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Double chromosome abnormalities-- mosaic monosomy 13 and extra marker iso(22q) in a new born. *C.W. Yu[1], H-G. Bock[1], M. LeBlanc[2], R.E. Shenefelt[3].* 1) Dept. of Preventive Medicine; 2) Dept. of Pediatrics; 3) Dept. of Pathology, Univ. of Mississippi Medical Ctr., Jackson.

Patient BGM was a 37 week new born to a 40 year old G6P5 black female. The birth weight was 2,325g, birth length 49cm, and head circumference 34.5cm. Mother had PIH, polyhydramnios, and non-reactive NST during pregnancy. Patient was admitted to hospital due to congenital anomalies and failure to thrive. Physical examination showed a soft and flat fontanelle, opacity of the right eye, epicanthal fold, small nose, smooth and flat philtrum, micrognathia, bilateral ear tag, preauricular pits, and widely spaced nipples.

Cytogenetic analysis was performed from 72 hour PHA stimulated peripheral blood cultures. GTG banding demonstrated that all cells had a small, extra bisatellited marker chromosome. Four of the fifty metaphases examined also had monosomy 13. FISH studies using alpha-satellite DNA probes and unique sequence DNA probes confirmed the marker chromosome was a bisatellited, dicentric isochromosome 22 with breakpoint at 22q11.2, containing the DiGeorge syndrome/ velocardiofacial syndrome (DGS/VCFS) region. Patient expired at the age of 22 days. Postmortem tissue from heart, lungs, kidneys, and skin all had the marker chromosome. Parental blood chromosome studies were normal.

The presence of three or four copies of proximal 22q11.2, including at least the locus D22S57, is the most common molecular finding of cat-eye syndrome (CES). Our patient had mild features of CES which may be attributed to the presence of a monosomy 13 cell line. FISH studies indicate this marker has a breakpoint distal to locus TUPLE1, possibly including locus D22S941. A region of overlap on 22q11.2 for genes responsible for CES and DGS/VCFS suggests the presence of dosage sensitive genes in this interval.

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Tourette syndrome in two brothers with balanced and unbalanced chromosome 12 rearrangements. *J. Yu[1], X. Guan[2], B. Pober[1], T. Yang-Feng[1].* 1) Genetics Dept, Yale Univ Sch Medicine, New Haven, CT; 2) Hong Kong University, Hong Kong.

A 9 year old boy was referred for genetics evaluation because of minor dysmorphic features and developmental delay. Medical problems included: recurrent otitis media, strabismus, mild motor and speech delays and Tourette syndrome (TS) diagnosed at age 5 years requiring treatment with Tenex. Pertinent physical findings were: low set ears, narrow palate and mild joint hyperextensibility. Family history was remarkable for a 4 year old brother with tics considered probable TS. Parents, brother and a sister are all developmentally normal; there is no family history of TS. Cytogenetic study on the proband revealed an increased size of band 12q15. Paternal karyotype was normal while maternal karyotype demonstrated a balanced intrachromosomal insertion [ins(12)(q15p12p11.2)] which was also present in the brother and sister. The proband thus appeared to have a duplication of 12p11.2-p12 inserted into band 12q15, possibly resulting from crossing over between the maternal normal and rearranged chromosomes 12. The proband's karyotype is designated as: 46,XX,rec(12)dup(12)(p11.2p12)ins(12)(q15p12 p11.2)mat. These findings were further confirmed by FISH using a chromosome 12 painting probe and the microdissected probe spanning breakage/reunion breakpoints in 12q15 of maternal ins(12). Both the proband and his brother have TS, however, the rearranged 12 is unbalanced in the proband but apparently balanced in his brother. Of further interest is that 2 female family members carry the presumably same balanced ins(12) but have no evidence of TS. TS has been considered a sex-influenced autosomal dominant disorder as 3/4 patients are male; multiple disease loci appear possible. This family suggests a link between TS and chromosome 12 particularly in the regions of insertion breakpoints, although coincidental occurrence of these two findings cannot be excluded. Additional phenotypic abnormalities in the proband are likely associated with the duplication of the 12p11.2-p12 region.

