Letters to the Editor

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Maternal Uniparental Disomy of Chromosome 1 with No Apparent Phenotypic Effects

To the Editor:
Uniparental disomy (UPD) arises when an individual inherits two copies of a specific chromosome from one parent and no copy from the other parent. This unusual non-Mendelian transmission of parental genes may lead to rare recessive disorders, or to developmental disturbances due to aberrant imprinting effects, in the zygote (Ledbetter and Engel 1995). However, UPD may also occur (at some unknown frequency) with no apparent phenotypic consequences. Recently, the *Journal* reported the first case of maternal chromosome 1 UPD (Pulkkinen et al. 1997) and the first case of paternal chromosome 1 UPD (Gelb et al. 1998), both ascertained through a rare recessive condition. We report here the third case of chromosome 1 UPD, and the first UPD to be ascertained inadvertently during a genome-screen linkage study. All three reports suggest that there are no imprinted genes on chromosome 1 with a major effect on phenotype.

The origin of UPD lies in meiotic nondisjunction events. UPD can result from nondisjunction during meiosis I or II in one parent, leading to a disomic gamete, followed by fertilization with a gamete nullisomic for that chromosome from the other parent (gamete complementation) or by postzygotic loss of the other parent's chromosome (trisomy rescue) (Engel 1993; Ledbetter and Engel 1995). If the nondisjunction occurs at meiosis I, the uniparental pair of chromosomes will contain the centromeric regions of both of the parent's homologues (primary heterodisomy), whereas if the nondisjunction occurs at meiosis II, the uniparental pair will contain the replicated centromeric region of one of the parent's homologues (primary isodisomy). Exchanges during meiosis I can introduce regions of homozygosity (secondary isodisomy) into a primary heterodisomy situation and, conversely, regions of heterozygosity (secondary heterodisomy) into a primary isodisomy situation. In addition to meiosis I and II errors, a third mechanism leading to UPD occurs when a normal monosomic gamete is fertilized by a nullisomic gamete, followed by postzygotic duplication of the single monosomic homologue (monosomy duplication)—this results in complete chromosome isodisomy, including the centromere, with no regions of heterozygosity (Engel 1993). Thus, centromeric heterodisomy (heterozygous markers) indicates a meiosis I error, whereas centromeric isodisomy (homozygous markers) indicates either a meiosis II error if there are other regions showing heterozygosity or postzygotic duplication if all other regions are homozygous. Since the homozygosity associated with UPD, generated either by primary or secondary isodisomy, consists of duplicate copies of alleles from a single chromosome, it carries an increased risk of homozygosity for deleterious recessive genes. Indeed, the presence of a recessive disease in the offspring has been the mode of ascertainment of many examples of UPD (reviewed in Pulkkinen et al. 1997). Similarly, if a chromosome carries imprinted genes, so that one active allele at the imprinted locus is necessary for normal growth and development of the embryo, UPD may be associated with intrauterine growth retardation and other developmental abnormalities (reviewed in Hall 1990; Ledbetter and Engel 1995). However, since the advent of comprehensive genome-wide genotyping for purposes of genetic linkage analysis, the possibility now exists that phenotypically "invisible" cases of UPD, not ascertained through recessive disease or through imprinting-associated abnormalities, will be discovered.

We have been performing genome screening of families having at least two children affected with type 1 (insulin-dependent) diabetes, in order to identify by linkage analysis genes predisposing to this disorder (Field et al. 1994, 1996). A subset of 77 families including 203 children and all their parents has been typed for 187 markers across all chromosomes. During the course of these studies, family BD94 (DNA obtained from the British Diabetes Association Warren Repository [Bain et al. 1990]) was noted to produce numerous marker-typing incompatibilities between the second diabetic child and her father. Closer inspection revealed that the incompatibilities between the father and the second child only involved some of the 14 marker loci typed on chromosome 1, whereas genotyping at 173 microsatellite loci on chromosomes 2 through X (multiple markers on all

chromosomes) produced no incompatibilities, proving conclusively that the putative father was the biological father. An additional 15 markers on chromosome 1 were then genotyped for all family members, and further clinical details about the family, particularly the second child, were obtained following a separate informed consent. Table 1 shows the results of typing 29 chromosome 1 markers and the human leukocyte antigen (HLA) types provided by the BDA. For simplicity, genotypes are shown as recoded alleles, with the mother's alleles and then the father's alleles numbered from smallest to largest and with alleles of identical size receiving the same number code (for example, at D1S159, the mother is 145/147, the father 147/149, the first child 147/149, and the second child 145/145). Markers are listed from pter to qter, with positions on the female genetic map indicated in centimorgans according to information from the Marshfield Center for Medical Genetics Website.

