying regions in N gene of the SARS-CoV are more sensitive than other regions as a target for diagnostic screening. It is possible that amplification of more than one genome region may increase the specificity of the test (Yam W. C., et al., 2003, *J. Clin. Microbiol.* 41:4521-24).

[0304] In conclusion, we have developed a new generation of RT-PCR diagnosis test which is more sensitive than conventional diagnostic test for the detection of the *coronavirus* associated with SARS. The assay provides a high throughput, highly sensitive screening platform, which enables us to scale up to test hundreds of thousands of suspected SARS cases each day in a single working line. Incorporation of PK-15 cell as an internal control in the assay and use of N gene as a diagnosis locus in addition to 1b gene can enhance the sensitivity and accuracy of the test. We are adapting the protocol to 96-well real-time quantitative PCR and sequencing format to shorten the time required for the test and to obtain information on genotypic variation of the virus.

[0305] Clinical Results

[0306] Clinical Findings:

[0307] All 50 patients with SARS were ethnic Chinese. They represented 5 different epidemiologically linked clusters as well as additional sporadic cases fitting the case definition. They were hospitalized at a mean of 5 days after the onset of symptoms. The median age was 42 years (range of 23 to 74) and the female to male ratio was 1.3. Fourteen (28%) were health care workers and five (10%) had a history of visit to a hospital experiencing a major outbreak of SARS. Thirteen (26%) patients had household contacts and 12 (24%) others had social contacts with patients with SARS. Four (8%) had a history of recent travel to mainland China.

[0308] The major complaints from most patients were fever (90%) and shortness of breath. Cough and myalgia

were present in more than half the patients (Table 4). Upper respiratory tract symptoms such as rhinorrhea (24%) and sore throat (20%) were present in a minority of patients. Diarrhea (10%) and anorexia (10%) were also reported. At initial examination, auscultatory findings, such as crepitations and decreased air entry, were present in only 38% of patients. Dry cough was reported by 62% of patients. All patients had radiological evidence of consolidation, at the time of admission, involving 1 zone (in 36), 2 zones (13) and 3 zones (1).

TABLE 4

Clinical symptoms	Number (percentage)
Fever	50 (100%)
Chill or rigors	37 (74%)
Cough	31 (62%)
Myalgia	27 (54%)
Malaise	25 (50%)
Running nose	12 (24%)
Sore throat	10 (20%)
Shortness of breath	10 (20%)
Anorexia	10 (20%)
Diarrhea	5 (10%)
Headache	10 (20%)
Dizziness	6 (12%)

* Truncal maculopapular rash was noted in 1 patient.

[0309] In spite of the high fever, most patients (98%) had no evidence of a leukocytosis. Lymphopenia (68%), leucopenia (26%), thrombocytopenia (40%) and anemia (18%) were present in peripheral blood examination (Table 5). Parenchymal liver enzyme, alanine aminotransferase (ALT) and muscle enzyme, creatinine kinase (CPK) were elevated in 34% and 26% respectively.

TABLE 5

Laboratory parameter	Mean (range)	Percentage of abnormal	Normal range
Haemoglobin	12.9 (8.9-15.9)		11.5-16.5 g/dl
Anaemia		9 (18%)	
White cell count	5.17 (1.1-11.4)		4-11 × 10 ⁹ /L
Leucopenia		13 (26%)	
Lymphocyte count	0.78 (0.3-1.5)		1.5-4.0 × 10 ⁹ /L
Significant lymphopenia (<1.0 × 10 ⁹ /L)		34 (68%)	
Platelet count	174 (88-351)		150-400 × 10 ⁹ /L
Thrombocytopenia		20 (40%)	
Alanine amino-transaminase (ALT)	63 (11-350)		6-53 U/L
Elevated ALT		17 (34%)	
Albumin	37 (26-50)		42-54 g/L
Low albumin		34 (68%)	
Globulin	33 (21-42)		24-36 g/L
Elevated globulin		10 (20%)	
Creatinine kinase	244 (31-1379)		34-138 U/L
Elevated creatinine kinase		13 (26%)	

[0310] Routine microbiological investigations for known viruses and bacteria by culture, antigen detection, and PCR were negative in most cases. Blood culture was positive for *Escherichia coli* in a 74-year-old male patient, who was admitted to intensive care unit, and was attributed to hospital acquired urinary tract infection. *Klebsiella pneumoniae* and *Hemophilus influenzae* were isolated from the sputum specimens of 2 other patients on admission.

