Am. J. Hum. Genet. 40:228–236, 1987

Mapping of DNA Markers Linked to the Cystic Fibrosis Locus on the Long Arm of Chromosome 7

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SUMMARY

We have used a panel of eight human/mouse somatic-cell hybrids, each containing various portions of human chromosome 7, and three patient cell lines with interstitial deletions on chromosome 7 for localization of six DNA markers linked to the cystic fibrosis locus. Our data suggest that *D7S15* is located in the region 7cen→q22, that *MET* is located in 7q22→31, and that *D7S8* and *7C22* are located in q22→q32. The hybridization results for *COL1A2* and *TCRB* are consistent with their previous assignment to 7q21→q22 and 7q32, respectively. Given the location of these six markers and their linkage relationships, it is probable that the cystic fibrosis locus is in either the distal region of band q22 or the proximal region of q31. Using the same set of cell lines, we have also examined the location of another chromosome 7 marker *PGY1*. The data show that *PGY1* is located in the region 7cen→q22, a position very different from its previous assignment.

INTRODUCTION

Recent genetic linkage studies have revealed a number of markers linked to the cystic fibrosis locus (*CF*) namely, *PON* (Eiberg et al. 1985; Schmiegelow et al. 1986), *D7S15* (Knowlton et al. 1985; Tsui et al. 1985), *MET* (White et al. 1985),

Received September 29, 1986.
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D7S8 (Wainwright et al. 1985), *COL1A2* (Scambler et al. 1985; Buchwald et al. 1986), *TCRB* (Wainwright et al. 1985), and *7C22* (Scambler et al. 1986). Although the linkage to *D7S15* (formerly *D0CRI-917*) first allowed the localization of *CF* to chromosome 7 (Knowlton et al. 1985), the two loci are >15 centimorgans (cM) apart (Tsui et al. 1985, 1986). On the basis of all available data, *MET* and *D7S8* appear to be most tightly linked to *CF;* both markers are <1 cM from the disease locus (Wainwright et al. 1985; White et al. 1985; Beaudet et al. 1986). Furthermore, these two markers are probably on opposite sides of *CF,* as suggested by the result of a collaborative study involving seven research groups (Beaudet et al. 1986). The most likely order for *CF* and its flanking markers, as deduced from the combined linkage data, is *COL1A2-D7S15-PON-MET-CF-D7S8-TCRB* (Tsui et al. 1986; Beaudet et al. 1986). The relative position for *7C22* is presently not known.

In order to obtain a better description of *CF*, a more precise chromosomal localization of the flanking markers is required. *COL1A2* has been mapped to 7q21→q22 (Junien et al. 1982) and, more recently, to region q21.3→q22.1 (Retief et al. 1985), but the positions of the other markers are not as well defined. *D7S15* has been assigned to 7cen→q31 (Knowlton et al. 1985; Tsui et al. 1986); *MET* has been assigned to 7q21→q31 (Dean et al. 1985); and *D7S8* has been assigned to 7cen→q22 (Bartels et al. 1986). *TCRB* has been localized to 7q3 (Isobe et al. 1985; Le Beau et al. 1985; Morton et al. 1985); however, the regional assignments were in conflict; different groups of investigators placed the gene at either 7q32 (Morton et al. 1985) or q35 (Isobe et al. 1985; Le Beau et al. 1985). In this paper, we present additional information on the chromosomal location of the above markers as well as on one additional chromosome 7 marker, *PGY1* (Trent et al. 1985). These data were obtained by using a panel of human cell lines carrying deletions and human/mouse somatic-cell hybrids containing portions of chromosome 7. Together with the previous linkage data, our analysis suggests that *CF* is most probably located in the proximal region of band q31.

MATERIAL AND METHODS

The somatic-cell hybrids and patient cell lines used in the hybridization analyses have been described elsewhere (Bartels et al. 1986). The cell lines GM1059, GM3240, GM3733, and GM3098 were obtained from the NIGMS Human Genetic Mutant Cell Repository (Camden, N.J.). The chromosome content and the extent of deletions in these lines are listed in table 1. High-molecular-weight DNA was prepared from each of the cell lines, extracted with phenol/chloroform, precipitated in ethanol, and redisolved in 1 mM Tris-HCl, 0.1 mM ethylenediaminetetraacetate (EDTA), pH 7.5 (Tsui et al. 1985; Buchwald et al. 1986). Restriction-enzyme (*Eco*RI and *Hin*dIII) digestions were performed under conditions recommended by the suppliers. The digested DNA samples were size-fractionated by electrophoresis on 0.7% agarose gels, transferred to Zetabind (AMFCuno) membranes, and hybridized with radioactively labeled probes as described elsewhere (Buchwald et al. 1986).