Of the 29 chromosome 1 markers, 16 markers, distributed across the entire chromosome, show incompatibility (indicated in table 1) between the father and the second diabetic child, labeled "Child2." For all 29 markers, the second child's genotype is either identical to the mother's genotype or (in a small region on the short arm) shows only a single allele found in the mother. For the latter cases, if the mother is heterozygous but the child is homozygous, then maternal isodisomy is present (indicated in table 1). The centromeric region is heterodisomic. This pattern is consistent with maternal uniparental primary heterodisomy (arising from nondisjunction during meiosis I), with an embedded region of homozygosity (secondary isodisomy) on the short arm

Table 1

Results of Typing 29 Chromosome 1 Microsatellites and Chromosome 6 HLA Loci

Marker or Status	Cytogenetic Location	Genetic Location (Female cM)	Mother	Father	Child1	Child2
D1S468	…	4.5	1,2	1,1	1,2	1,2
D1S1612	…	17.8	1,2	3,4	2,4	1,2[a]
D1S1368	…	…	1,2	1,3	1,2	1,2
D1S1622	…	68.5	1,1	2,3	1,2	1,1[a]
D1S186	…	84.6	1,2	3,4	1,4	1,2[a]
D1S2134	…	100	1,2	2,2	1,2	1,2
D1S405	…	117	1,1	1,1	1,1	1,1
D1S3728	…	122	1,1	2,2	1,2	1,1[a]
D1S198	p32-p33	132	1,2	3,4	2,4	1,2[a]
D1S159	p32	…	1,2	2,3	2,3	1,1[a,b]
D1S410	…	135	1,1	1,2	1,2	1,1
D1S1665	…	137	1,2	1,3	1,1	2,2[a,b]
D1S550	…	…	1,2	2,3	2,2	1,1[a,b]
D1S1728	…	144	1,2	2,3	1,3	2,2[b]
D1S551	…	151	1,1	1,2	1,1	1,1
D1S1159	…	151	1,2	2,3	1,3	2,2[b]
D1S116	p21-p31	…	1,1	1,2	1,1	1,1
D1S1588	…	167	1,2	3,4	2,4	1,2[a]
AMY2B	p21	…	1,2	1,3	1,1	1,2
D1S1631	…	177	1,2	2,3	1,2	1,2
D1S305	…	210	1,1	2,3	1,3	1,1[a]
APOA2	q21-q23	227	1,2	3,4	1,4	1,2[a]
D1S1589	…	245	1,2	1,3	2,3	1,2
D1S117	q23-q25	…	1,2	3,3	1,3	1,2[a]
D1S1660	…	271	1,2	3,4	2,3	1,2[a]
GATA124F08	…	…	1,2	1,1	1,2	1,2
D1S213	q32-q44	312	1,2	3,4	2,4	1,2[a]
D1S103	q32-q44	317	1,2	3,4	2,4	1,2[a]
D1S547	…	351	1,2	3,4	2,4	1,2[a]
HLA-A			1,2	3,31	1,31	1,31
HLA-B			8,62	65,60	8,60	8,60
HLA-C			7,3	8,3	7,3	7,3
HLA-DRB			3,4	13,4	3,4	3,4
HLA-DQB			2,3	1,8	2,8	2,8
+ = high risk HLA haplotype			+,+	−,+	+,+	+,+
Type 1 diabetes present			Yes	No	Yes	Yes

[a] Incompatibility with father.
[b] Demonstrable maternal isodisomy.

created by a double exchange event. The isodisomic region within the double exchange includes markers D1S159, D1S410, D1S1665, D1S550, D1S1728, D1S551, D1S1159, and possibly D1S116 (the mother is uninformative for the latter), which have all been cytogenetically localized between 1p21 and 1p32. Advanced maternal age is often associated with increased risk of nondisjunction, but this is not relevant in the present study, since the mother was 21 years old at the time of the birth of her second child.

The region of homozygosity encompassed by the two recombination events appears to be quite small: the estimated genetic distance between D1S159 and D1S1159 is 16–35 cM (see table 1: $151 - 135 = 16$, and $167 - 132 = 35$) in a total female-chromosome length of ~365 cM, according to the Marshfield maps. The other case of maternal chromosome 1 UPD primary heterodisomy also shows only a single region of secondary isodisomy (~35 cM on the long arm), created by a double meiotic exchange event (Pulkkinen et al. 1997). It is possible that unusual recombination patterns (e.g., decreased number of chiasmata or closely adjacent chiasmata) predispose to nondisjunction in meiosis I and thus increase the probability of UPD (Koehler et al. 1996). Alternatively, possession of larger regions of homozygosity in heterodisomic UPD zygotes would increase the risk of recessive lethal conditions, so that these zygotes may be selected against early in development. However, it also is possible that the actual number of detected exchanges (i.e., two) may not be particularly unusual. The expected number of chiasmata occurring between chromatids of paired homologues for a chromosome 365 cM long, which is the size of chromosome 1, is on average seven. We have calculated (on the basis of probabilities from table 2 in Robinson et al. 1993) that the chance of observing ≤2 transitions in a UPD zygote, when seven chiasmata have occurred during meiosis, is 8.6%. (The term "exchange" refers to a chiasma that has occurred in the meiosis I tetrad, whereas "transition" refers to a transition from heterodisomy to isodisomy, or vice versa, in a disomic gamete.) The probability of observing ≤2 transitions would be even higher if there was incomplete marker coverage such that a transition event could be missed (which is possible in the present study) and/or if 365 cM is an overestimate of the true map length due to typing errors (genetic maps are commonly inflated for this reason), so that the expected number of chiasmata is actually less than seven. The reason that so few transitions might be observed, even if as many as seven chiasmata have taken place, is that for a transition to be observable by extensive marker typing in a UPD zygote, the exchange event must occur between a transmitted and a nontransmitted chromatid (i.e., about half of exchanges result in potentially observable transitions, when random involvement of chromatids in chiasmata formation is assumed). Furthermore, for a transition to be observable, the mother must be heterozygous for one or more markers proximal to the exchange. Thus, although it may seem that few exchanges have occurred during the meiosis I event leading to this zygote with chromosome 1 UPD, the actual number of transitions is not significantly different from the expected number.