[0311] Oral levofloxacin 500 mg q24h was given in 9 patients and intravenous (1.2 g q8h)/oral (375 mg tid) amoxicillin-clavulanate and intravenous/oral clarithromycin 500 mg q12h were given in another 40 patients. Four patients were given oral oseltamivir 75 mg bid. In one patient, intravenous ceftriaxone 2 gm q24h, oral azithromycin 500 mg q24h, and oral amantadine 100 mg bid were given for empirical coverage of typical and atypical pneumonia.

[0312] Nineteen patients progressed to severe disease with oxygen desaturation and were required intensive care and ventilatory support. The mean number of days of deterioration from the onset of symptoms was 8.3 days. Intravenous ribavirin 8 mg/kg q8h and steroid was given in 49 patients at a mean day of 6.7 after onset of symptoms.

[0313] The risk factors associated with severe complicated disease requiring intensive care and ventilatory support were older age, lymphopenia, impaired ALT, and delayed initiation of ribavirin and steroid (Table 6). All the complicated cases were treated with ribavirin and steroid after admission to the intensive care unit whereas all the uncomplicated cases were started on ribavirin and steroid in the general ward. As expected, 31 uncomplicated cases recovered or improved whereas 8 complicated cases deteriorated with one death at the time of writing. All 50 patients were monitored for a mean of 12 days at the time of writing.

TABLE 6

	Complicated case (n = 19)	Uncomplicated case (n = 31)	P value
Mean (SD) age (range)	49.5 ± 12.7	39.0 ± 10.7	P < 0.01
Male/Female ratio	8/11	14/17	N.S.
Underlying illness	5 †	1 ‡	P < 0.05
Mode of contact			
Travel to China	1	3	N.S.
Health care worker	5	9	N.S.
Hospital visit	1	4	N.S.
Household contact	8	5	P < 0.05
Social contact	4	10	N.S.
Mean (SD) duration of symptoms to admission (days)	5.2 ± 2.0	4.7 ± 2.5	N.S.
Mean (SD) admission temperature (° C.)	38.8 ± 0.9	38.7 ± 0.8	N.S.
Mean (SD) initial total peripheral WBC count (×10 ⁹ /L)	5.1 ± 2.4	5.2 ± 1.8	N.S.
Mean (SD) initial lymphocyte count (×10 ⁹ /L)	0.66 ± 0.3	0.85 ± 0.3	P < 0.05
Presence of thrombocytopenia (<150 × 10 ⁹ /L)	8	12	N.S.
Impaired liver function test	11	6	P < 0.01
CXR changes (number of zone affected)	1.4	1.2	N.S.
Mean (SD) day of deterioration from the onset of symptoms §	8.3 ± 2.6	Not applicable	
Mean (SD) day of initiation of Ribavirin & steroid from the onset of symptoms	7.7 ± 2.9	5.7 ± 2.6	P < 0.05
Initiation of ribavirin & steroid after deterioration	12	0	P < 0.001

TABLE 6-continued

	Complicated case (n = 19)	Uncomplicated case (n = 31)	P value
Response to ribavirin & steroid Outcome	11	28	P < 0.05
Improved or recovered	10	31	P < 0.01
Not improving	8	0	P < 0.01

* Multi-variant analysis is not performed due to low number of cases;

†2 patients had diabetic mellitus, 1 had hypertrophic obstructive cardiomyopathy, 1 had chronic active hepatitis B, and 1 had brain tumour;

‡1 patient had essential hypertension;

§ desaturation requiring intensive care support;

|| 1 died.

