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Maternal Uniparental Disomy 22 Has No Impact on the Phenotype

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Summary

A 25-year-old normal healthy male was karyotyped because five of his wife's pregnancies terminated in spontaneous abortions at 6–14 wk of gestation. Cytogenetic investigation disclosed a de novo balanced Robertsonian t(22q;22q) translocation. Molecular studies revealed maternal only inheritance for chromosome 22 markers. Reduction to homozygosity for all informative markers indicates that the rearranged chromosome is an isochromosome derived from one of the maternal chromosomes 22. Except for the possibility of homozygosity for recessive mutations, maternal uniparental disomy 22 does not seem to have an adverse impact on the phenotype, apart from causing reproductive failure. It can be concluded that no maternally imprinted genes with major effect map to chromosome 22.

Introduction

Apart from chromosome 15, there is still very limited information on the effect of uniparental disomy (UPD) in humans. Some isolated cases have been identified with UPD for chromosomes 4, 6, 7, 11, 14, 21, 22, and X (see Blouin et al. 1993; Schinzel et al. 1993). For chromosome 22, the presence of maternal UPD was inferred from the observation of two females with 22/22 translocations 45,XX,−22,−22,+t(22q;22q), who each had, in addition to multiple spontaneous abortions, one child with the same balanced rearrangement (Kirkels et al. 1980; Palmer et al. 1980). We present the first instance of maternal UPD 22 confirmed by molecular analysis and shown to be homozygous for one maternal allele for all informative markers tested.

Case and Methods

Case

The proband, a 25-year-old male, works as a construction worker, as do several of his brothers. At his birth, both of his parents were 17 years old. Delivery occurred at home in a small village in eastern Anatolia, and thus no birth measurements were obtained. However, the parents stated that his birth weight was average and did not differ markedly from that of his siblings. The patient measures 1.77 m; heights of other family members are as follows: father 1.78, mother 1.65, older brother 1.80, and second and third brothers ~1.77 m. Thus, he does not deviate significantly from family standards in either growth or performance.

The proband and his wife came to medical attention because all five pregnancies of the wife had terminated in spontaneous abortions, at 10, 6, 14, 14, and 14 wk of gestation. During the course of the examination, the wife became pregnant again, and transcervical chorionic villus biopsy was performed at 11 wk of this gestation. No fetal activity was observed at the time of biopsy, and the fetus aborted spontaneously 4 d thereafter. Fetal autopsy could not be performed.

Cytogenetic Examinations

GTG banded chromosome examinations were performed from lymphocyte cultures in the proband and his wife and, subsequently, in his parents and from chorionic villus samples in the product of the wife's sixth pregnancy. Twenty metaphases were analyzed from each sample.

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Table 1

Molecular Results in the Proband and His Parents

Locus	Probe	Location	Allele		
			Proband	Mother	Father
D22S9	p22/34	22q11	1.9	1.9	1.9
D22S1	pms3-18	22q11.2-13	5.8	5.8	5.8/3.2
D22S163	p607	22	aa	aa	aa
D22S156	PCR	22q11.2-12.2	**bb**	**bb**	**ac**
D22S264	PCR	22q11.2	bb	bc	ab
D22S258	PCR	22q11.2	**bb**	**bb**	**ac**
CYP2D	PCR	22q13	cc	ac	bc
D22S315	PCR	22	aa	aa	bc
D22S274	PCR	22	bb	ab	bb
D22S283	PCR	22	**cc**	**cd**	**ab**
D15S114	PCR	15q	ac	cc	ab
IPM15M9	PCR	15q	ad	ab	cd
D15S99	PCR	15q	ab	ab	ab
D14S49	PCR	14q	ab	ac	ab

NOTE.—Boldface indicates an informative allele constellation.

Molecular Investigations

Molecular investigations were performed using the markers given in table 1. Primers for microsatellite loci were obtained from Research Genetics and were amplified on a Perkin-Elmer Thermocycler with 30 cycles, using 94°C-denaturation, 55°C-annealing, and 72°C-extension temperatures. Primers and map location, when known, are given in table 1. The primers D22S315 and D22S274 are the most proximal and distal markers, respectively, of the chromosome 22 linkage map reported by Weissenbach et al. (1992), with D22S283 centrally located in this map. PCR samples including ^{32}P-labeled cytosine were run on 6% polyacrylamide gel and were visualized by exposure to X-ray film. In addition, several probes detectable by conventional Southern blotting methods using *Taq*I-digested DNA were also analyzed. Paternity was confirmed using microsatellite markers from chromosomes 14 and 15, also obtained from Research Genetics: D15S114, D15S99, IPM15M9, and D14S49.

Results

Cytogenetic Examinations

Cytogenetic examinations revealed a nonmosaic 45,XY,−22,−22,+t(22q;22q) chromosome complement in the proband and normal 46,XX/46,XY karyotypes in the proband's wife and parents. Examination of the chorionic villi from the sixth gestation product revealed translocation-trisomy 22: 46,XX,−22,+t(22q;22q).

Molecular Investigations

No inheritance of paternal alleles was seen for several different chromosome 22 microsatellites: D22S156, D22S258 (fig. 1), D22S283 (fig. 2), and D22S315. Reduction of maternal heterozygosity to homozygosity in the proband was seen at four loci including at least one mapping to 22q11.2 (D22S264) and one mapping to 22q13 (CYP2D) (fig. 2). Although the possibility of recombination very near to the centromere or on the

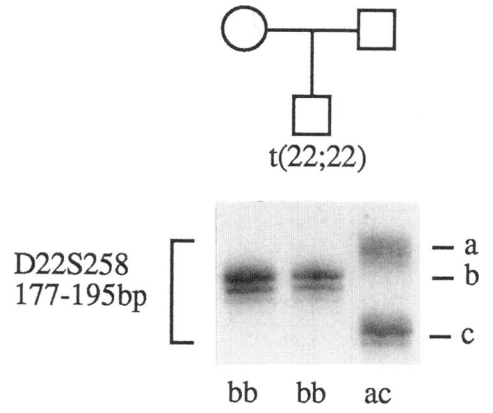

Figure 1 PCR amplification of the D22S258 microsatellite locus showing a maternal allele, but no paternal allele, in the proband.