The DNA probes for *D7S15* (Lam4-917 [Tsui et al. 1985]), *MET* (metD [Dean

TABLE 1

SOMATIC-CELL LINES

Cell Line	Human Chromosome 7 Marker
5387 3 cl 10	Whole 7 only
Ru-Rag 6-19	del7 (qter→cen:)
Ru-Rag 4-13	del7 (pter→cen:)
Ru-Rag 1a-5-11	del7 (qter→cen:)
MH-Rag 8-7	t(7;15)(7qter→q32::15q13→qter)
IT-9a 2-21-14	t(6;7)(6qter→q12::7p14→qter)
194-Rag 6-13	del7 (pter→q32:), $3q^-$
IT-A9 X-28-13	t(6;7)(6pter→q12::7p14→pter)
GM3240	46,XY;del7 (pter→q34:)
GM3733	46,XY; del7 (pter→q34:)
GM1059	46,XX; del7 (pter→q22::q32→qter)
GM3098	46,XX
A9	Mouse only
RAG	Mouse only

et al. 1985]), *D7S8* (pJ3.11 [Bartels et al. 1986]), *7C22* [Scambler et al. 1986], *COL1A2* (NJ-1 [Tsipouras et al. 1984]), and *TCRB* (Jurkat-2 [Yanagi et al. 1984]) have been described previously. RP1 is a 2-kb cDNA clone corresponding to the 3′ end of the human P-glycoprotein gene (Riordan et al. 1985, and unpublished data).

The presence or absence of probe hybridization in each somatic-cell hybrid was determined by inspection of the autoradiograms. For the patient cell lines with deletions, band intensities were used to determine the relationship between the probe-hybridizing sequences and the deleted region. X-ray films of various exposures within the linear range were traced with an LKB-Chromoscan 300 densitometer, and the band intensities were normalized to that of a diploid fibroblast control hybridized with Jurkat-2 or other known probes on the same Zetabind membrane.

RESULTS AND DISCUSSION

A panel of eight human/mouse somatic-cell hybrids containing various portions of human chromosome 7 and three patient cell lines harboring deletions on 7q were used to study the locations of DNA markers closely linked to *CF*. The results are shown in figure 1 and summarized in figure 2. While most of the hybridization data are consistent with the previous chromosomal assignments of the test markers, additional information has been derived from the present study.

The most informative cell line in this analysis is GM1059, a patient cell line with a single interstitial deletion spanning band q31(46,XX;del7[pter→q22 :: q32→qter]). On the basis of probe hybridization signal intensity in GM1059, it was possible to determine whether a test marker is located in the deleted region (table 2). It is clear that *MET*, *D7S8*, and *7C22* are all deleted from the del7 chromosome in GM1059, suggesting that these markers are located in