[0314] Two virus isolates, subsequently identified as a member of Coronaviridae (see below), were isolated from two patients. One was from an open lung biopsy tissue of a 53-year-old Hong Kong Chinese resident and the other from a nasopharyngeal aspirate of a 42 year-old female with good previous health. The 53-year old male had a history of 10-hour household contact with a Chinese visitor who came from Guangzhou and later died from SARS. Two days after this exposure, he presented with fever, malaise, myalgia, and headache. Crepitations were present over the right lower zone and there was a corresponding alevolar shadow on the chest radiograph. Hematological investigation revealed lymphopenia of $0.7 \times 10^9/l$ with normal total white cell and platelet counts. Both ALT (41 U/L) and CPK (405 U/L) were impaired. Despite a combination of oral azithromycin, amantadine, and intravenous ceftriaxone, there was increasing bilateral pulmonary infiltrates and progressive oxygen desaturation. Therefore, an open lung biopsy was performed 9 days after admission. Histopathological examination showed a mild interstitial inflammation with scattered alveolar pneumocytes showing cytomegaly, granular amphophilic cytoplasm and enlarged nuclei with prominent nucleoli. No cells showed inclusions typical of herpesvirus or adenovirus infection. The patient required ventilation and intensive care after the operative procedure. Empirical intravenous ribavirin and hydrocortisone were given. He succumbed 20 days after admission. In retrospect, *coronavirus*-like RNA was detected in his nasopharyngeal aspirate, lung biopsy and post-mortem lung. He had a significant rise in titer of antibodies against his own hSARS isolate from 1/200 to 1/1600.

[0315] The second patient from whom a hSARS virus was isolated, was a 42-year-old female with good past health. She had a history of travel to Guangzhou in mainland China for 2 days. She presented with fever and diarrhea 5 days after her return to Hong Kong. Physical examination showed crepitation over the right lower zone which had a corresponding alveolar shadow on the chest radiograph. Investigation revealed leucopenia ($2.7 \times 10^9/L$), lymphopenia ($0.6 \times 10^9/L$), and thrombocytopenia ($104 \times 10^9/L$). Despite the empirical antimicrobial coverage with amoxicillin-clavulanate, clarithromycin, and oseltamivir, she deteriorated 5 days after admission and required mechanical ventilation and intensive care for 5 days. She gradually improved without receiving treatment with ribavirin or steroid. Her nasopharyngeal aspirate was positive for the virus in the RT-PCR and she was seroconverted from antibody titre <1/50 to 1/1600 against the hSARS isolate.

[0316] Virological Findings:

[0317] Viruses were isolated on FRhk-4 cells from the lung biopsy and nasopharyngeal aspirate respectively, of two patients described above. The initial cytopathic effect appeared between 2 and 4 days after inoculation, but on subsequent passage, cytopathic effect appeared in 24 hours. Both virus isolates did not react with the routine panel of reagents used to identify virus isolates including those for influenza A, B parainfluenza types 1,2,3, adenovirus and respiratory syncytial virus (DAKO, Glostrup, Denmark). They also failed to react in RT-PCR assays for influenza A and HMPV or in PCR assays for mycoplasma. The virus was ether sensitive, indicating that it was an enveloped virus. Electron microscopy of negatively stained (2% potassium phospho-tungstate, pH 7.0) cell culture extracts obtained by ultracentrifugation showed the presence of pleomorphic enveloped viral particles, of about 80-90 nm (ranging 70-130 nm) in diameter, whose surface morphology appeared comparable to members of Coronaviridae (**FIG. 5a**). Thin section electron microscopy of infected cells revealed virus particles of 55-90 nm diameter within the smooth-walled vesicles in the cytoplasm (**FIG. 5b**). Virus particles were also seen at the cell surface. The overall findings were compatible with infections in the cells caused by viruses of Coronaviridae.