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Direct evidences for skewed X-chromosome inactivation at Rett syndrome by combination of FISH and BrdU+Hoechst staining techniques. *Y.B Yurov[1,2], S.G. Vorsanova[1,2], A.D. Kolotii[2], V.O. Sharonin[1,2], I.V. Soloviev[1].* 1) National Centre of Mental Health, RAMS, Moscow, Russia; 2) Institute of Pediatrics and Children Surgery MH, Moscow, Russia.

Rett syndrome (RS) is a developmental disorder, affecting girls. The aetiology of RS is unknown, but genetic factors are important. RS is commonly thought of as an X linked dominant disorder lethal to hemizygous males. However, at present time its biological and genetic basis remains obscure. There is one remarkable finding in cytogenetic studies of RS, indicating on specific alterations in replication pattern of inactive X chromosome in girls with RS. X inactivation is thought to be a random process with 50%:50% ratio for maternal and paternal chromosomes X. However, for some X-linked disorders, non-random X-inactivation could take place leading to completely skewing of X-inactivation and selection against cells in which the mutant gene is on the active X chromosome. We have performed cytogenetic studies to establish that skewed X inactivation could take place at RS. In preliminary FISH studies using centromeric alphoid DNA probe we have detected three RS girls from 20 studied with heteromorphism of homologous chromosomes X on amount of alphoid DNA. This phenomenon allows us to clearly differentiate maternal and paternal X-chromosomes by FISH in metaphase cells of these girls. Step-wise application of BrdU + Hoechst staining to identify early (active) and late (inactive) replicating chromosomes X and FISH technique to clearly differentiate two homologous chromosomes X allows directly determine the origin of inactive chromosome X. We have detected non-random X-inactivation in RS patients with preferential inactivation of one X chromosome over the other X chromosome in 100% of cells of two RS girls and 70% cells of the third girl. Therefore, RS similarly to X-linked diseases, could be characterized by skewed X inactivation with variable penetrance in peripheral blood cells. Supported in parts by INTAS and IRSA grants.

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Prenatal Diagnosis of Trisomy 4 Mosaicism. *A. Zaslav[1], D. Blumenthal[2], J. Willner[3], G. Pierno[4], J. Fox[2].* 1) Dept. of Pathology, Long Island Jewish Medical Center, The Long Island Campus of The Albert Einstein College of Medicine, New Hyde Park, NY; 2) Dept. of Pediatrics Schneiders Childrens Hospital, The Long Island Campus of The Albert Einstein College of Medicine, New Hyde Park, NY; 3) Dept. of Human Genetics, Mount Sinai School of Medicine, New York, NY; 4) Sonoscan Genetic Sciences, Forest Hills, NY.

Trisomy 4 mosaicism is rare. We present a prenatally diagnosed case of trisomy 4 mosaicism. Amniocentesis was performed for AMA. The karyotype was 47,XY,+4[3]/46,XY[33]. Trisomy 4 was found in three cells from two different vessels, indicating true mosaicism. A high-resolution US and fetal echo were performed at 23 wk and neither revealed abnormalities. The infant was delivered at 37 wk. Apgar scores were 9 and 9 at 1 and 5 min. The infant had a normal examination. Chromosome analysis of 150 cells from cord and peripheral blood, foreskin and umbilical cord revealed 46,XY in all cells. There was no evidence of trisomy 4. Only 2 prenatally diagnosed cases of mosaic trisomy 4 have been reported. One resulted in a live born male who was developmentally and physically normal at one year. Normal cells were found in PUBS and foreskin (Hsu, et al., 1997, Prenat Diag 17:201). The other resulted in an abnormal live born female with multiple congenital anomalies, but no significant developmental delay at one year (Marion, et al., 1990, Am J Med Genet 37:362). PUBS and peripheral blood were normal. Trisomy 4 was found in placental and bilateral forearm biopsies. The absence of trisomy 4 cells postnatally in our patient indicates that the trisomy 4 mosaicism was most likely placental. Prenatally diagnosed chromosome mosaicism presents a diagnostic dilemma for both patient and clinician. This is only the third report of trisomy 4 mosaicism. Additional cases of prenatally diagnosed mosaicism for rare trisomies are necessary to accurately access the significance of these findings.