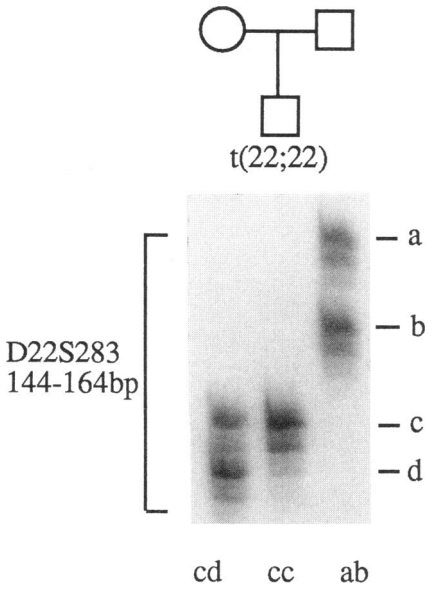

Figure 2 PCR amplification of the D22S283 microsatellite locus, showing no paternal inheritance and showing reduction of maternal heterozygosity to homozygosity in the proband.

distal long arm cannot be excluded, the molecular evidence indicates that this is an isochromosome with complete homozygosity of maternal markers.

Discussion

UPD has recently attracted attention because it has been found that it may cause a distinct clinical phenotype. The Prader-Willi syndrome is presumed to result from loss of a functional paternal copy of one or more maternally imprinted (inactivated) genes on 15q12, either through deletion or through maternal UPD. In contrast, a maternal mutation, a maternal deletion, or paternal disomy 15 results in the Angelman syndrome, presumably as the consequence of loss of a maternally active, paternally imprinted gene on 15q12, mapping very close to the Prader-Willi gene (or genes). It has subsequently been shown that the Wiedemann-Beckwith syndrome may be associated with either paternal duplication of the segment 11p15.5 or somatic rearrangements causing mosaicism for paternal UPD of the segment 11p15.5 (Henry et al. 1993). In this case, overexpression of a paternally active gene is probably responsible for the disease phenotype. In addition, for chromosomes 7 and 16, there are some hints that maternal UPD may cause growth retardation, and both maternal and paternal UPD 14 have been found to be associated with abnormal phenotypes. However, no consistent clinical picture of either of the two phenotypes, maternal and paternal UPD 14, is yet clear (see Antonarakis et al. 1993; Schinzel et al. 1993).

Two probable cases of UPD 22 have been reported elsewhere for two females with very similar histories: in both instances, a female who had multiple spontaneous abortions and one healthy daughter was shown to carry a Robertsonian 22/22 translocation or isochromosome. The healthy daughter revealed the same balanced rearrangement as the mother (Kirkels et al. 1980; Palmer et al. 1980). This finding can only be explained by transmission of the rearranged chromosome 22 from mother to daughter and simultaneous loss of the paternal homologue, resulting in maternal UPD 22. No molecular investigation has been performed in either of these two cases, and thus no distinction between hetero- and isodisomy can be made.

The proband of the present report, with a 45,XY,−22,−22,+t(22q;22q) karyotype, was shown to be homozygous for maternal alleles for all informative markers on chromosome 22 investigated. Therefore, he most likely has complete isodisomy for chromosome 22, as the result of an isochromosome formation. The lack of any maternal heterozygosity indicates that the isochromosome has been formed either in the zygote or at a very early postzygotic stage. De novo isochromosomes leading to UPD have been observed for chromosomes 14 (Pentao et al. 1992), 15 (Freeman et al. 1993; Robinson et al. 1994; D. H. Ledbetter, personal communication) and 21 (Blouin et al. 1993). It is interesting that, of individuals ascertained to have a balanced de novo homologous translocation, four showed maternal and paternal inheritance (postmeiotic Robertsonian translocation) and four showed UPD due to an isochromosome with complete reduction to homozygosity (probable postmeiotic isochromosome) (Robinson et al. 1994). Therefore, both isochromosomes and Robertsonian translocations between homologous chromosomes seem to mostly occur after meiosis, in the zygote or at an early postzygotic stage.

The phenotype of our proband, including intelligence and growth, is completely normal, and therefore, except for spontaneous abortions in his wife, UPD 22 seems to have no adverse effect on him. Loss of almost the entire 22p is known from homologous and nonhomologous Robertsonian translocations not to have any adverse impact on the phenotype. Reproductive failure in the wife of our proband is presumed to be caused by full trisomy or monosomy 22 in the offspring. This is shown by the trisomic product of the last pregnancy. Although two rescued offspring with a maternally inherited t(22q;22q) chromosome and presumed loss of

the paternal homologue have been described in two reports (Kirkels et al. 1980; Palmer et al. 1980), such a loss is assumed to occur very rarely, and the reproductive situation for the couple in the present report is very unfavorable, with a very low chance of a pregnancy lasting to term. Rarely, a pregnancy with a fully trisomic 22 fetus might be carried to term, but the newborn will certainly have multiple congenital malformations and poor outcome. Thus, the couple are candidates for artificial insemination with normal donor sperm. In conclusion, there are no imprinted genes on chromosome 22 which result in an abnormal phenotype due to over- or underexpression in maternal disomy.

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