[0318] A thin section electron micrograph of the lung biopsy of the 53 year old male contained 60-90-nm viral particles in the cytoplasm of desquamated cells. These viral particles were similar in size and morphology to those observed in the cell-cultured virus isolate from both patients (**FIG. 4**).

[0319] The RT-PCR products generated in a random primer RT-PCR assay were analyzed and unique bands found in the virus infected specimen was cloned and sequenced. Of 30 clones examined, a clone containing 646 base pairs (SEQ ID NO:1) of unknown origin was identified. Sequence analysis of this DNA fragment suggested this sequence had a weak homology to viruses of the family of Coronaviridae (data not shown). Deducted amino acid sequence (215 amino acids: SEQ ID NO:2) from this unknown sequence, however, had the highest homology (57%) to the RNA polymerase of bovine *coronavirus* and murine hepatitis virus, confirming that this virus belongs to the family of Coronaviridae. Phylogenetic analysis of the protein sequences showed that this virus, though most closely related to the group II coronaviruses, was a distinct virus (**FIGS. 5a** and **5b**).

[0320] Based on the 646 bp sequence of the isolate, specific primers for detecting the new virus was designed for RT-PCR detection of this hSARS virus genome in clinical specimens. Of the 44 nasopharyngeal specimens available from the 50 SARS patients, 22 had evidence of hSARS RNA. Viral RNA was detectable in 10 of 18 fecal samples tested. The specificity of the RT-PCR reaction was confirmed by sequencing selected positive RT-PCR amplified

products. None of 40 nasopharyngeal and fecal specimens from patients with unrelated diseases were reactive in the RT-PCR assay.

[0321] To determine the dynamic range of real-time quantitative PCR, serial dilutions of plasmid DNA containing the target sequence were made and subjected to the real-time quantitative PCR assay. As shown in **FIG. 7A**, the assay was able to detect as little as 10 copies of the target sequence. By contrast, no signal was observed in the water control (**FIG. 7A**). Positive signals were observed in 23 out of 29 serologically confirmed SARS patients. In all of these positive cases, a unique PCR product ($T_m=82^\circ\text{C}$) corresponds to the signal from the positive control was observed (**FIG. 7B**, and data not shown). These results indicated this assay is highly specific to the target. The copy numbers of the target sequence in these reactions range from 4539 to less than 10. Thus, as high as 6.48×10^5 copies of this viral sequence could be found in 1 ml of NPA sample. In 5 of the above positive cases, it was possible to collect NPA samples before sero-conversion. Viral RNA was detected in 3 of these samples, indicating that this assay can detect the virus even at the early onset of infection.

[0322] To further validate the specificity of this assay, NPA samples from healthy individuals (n=11) and patients suffered from adenovirus (n=11), respiratory syncytial virus (n=11), human metapneumovirus (n=11), influenza A virus (n=13) or influenza B virus (n=1) infection were recruited as negative controls. All of these samples, except one, were negative in the assay. The false positive case was negative in a subsequent test. Taken together, including the initial false positive case, the real-time quantitative PCR assay has sensitivity of 79% and specificity of 98%.

[0323] Epidemiological data suggest that droplet transmission is one of the major route of transmission of this virus. The detection of live virus and the detection of high copies of viral sequence from NPA samples in the current study clearly support that cough and sneeze droplets from SARS patients might be the major source of this infectious agent. Interestingly, 2 out of 4 available stool samples from the SARA patients in this study were positive in the assay (data not shown). The detection of the virus in feces suggests that there might be other routes of transmission. It is relevant to note that a number of animal coronaviruses are spread via the fecal-oral route (McIntosh K., 1974, *Coronaviruses: a comparative review. Current Top Microbiol Immunol.* 63: 85-112). However, further studies are required to test whether the virus in feces is infectious or not.