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High throughput mapping of Cri du Chat deletions on 5p using comparative genomic hybridization to DNA microarrays. *X. Zhang[1], R. Segraves[1], L. Bolund[2], H.M. Yang[2], E. Niebuhr[3], J. Gray[1], D. Albertson[1], D. Pinkel[1].* 1) Cancer Center, UCSF, San Francisco, CA; 2) Inst. of Human Genetics,Aauhus University, Danmark; 3) Medical Genetics, University of Copenhagen, Copenhagen, Denark.

Cri du Chat is caused by 5p deletions, with the detailed phenotype dependent on the deleted region. High resolution mapping of the deletions will permit localization of genes that may be associated with the phenotype. We have developed a microarray form of comparative genomic hybridization, array CGH, that permits reliable detection of these deletions. The array elements consist of genomic BAC and P1 clones, each containing a mapped STS or EST, spaced at approximately 1 Mb intervals along 5p. A higher density of elements was used for the established critical area at 5p15.2, as well as at 5p13. Hybridization employed 400 ng each of specimen and normal reference genomic DNA labeled with fluorescein and Alexa 568 respectively. Fluorescence data for each fluorochrome was obtained from the entire array in a few seconds using a custom designed CCD imaging system. Illumination was supplied by a mercury arc lamp. Fluorescence ratios for diploid targets were 1.0 +/- 0.07 while ratios on deleted clones were 0.55 +/- 0.05 (mean +/- s.d.). This measurement precision is expected to permit recognition of deletions with false positive and negative rates below one in several thousand. One clone was found to have a ratio of 0.75 when included in some deletions. FISH mapping showed that this clone hybridized to two locations on chromosome 5p, indicating its probable duplication in the normal genome. Thus copy number of this clone decreased from 4 to 3 copies in the deletions. Array CGH analysis of 91 Cri du Chat cases will be presented. The measurement precision obtained in this work indicates that arrays containing clones that map to established loci involved in deletion/duplication syndromes plus clones at regular intervals throughout the genome could be used to provide a rapid high resolutions diagnostic capability for constitutional aberrations. Work supported by NICHD RO1 HD 17665 and Vysis Inc. ±±±±±±±.

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Telomere-telomere fusion of chromosomes 7 and 22 with an interstitial deletion of chromosome 7p11.2-p15.1: phenotypic consequences and possible mechanisms. *S.M. Zneimer, S.D. Stewart.* Cytogenetics Laboratory, SmithKline Beecham Clinical Laboratories, Van Nuys, CA.

We report a rare, if not unique, case of a telomere-telomere fusion of chromosomes 7 and 22 as well as an interstitial deletion of chromosome 7p11.2p15.1 in a newborn with congenital anomalies. This newborn presented for chromosome analysis with bilateral cataracts, distal limb abnormalities and renal dysmorphogenesis. Chromosome analysis showed 45,XY,-7,der(22)psudic(7;22)(p22;p13)del(7)(p11.2p15.1)[20]. This short arm to short arm fusion of chromosomes 7 and 22 results in a psuedodicentric chromosome. C-banding confirms the presence of 2 centromeres with the active centromere derived from chromosome 22. In addition, the chromosome also appears to have a deletion of chromatin from bands p11.2 to p15.1. Parental blood chromosome analysis revealed normal karyotypes. Fluorescence in situ hybridization studies are underway to better characterize this complex rearrangement. Loss of genetic material in this region of chromosome 7p has been implicated in the pathophysiology of craniosynostosis syndromes, cephalosyndactyly syndrome and ocular manifestation syndrome. Given the number of reports in the literature describing syndromes associated with deletions in chromosome 7p, this region of the genome may be predisposed to deletions/duplications due to misalignment of conserved homologous sequences. It is also a region involving at least 3 different syndromes described, suggesting contiguous genes with microdeletion syndromes. The few reports in the literature describing telomere fusions have been associated with a neoplastic process. There is a paucity of information describing telomere fusions which are constitutional in origin, let alone in combination with an interstitial deletion causing clinical consequences. Telomere fusions have been shown to be a part of chromosome replication by the formation of "hairpin" 5' to 3' covalent binding, and since telomeres contain repeated short base pair sequences, it is possible to fuse two telomeres with a lack of fidelity and loose DNA sequences in the process causing deletions near the telomeres.