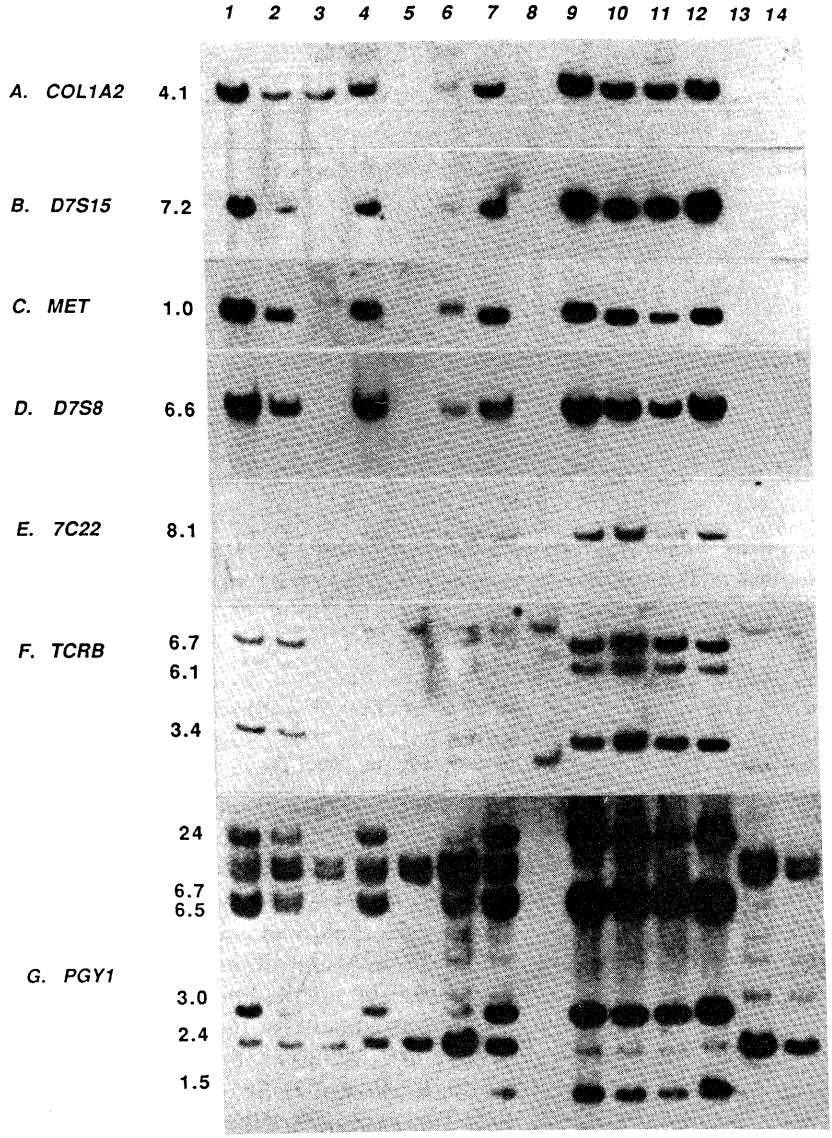
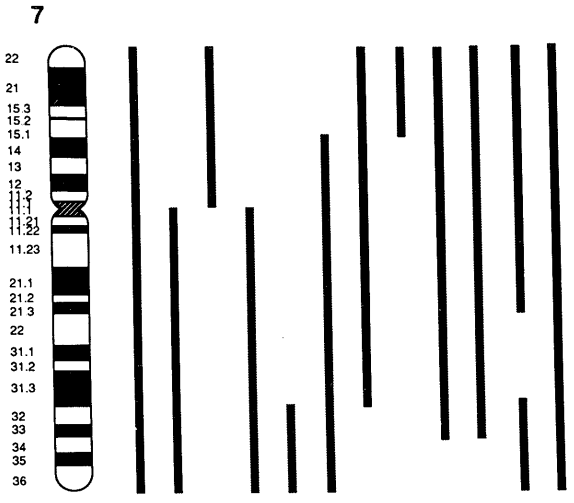


FIG. 1.—Hybridization analyses of chromosome 7 markers. Panel *A: COL1A2* (probe, NJ-1); panel *B: D7S15* (probe, Lam4-917); panel *C: MET* (probe, pmetD); panel *D: D7S8* (probe, pJ3.11); panel *E: 7C22* (probe, 7C22); panel *F: TCRB* (probe, Jurkat-2); and panel *G: PGY1* (probe, RP-1). Lane 1, 5387 3 cl 10; 2, Ru-Rag 6-19; lane 3, Ru-Rag 4-13; lane 4, Ru-Rag 1a-5-11; lane 5, MH-Rag 8-7; lane 6, IT-9a 2-21-14; lane 7, 194-Rag 6-13; lane 8, IT-A9 X-28-13; lane 9, GM3240; lane 10, GM3733; lane 11, GM1059; lane 12, GM3098; lane 13, A9; and lane 14, RAG. Descriptions of these cell lines are listed in table 1. All lanes contain DNA digested with *Eco*RI, except for panels *E* and *F*, where *Hin*dIII-digested samples are shown. Sizes of the hybridizing bands are in kilobases. These autoradiograms have been overexposed to reveal weak hybridizing signals. (Shorter exposures within the linear range of the X-ray film were used for densitometric tracing; see table 2.) Lane 8 in panel *G* is missing.



	1	2	3	4	5	6	7	8	9	10	11	12
COL1A2	+	+	(+)	+	-	+	+	-	++	++	++	++
D7S15	+	+	-	+	-	+	+	-	++	++	++	++
MET	+	+	-	+	-	+	+	-	++	++	+	++
D7S8	+	+	-	+	-	+	+	-	++	++	+	++
7C22	+	+	-	+	-	+	+	-	++	++	+	++
TCRB	+	+	-	(-)	-	+	+	-	++	++	++	++
PGY1	+	+	-	+	-	+	+	-	++	++	++	++

FIG. 2.—Summary of hybridization data. The top panel shows the fraction of chromosome 7 contained in each cell line (see table 1 for details). The hybridization data in the lower panel are derived from results shown in fig. 1. Lanes 1–8: + = presence of hybridization signal; − = absence of signal; / = not done; and () = a result in conflict with regional assignment. Lanes 9–12: ++ = full hybridization intensity; + = half intensity (see table 2 for densitometric measurements).

q22→q31, whereas *COL1A2*, *TCRB*, *D7S15*, and *PGY1* are retained and therefore located outside the deleted region. The results for *COL1A2* and *TCRB* are consistent with the previous regional assignment for the two markers, *COL1A2* to 7q21.3→q22.1 (Retief et al. 1985) and *TCRB* to 7q32 or q35 (Isobe et al. 1985; Le Beau et al. 1985; Morton et al. 1985). *D7S15* has been localized to 7qcen→q31 (Knowlton et al. 1985; Tsui et al. 1986); the present data allow us to further localize it to 7qcen→q22.

