American Journal of Medical Genetics 83:69–71 (1999)

Rapid Publication

Maternal Uniparental Disomy of Chromosome 21 in a Normal Child

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Maternal uniparental disomy of chromosome 21 [upd(21)mat] was found previously in a normal female and in 2 cases of early embryonic failure. We present a phenotypically normal child with upd(21)mat due to a de novo der(21;21)(q10;10). This finding suggests that chromosome 21 is not imprinted in the maternal germline. Am. J. Med. Genet. 83:69–71, 1999. © 1999 Wiley-Liss, Inc.

KEY WORDS: uniparental disomy; imprinting; chromosome 21; maternal inheritance

INTRODUCTION

Uniparental disomy (UPD) can result in an abnormal phenotype due to homozygosity for recessive disease [e.g., Woodage et al., 1994], or imprinted traits [Ledbetter and Engel, 1995]. UPD for certain chromosomes can also produce normal offspring, presumably because these chromosomes do not contain imprinted genes that are required for normal development [Ledbetter and Engel, 1995].

Maternal [upd(21)mat] and paternal [upd(21)pat] uniparental disomy of chromosome 21 has been reported in normal individuals and in products of conception. The previous case of liveborn upd(21)mat was a de novo balanced t(21q;21q) [Créau-Goldberg et al., 1987] in a normal female. Complete isodisomy has been found in individuals with upd(21)pat [Blouin et al., 1993; Robinson et al., 1994], suggesting that disomy arose either from meiosis II nondisjunction, a postzygotic segregation error or isochromosome formation. Meiosis II nondisjunction without recombination occurs rarely in patients with Down syndrome [Savage et al., 1998], making it more likely that upd(21)pat was postzygotically derived. In fact, age-related, somatic nondisjunction of chromosome 21 in patients with Down syndrome leads to upd(21) [Percy et al., 1993]. "Compensatory" UPD may also occur when a structurally abnormal chromosome is lost during development, and the normal chromosome missegrates [Petersen et al., 1992; Bartsch et al., 1994; Rogan et al., 1996].

The existence of normal individuals born with upd(21)mat [Créau-Goldberg et al., 1987] and upd(21)pat [Blouin et al., 1993; Robinson et al., 1994] is consistent with the possibility that chromosome 21 is not imprinted in the germline. However, maternal heterodisomy [hetero-upd(21)mat] in 2 unrelated products of conception led to the proposal that chromosome 21 might contain imprinted genes [Henderson et al., 1994]. The present report documents a second case of upd(21)mat in a normal male.

CASE HISTORY

A karyotype of 45,XY,der(21;21)(q10;q10) was found on analysis of amniocytes from a 38-year-old gr2 woman referred for prenatal testing. A subsequent percutaneous umbilical blood sample ruled out possible mosaicism for a trisomic line. All 100 metaphases examined were also 45,XY,der(21;21). The karyotypes of both parents and an older sib were normal. At age one year, the child was clinically and developmentally normal. Informed consent was granted at that time to perform additional DNA studies on the child and his parents.

METHODS

DNA was isolated from leukocytes and polymorphic genetic loci were amplified using the polymerase chain reaction (PCR). The following markers (obtained from Research Genetics, Huntsville, AL) were analyzed: D21S369, D21S120, D21S11, D21S1436, D21S265, D21S1270, D21S213, D21S263, D21S1280, D21S212 and PFKL (for PCR conditions, genetic and physical locations, refer to the Genome Database [Johns Hopkins University]). Amplification products were radiolabeled, separated on denaturing polyacrylamide gels, and scored as previously described [Woodage et al., 1994].