[0324] Currently, apart from this hSARS virus, there are two known serogroups of human coronaviruses (229E and OC43) (Hruskova J. et al., 1990, Antibodies to human coronaviruses 229E and OC43 in the population of C. R., *Acta Virol.* 34:346-52). The primer set used in the present assay does not have homology to the strain 229E. Due to the lack of available corresponding OC43 sequence in the Genebank, it is not known whether these primers would cross-react with this strain. However, sequence analyses of available sequences in other regions of OC43 polymerase

gene indicate that the novel human virus associated with SARS is genetically distinct from OC43. Furthermore, the primers used in this study do not have homology to any of sequences from known coronaviruses. Thus, it is very unlikely that these primers would cross-react with the strain OC43.

[0325] Apart from the novel pathogen, metapneumovirus was reported to be identified in some of SARS patients (Center for Disease Control and Prevention, 2003, *Morbidity and Mortality Weekly Report* 52: 269-272). No evidence of metapneumovirus infection was detected in any of the patients in this study (data not shown), suggesting that the novel hSARS virus of the invention is the key player in the pathogenesis of SARS.

[0326] Immunofluorescent Antibody Detection:

[0327] Thirty-five of the 50 most recent serum samples from patients with SARS had evidence of antibodies to the hSARS (see FIG. 3). Of 27 patients from whom paired acute and convalescent sera were available, all were seroconverted or had >4 fold increase in antibody titer to the virus. Five other pairs of sera from additional SARS patients from clusters outside this study group were also tested to provide a wider sampling of SARS patients in the community and all of them were seroconverted. None of 80 sera from patients with respiratory or other diseases as well as none of 200 normal blood donors had detectable antibody.

[0328] When either seropositivity to HP-CV in a single serum or viral RNA detection in the NPA or stool are considered evidence of infection with the hSARS, 45 of the 50 patients had evidence of infection. Of the 5 patients without any virological evidence of Coronaviridae viral infection, only one of these patients had their sera tested >14 days after onset of clinical disease.

[0329] Discussion

[0330] The outbreak of SARS is unusual in a number of aspects, in particular, in the appearance of clusters of patients with pneumonia in health care workers and family contacts. In this series of patients with SARS, investigations for conventional pathogens of atypical pneumonia proved negative. However, a virus that belongs to the family Coronaviridae was isolated from the lung biopsy and nasopharyngeal aspirate obtained from two SARS patients, respectively. Phylogenetically, the virus was not closely related to any known human or animal *coronavirus* or *torovirus*. The present analysis is based on a 646 bp fragment (SEQ ID NO:1) of the polymerase gene, which indicates that the virus relates to antigenic group 2 of the coronaviruses along with murine hepatitis virus and bovine *coronavirus*. However, viruses of the Coronaviridae can undergo heterologous recombination within the virus family and genetic analysis of other parts of the genome needs to be carried out before the nature of this new virus is more conclusively defined (Holmes K V. Coronaviruses. Eds Knipe D M, Howley P M Fields Virology, 4th Edition, Lippincott Williams & Wilkins, Philadelphia, 1187-1203). The biological, genetic and clinical

data, taken together, indicate that the new virus is not one of the two known human coronaviruses.

[0331] The majority (90%) of patients with clinically defined SARS had either serological or RT-PCR evidence of infection by this virus. In contrast, neither antibody nor viral RNA was detectable in healthy controls. All 27 patients from whom acute and convalescent sera were available demonstrated rising antibody titers to hSARS virus, strengthening the contention that a recent infection with this virus is a necessary factor in the evolution of SARS. In addition, all five pairs of acute and convalescent sera tested from patients from other hospitals in Hong Kong also showed seroconversion to the virus. The five patients who has not shown serological or virological evidence of hSARS virus infection, need to have later convalescent sera tested to define if they are also seroconverted. However, the concordance of the hSARS virus with the clinical definition of SARS appears remarkable, given that clinical case definitions are never perfect.