MET has been localized to 7q21→q31 by in situ hybridization (Dean et al. 1985). Since we now show that MET sequences are deleted from the del7 chromosome in GM1059 (table 2), the smallest region of overlap for *MET* can be reduced to q22→q31. GM1059 was also used in the analysis of *D7S8*. Our results clearly showed that the hybridization signal intensity of pJ3.11 is only half that of *TCRB* and other sequences located outside the deleted region in GM1059 (fig. 1, lane 11; table 2). However, we should point out that the previous regional assignment of *D7S8* to 7cen→q22 was also derived from hybridization analysis, using a similar set of cell lines including GM1059 (Bartels et al. 1986). On reexamination of the original autoradiogram presented in that report,

TABLE 2

PROBE HYBRIDIZATION RESULTS

MARKER	PROBE	HYBRIDIZATION SIGNAL INTENSITIES			
		GM3240	GM3733	GM1059	GM3098
COL1A2	NJ-1	1.1	1.0	1.1	1.0
TCRB	Jurkat-2	1.0	1.0	0.9	1.0
D7S15	Lam4-917	1.1	0.9	0.8	1.0
MET	pMETD	0.8	0.7	0.4	1.0
D7S8	pJ3-11	1.0	0.8	0.5	1.0
7C22	7C22	1.0	1.2	0.4	1.0
PGY1	RP1	0.8	0.7	0.7	1.0

NOTE.—The hybridization band intensities were derived from densitometric tracings of various exposures of autoradiograms similar to those shown in fig. 1. The signals in GM3240, GM3733, and GM1059 were normalized to those in GM3098 using the Jurkat-2 hybridizing bands as internal controls on the same blot. Similar data were obtained when several short-arm probes were used as controls (data not shown).

it was apparent that GM1059 showed a weaker hybridizing signal with pJ3.11. Therefore, we are convinced that *D7S8* is located at q22→q32. The assignment of *7C22* to 7q22→q32 is in good agreement with the in situ hybridization data that localized this marker to q31.1→q31.2 (V. Buckle and R. Williamson, personal communication).

The chromosomal location for *PGY1* was also reexamined. As shown in figure 1 (lane 11), the probe RP1 detected multiple *Eco*RI fragments within the human genome. This complex band pattern is expected because RP1 contains part of a highly conserved, duplicated region found in all P-glycoprotein sequences studied thus far. Although it is not yet clear whether all the fragments detected by RP1 correspond to a single P-glycoprotein gene or several related members of a gene family, the six human-specific bands are either all present or all absent in the somatic-cell hybrids, suggesting that these sequences are clustered in the long arm of chromosome 7 (fig. 1, lanes 1–7). As indicated above, hybridization signal–intensity analysis revealed that P-glycoprotein sequences are not deleted in GM1059 and are therefore located outside the deleted region, q22→q32 (fig. 1, lane 11; table 2).

PGY1 has been assigned to 7q36 by in situ hybridization using a CHO cDNA probe (Trent et al. 1985). Surprisingly, our analyses clearly show that P-glycoprotein sequences are not deleted in GM3240 or GM3733, both of which contain a del7 chromosome missing q34 to qter (table 2). Furthermore, RP1-hybridizing sequences are absent in MH-Rag 8-7, a human/mouse hybrid containing a small portion of chromosome 7 from q32 to qter(t[7;15][7qter→q32::15q13→pter]) (fig. 1, lane 5). Therefore, our data suggest that *PGY1* maps to 7cen→q22. The reason for this discrepancy is unknown. However, it is interesting to note that *TCRB* has also been localized to different regions in different studies (Isobe et al. 1985; Le Beau et al. 1985; Morton et al. 1985). The result of our analyses is consistent with the assignment of *TCRB* to q32. It is possible that these discrepancies are results of rearrangements frequently associated with the distal long arm of chromosome 7 in somatic cells (Isobe et al.