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Received 5 October 1998; Accepted 30 December 1998

TABLE I. Marker Genotypes

Marker	Location	Patient	Father	Mother	Interpretation[a]
D21S369	21q11.1	12	11	12	if UPD, hetero-upd(21)mat
D21S11	21q21	24	13	24	hetero-upd(21)mat
D21S265	21q21-21q22.1	23	13	23	if UPD, hetero-upd(21)mat
D21S1270	21q	22	13	22	upd(21)mat
D21S213	21q21	14	23	14	hetero-upd(21)mat
D21S263	21q21	13	12	13	if UPD, hetero-upd(21)mat
D21S1280	21q21	24	13	24	hetero-upd(21)mat
D21S212	21q22.3-21 qter	22	13	23	iso-upd(21)mat
PFKL	21q22.3	33	23	13	iso-upd(21)mat

[a]Informative loci ordered centromere to telomere are shown. D21S120 and D21S1436 are not included because both parents were homozygous for the same allele.

RESULTS AND DISCUSSION

D21S11, D21S1270, D21S213, D21S1280, D21S212 and PFKL demonstrated upd(21)mat in the child (Table I). Hetero-upd(21)mat was observed at D21S11, D21S213 and D21S1280, and isodisomy [iso-upd(21)mat] was seen at D21S212 and PFKL (Fig. 1). Meiotic recombination occurred between D21S1280 and D21S212. D21S369, D21S265 and D21S263 were each heterozygous for a maternally-derived and a shared allele. Heterozygosity at D21S369, a locus which is close to the centromere, implies that the homologous chromosomes fused to form a Robertsonian translocation prior to or during maternal meiosis I. Postzygotic loss of the paternally-derived chromosome is presumed to have resulted in upd(21)mat.

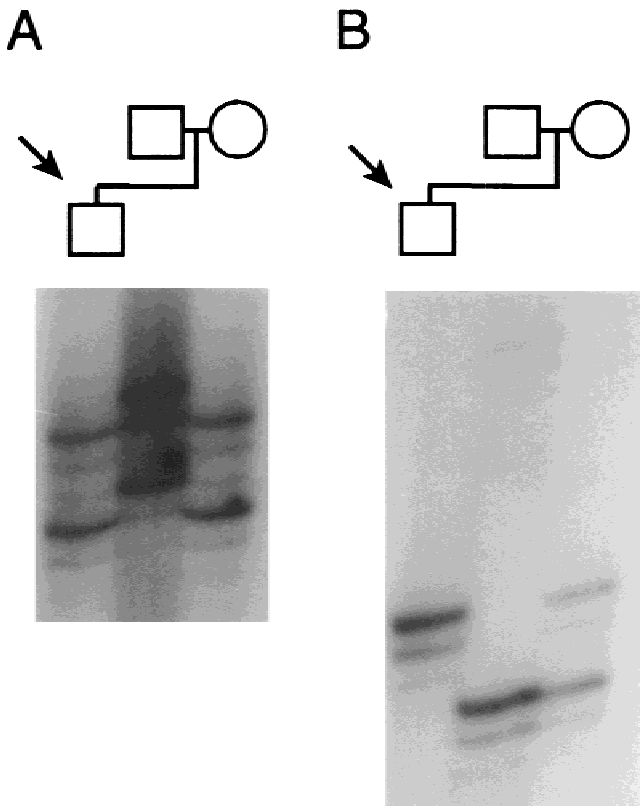

Fig. 1. Representative PCR amplification results for polymorphic chromosome 21 markers. Genotypes of the subject and his parents are shown for the following loci: (**A**) D21S1280, which shows hetero-upd(21)mat and (**B**) D21S212, which shows iso-upd(21)mat.

Fetal death in the upd(21)mat cases reported by Henderson et al., (1994) might have been caused by genetic defects on other chromosomes or by mutations in non-imprinted genes on chromosome 21. Genetic abnormalities involving other chromosomes were documented in one of these cases. Because only a limited number of polymorphic markers was informative, the possibility of a homozygous recessive disorder arising from expression of mutant genes in an undetected iso-upd(21)mat interval cannot be excluded. Additional genetic studies of fetal losses have failed to confirm UPD as a major contributing factor in early embryonic failure [Lindor et al., 1995; Shaffer et al., 1998]. In contrast, the normal phenotype and meiotic origin of upd(21)mat in our case and that of Créau-Goldberg et al. (1987) demonstrate that the paternally-derived chromosome 21 is not required for normal development.

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