[0332] No evidence of HMPV infection, either by RT-PCR or rising antibody titer against HMPV, was detected in any of these patients. No other pathogen was consistently detected in our group of patients with SARS. It is therefore highly likely that that this hSARS virus is either the cause of SARS or a necessary pre-requisite for disease progression. Whether or not other microbial or other co-factors play a role in progression of the disease remains to be investigated.

[0333] The family Coronaviridae includes the genus *Coronavirus* and *Torovirus*. They are enveloped RNA viruses which cause disease in humans and animals. The previously known human coronaviruses, types 229E and OC43 are the major causes of the common cold (Holmes K V. Coronaviruses. Eds Knipe D M, Howley P M Fields Virology, 4th Edition, Lippincott Williams & Wilkins, Philadelphia, pp. 1187-1203). But, while they can occasionally cause pneumonia in older adults, neonates or immunocompromised patient (El-Sahly H M, Atmar R L, Glezen W P, Greenberg S B. Spectrum of clinical illness in hospitalized patients with "common cold" virus infections. *Clin Infect Dis*. 2000; 31: 96-100; and Foltz E J, Elkordy M A. *Coronavirus* pneumonia following autologous bone marrow transplantation for breast cancer. *Chest* 1999; 115: 901-905), Coronaviruses have been reported to be an important cause of pneumonia in military recruits, accounting for up to 30% of cases in some studies (Wenzel R P, Hendley J O, Davies J A, Gwaltney J M, *Coronavirus* infections in military recruits: Three-year study with *coronavirus* strains OC43 and 229E. *Am Rev Respir Dis*. 1974; 109: 621-624). Human coronaviruses can infect neurons and viral RNA has been detected in the brain of patients with multiple sclerosis (Talbot P J, Cote G, Arbour N. Human *coronavirus* OC43 and 229E persistence in neural cell cultures and human brains. *Adv Exp Med Biol.*—in press). On the other hand, a number of animal coronaviruses (eg. *Porcine Transmissible Gastroenteritis Virus*, *Murine Hepatitis Virus*, *Avian Infectious Bronchitis Virus*) cause respiratory, gastrointestinal, neurological or hepatic disease in their respective hosts

(McIntosh K. *Coronaviruses: a comparative review. Current Top Microbiol Immunol.* 1974; 63: 85-112).

[0334] We describe for the first time the clinical presentation and complications of SARS. Less than 25% of patients with coronaviral pneumonia had upper respiratory tract symptoms. As expected in atypical pneumonia, both respiratory symptoms and positive auscultatory findings were very disproportional to the chest radiographic findings. Gastrointestinal symptoms were present in 10%. It is relevant that the virus RNA is detected in faeces of some patients and that coronaviruses have been associated with diarrhoea in animals and humans (Caul E O, Egglestone S I. Further studies on human enteric coronaviruses *Arch Virol.* 1977; 54: 107-17). The high incidence of deranged liver function test, leucopenia, significant lymphopenia, thrombocytopenia and subsequent evolution into adult respiratory distress syndrome suggests a severe systemic inflammatory damage induced by this hSARS virus. Thus immuno-modulation by steroid may be important to complement the antiviral therapy by ribavirin. In this regard, it is pertinent that severe human disease associated with the avian influenza subtype H5N1, another virus that recently crossed from animals to humans, has also been postulated to have an immuno-pathological component (Cheung C Y, Poon L L M, Lau A S Y et al. Induction of proinflammatory cytokines in human macrophages by influenza A (H5N1) viruses: a mechanism for the unusual severity of human disease. *Lancet* 2002; 360: 1831-1837). In common with H5N1 disease, patients with severe SARS are adults, are significantly more lymphopenic and have parameters of organ dysfunction beyond the respiratory tract (Table 4) (Yuen K Y, Chan P K S, Peiris J S M, et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. *Lancet* 1998; 351: 467-471). It is important to note that a window of opportunity of around 8 days exists from the onset of symptoms to respiratory failure. Severe complicated cases are strongly associated with both underlying disease and delayed use of ribavirin and steroid therapy. Following our clinical experience in the initial cases, this combination therapy was started very early in subsequent cases which were largely uncomplicated cases at the time of admission. The overall mortality at the time of writing is only 2% with this treatment regimen. There were still 8 out of 19 complicated cases who had not shown significant response. It is not possible to a detail analysis of the therapeutic response to this combination regimen due to the heterogeneous dosing and time of initiation of therapy.