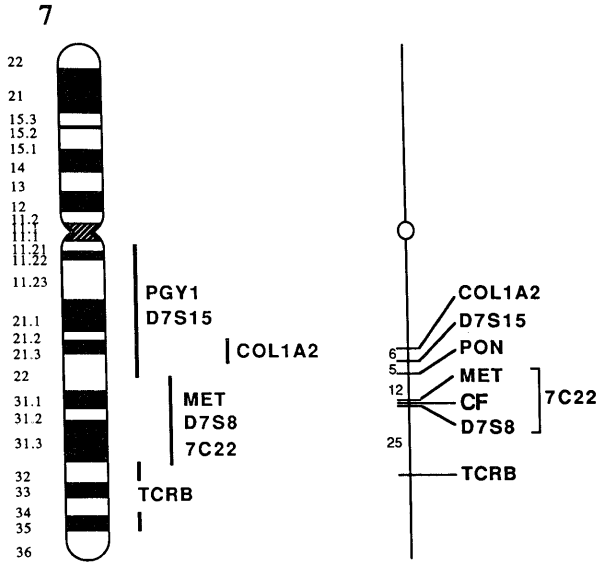


FIG. 3.—Regional localization of *COL1A2*, *TCRB*, *D7S15*, *MET*, *D7S8*, *7C22*, and *PGY1*. The smallest region of overlaps (represented by vertical bars) is derived from this and previous studies as discussed in the text. The corresponding genetic map is shown on the right (numbers in centimorgans).

1985; Morton et al. 1985). Further investigations are required to delineate this chromosomal region.

While the human/rodent hybrid cell lines are useful for localizing DNA markers to specific regions of chromosome 7, probe hybridization, in turn, serves to confirm the presence or absence of chromosomal materials in these cells. First, we detected the presence of COL1A2 sequence in Ru-Rag 4-13 (del7[pter→cen:]) (fig. 1, lane 3), a hybrid cell line with multiple chromosomal rearrangements but no discernible long arm of chromosome 7 (Bartels et al. 1986). However, since no other long-arm markers that we studied were present in Ru-Rag 4-13, it is likely that only a small segment of 7q has been retained in this cell line. Second, we failed to detect *TCRB* sequences in Ru-Rag 1a-5-11(del7[qter→cen:]) (fig. 1, lane 4), suggesting that the long arm of human chromosome 7 retained in this cell line might not be intact. Therefore, Ru-Rag 4-13 and Ru-Rag 1a-5-11 should be particularly useful for studying markers that are closely linked to *COL1A2* or *TCRB*.

Although recent studies (Frizzell et al. 1986; Welsh and Liedtke 1986) have indicated that the regulation of chloride channels might be defective in cystic fibrosis, the basic lesion in this disease remains largely unknown. Linkage analysis based on a large number of genetic markers has allowed for the first time an unambiguous assignment of *CF* on the long arm of chromosome 7. Figure 3 summarizes our current understanding of the genetic and physical relationships of the disease locus and the other markers studied. The recombination distances have been derived from extensive linkage analyses (Eiberg et

al. 1985; Knowlton et al. 1985; Scambler et al. 1985, 1986; Tsui et al. 1985, 1986; Wainwright et al. 1985; White et al. 1985; Buchwald et al. 1986; Schmiegelow et al. 1986; Beaudet et al., in press) and the map positions of the DNA markers from the present and other studies (Junien et al. 1982; Dean et al. 1985; Isobe et al. 1985; Le Beau et al. 1985; Morton et al. 1985; Retief et al. 1985; Trent et al. 1985; Bartels et al. 1986). Given the chromosomal location of these DNA markers and assuming a direct correlation between the physical and genetic distances, we think that it is reasonable to suggest that *CF* maps to either the distal region of band q22 or the proximal region of q31. Moreover, our analysis reveals that all the markers that are closely linked to *CF*—i.e., *D7S8*, *MET*, and *7C22*—are located within the deleted chromosome region in GM1059 whereas the distantly linked markers are not. This information should be useful for the isolation of additional markers for linkage studies and for the eventual identification of the affected gene in cystic fibrosis.

ACKNOWLEDGMENTS

The authors wish to thank Chin Ho and Ikuko Teshima for expert assistance in cytological examination of GM1059 and Shirley Sauve for preparing the manuscript. We also wish to thank Ray White and George Vande Woude for sharing the metD probe, Petros Tsipouras for providing NJ-1, Jorg Schmidtke for sending pJ3.11, and Pete Scambler for making 7C22 available. This work was supported by grants from the Canadian Cystic Fibrosis Foundation (CCFF), the National Institutes of Health (U.S.A.) (AM34944-02), and the Medical Research Council of Canada. S.Z. is a predoctoral student of the Deutscher Akademischer Austauschdienst. L.-C.T. is a research scholar of CCFF.

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