[0335] Other factors associated with severe disease is acquisition of the disease through household contact which may be attributed to a higher dose or duration of viral exposure and the presence of underlying diseases.

[0336] The clinical description reported here pertains largely to the more severe cases admitted to hospital. We presently have no data on the full clinical spectrum of the emerging Coronaviridae infection in the community or in an out-patient-setting. The availability of diagnostic tests as described here will help address these questions. In addition,

it will allow questions pertaining to the period of virus shedding (and communicability) during convalescence, the presence of virus in other body fluids and excreta and the presence of virus shedding during the incubation period, to be addressed.

[0337] The epidemiological data at present appears to indicate that the virus is spread by droplets or by direct and indirect contact although airborne spread cannot be ruled out in some instances. The finding of infectious virus in the respiratory tract supports this contention. Preliminary evidence also suggests that the virus may be shed in the feces. However, it is important to note that detection of viral RNA does not prove that the virus is viable or transmissible. If viable virus is detectable in the feces, this would be a potentially additional route of transmission that needs to be considered. It is relevant to note that a number of animal coronaviruses are spread via the fecal-oral route (McIntosh K. *Coronaviruses: a comparative review. Current Top Microbiol Immunol.* 1974; 63: 85-112).

7. Deposit

[0338] A sample of isolated hSARS virus was deposited with China Center for Type Culture Collection (CCTCC) at Wuhan University, Wuhan 430072 in China on Apr. 2, 2003 in accordance with the Budapest Treaty on the Deposit of Microorganisms, and accorded accession No. CCTCC-V200303, which is incorporated herein by reference in its entirety.

8. Market Potential

[0339] The hSARS virus can now be grown on a large scale, which allows the development of various diagnostic tests as described hereinabove as well as the development of vaccines and antiviral agents that are effective in preventing, ameliorating or treating SARS. Given the severity of the disease and its rapid global spread, it is highly likely that significant demands for diagnostic tests, therapies and vaccines to battle against the disease, will arise on a global scale. In addition, this virus contains genetic information which is extremely important and valuable for clinical and scientific research applications.

9. Equivalents

[0340] Those skilled in the art will recognize, or be able to ascertain many equivalents to the specific embodiments of the invention described herein using no more than routine experimentation. Such equivalents are intended to be encompassed by the following claims.

[0341] All publications, patents and patent applications mentioned in this specification are herein incorporated by reference into the specification to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference.

[0342] Citation or discussion of a reference herein shall not be construed as an admission that such is prior art to the present invention.

SEQUENCE LISTING

The patent application contains a lengthy "Sequence Listing" section. A copy of the "Sequence Listing" is available in electronic form from the USPTO web site (<http://seqdata.uspto.gov/sequence.html?DocID=20050181357>). An electronic copy of the "Sequence Listing" will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

What is claimed:

1. An isolated nucleic acid molecule consisting essentially of a nucleic acid sequence of SEQ ID NO:2471, or a complement thereof.

2. An isolated nucleic acid molecule consisting essentially of a nucleic acid sequence of SEQ ID NO:2473, or a complement thereof.

3. An isolated nucleic acid molecule which hybridizes under stringent conditions to a nucleic acid molecule having the nucleotide sequence of claim 1 or 2, or a complement thereof.

4. The nucleic acid molecule of claim 1 or 2 wherein the molecule is RNA.

5. The nucleic acid molecule of claim 1 or 2 wherein the molecule is DNA.

6. An isolated nucleic acid molecule which hybridizes under stringent conditions to the nucleic acid molecule of claim 1 or 2, or a complement thereof, wherein the nucleic acid molecule encodes an amino acid sequence which has a biological activity exhibited by a polypeptide encoded by the nucleotide sequence of SEQ ID NO:2471 or 2473.

7. An isolated polypeptide encoded by the nucleic acid molecule of claim 1 or 2.

8. An antibody or an antigen-binding fragment thereof which immunospecifically binds to the N-gene protein of a hSARS virus.

9. An antibody or an antigen-binding fragment thereof which immunospecifically binds to the S-gene protein of a hSARS virus.

10. The antibody of claim 8, 9, or an antigen-binding fragment thereof which neutralizes the hSARS virus.

11. An antibody which immunospecifically binds to the polypeptide of claim 7, or an antigen-binding fragment of said antibody.

12. A method for detecting the presence of a N-gene of the hSARS virus in a biological sample, said method comprising:

(a) contacting the sample with a compound that selectively binds to said N-gene; and

(b) detecting whether the compound binds to said N-gene in the sample.

13. The method of claim 12, wherein the compound that binds to said N-gene is a nucleic acid molecule comprising a nucleotide sequence having at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1,000, 1,050, 1,100, 1,150 or 1,200 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:2471, or a complement thereof.

14. The method of claim 12, wherein the compound that binds to said N-gene is a nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO:2475, 2476, 2480 and/or 2481.

15. A method for detecting the presence of a S-gene of the hSARS virus in a biological sample, said method comprising:

(a) contacting the sample with a compound that selectively binds to said S-gene; and

(b) detecting whether the compound binds to said S-gene in the sample.

16. The method of claim 15, wherein the compound that binds to said S-gene is a nucleic acid molecule comprising a nucleotide sequence having at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1,000, 1,050, 1,100, 1,150, 1,200, 2,000, or 3,000 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:2473, or a complement thereof.

17. The method of claim 15, wherein the compound that binds to said S-gene is a nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO:2477 and/or 2478.

18. A method for detecting the presence of the polypeptide of claim 7 in a sample, said method comprising:

(a) contacting the sample with a compound that selectively binds to said polypeptide; and

(b) detecting whether the compound binds to said polypeptide in the sample.

19. The method of claim 18, wherein the compound that binds to the polypeptide is an antibody.

20. A method for identifying a subject infected with the hSARS virus, said method comprising:

(a) obtaining total RNA from a biological sample obtained from the subject

(b) reverse transcribing the total RNA to obtain cDNA; and

(c) subjecting the cDNA to real-time PCR assay using a set of primers derived from a nucleotide sequence of the N-gene of the hSARS.

21. The method of claim 20, wherein the set of primers have nucleotide sequences of SEQ ID NOS:2475 and 2476, respectively.

22. The method of claim 20, wherein the set of primers have nucleotide sequences of SEQ ID NOS:2480 and 2481, respectively.

23. A method for identifying a subject infected with the hSARS virus, said method comprising:

- (a) obtaining total RNA from a biological sample obtained from the subject
- (b) reverse transcribing the total RNA to obtain cDNA; and
- (c) subjecting the cDNA to real-time PCR assay using a set of primers derived from a nucleotide sequence of the S-gene of the hSARS.

24. The method of claim 23, wherein the set of primers have nucleotide sequences of SEQ ID NOS:2477 and 2478, respectively.

25. A kit comprising in one or more containers one or more isolated nucleic acid molecules comprising a nucleotide sequence of SEQ ID NO:2475 and/or SEQ ID NO:2476.

26. A kit comprising in one or more containers one or more isolated nucleic acid molecules comprising a nucleotide sequence of SEQ ID NO:2480 and/or SEQ ID NO:2481.

27. A kit comprising in one or more containers one or more isolated nucleic acid molecules comprising a nucleotide sequence of SEQ ID NO:2477 and/or SEQ ID NO:2478.

28. A kit comprising in one or more containers one or more antibodies of claim 8 or 9.

29. A kit comprising in one or more containers one or more antibodies of claim 11.

* * * * *