Trisomy 1 conceptuses have not been observed in spontaneous abortions (Hassold et al. 1996), except for one report of a lost pregnancy with no fetal development (Hanna et al. 1997), or among cases of prenatally diagnosed placental or fetal mosaicism (Ledbetter et al. 1992; Teshima et al. 1992; Hahnemann and Vejerslev 1997). To our knowledge, there are only two reports of trisomy 1 mosaicism in humans (outside of cancer cells) (Neu et al. 1988; Howard et al. 1995). However, molecular studies to determine the origin of the trisomy were not performed in either case, and in at least one case both monosomy and trisomy 1 cells were present, indicating that the trisomy arose as a somatic event during development (Neu et al. 1988). On the other hand, sperm or oocytes aneuploid for chromosome 1 are not uncommon (Martin et al. 1991, 1995; Spriggs et al. 1996). This suggests that trisomy 1 conceptuses occur but die prior to implantation. Thus, the finding of chromosome 1 UPD of maternal meiotic origin is most likely due to a gamete complementation mechanism (fertilization of a disomic egg with a sperm nullisomic for chromosome 1) rather than a trisomy-rescue mechanism (postzygotic loss of the father's chromosome 1), unless the trisomy rescue occurred in the first one or two cell divisions with complete selection against the trisomic cells.

The mother and both of the two children in this family have type 1 diabetes, and all three individuals have HLA genotypes associated with a high risk of developing diabetes (see table 1). It is well established that the HLA region contains the strongest susceptibility genes for this disease (for a review of insulin-dependent diabetes mellitus [IDDM] genetics, see Field and Tobias 1997). Thus, we assume that the presence of chromosome 1 UPD in one of the diabetic children is unrelated to her IDDM. Apart from her diabetes, she has no other unusual conditions. There was no evidence of dysmorphic features at birth. She had a full-term birth weight of 2,930 g (consistent with that of her mother and older brother, whose full-term birth weights were 2,840 g and 2,870 g, respectively), with no indication of intrauterine growth retardation. Subsequently (she is now 23 years old), she showed no signs of mental or developmental retardation or precocious puberty.

In the two other cases of chromosome 1 UPD (Pulkkinen et al. 1997; Gelb et al. 1998), ascertainment was through a rare recessive disorder, but there were no features suggestive of imprinting, such as growth or de-

velopmental abnormalities. However, since the infant with maternal chromosome 1 UPD died at 2 mo of age (Pulkkinen et al. 1997), the present case of maternal chromosome 1 UPD in a developmentally normal adult provides valuable additional evidence that there are no imprinted genes on chromosome 1 with major phenotypic effects. This has potential implications for prenatal diagnosis if chorionic villus sampling (CVS) reveals trisomy mosaicism and later amniotic fluid sampling shows fetal disomy (apparent trisomy rescue), since these cases theoretically have a one in three risk of UPD for the relevant chromosome and any associated imprinting effects (Ledbetter and Engel 1995). However, as discussed above, it is probable that conceptuses trisomic for chromosome 1 die before implantation and therefore are unlikely to be detected by CVS.

The data presented here, combined with that from other reports of UPD (Jones et al. 1995; Ledbetter and Engel 1995), suggest that, in the absence of isodisomy for recessive deleterious genes, uniparental disomy for chromosomes that do not harbor imprinted loci may be quite harmless. If so, it would be of interest to know the frequency of this phenomenon in the normal general population. In our laboratory, we have typed >200 children (and their parents) for markers relatively densely distributed across the genome, and this is the first case of UPD that we have recognized. Other laboratories performing large-scale linkage-mapping projects may encounter UPD but may attribute it to lab typing errors, null alleles, or nonpaternity. The possibility of UPD should be considered when typing incompatibilities occur repeatedly for the same family in genome-screen projects, since such studies represent an important source for discovery of additional cases of UPD with no apparent phenotypic effects.

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Electronic-Database Information

URL for data in this article is as follows:

Marshfield Center for Medical Genetics, http://www.marshmed.org/genetics (for marker mapping information)

References

Bain SC, Todd JA, Barnett AH (1990) The British Diabetes Association–Warren Repository. Autoimmunity 7:83–85

Engel E (1993) Uniparental disomy revisited: the first twelve years. Am J Med Genet 46:670–674

Field LL, Tobias R (1997) Unravelling a complex trait: the genetics of insulin-dependent diabetes mellitus. Clin Invest Med 20:41–49

Field LL, Tobias R, Magnus T (1994) A locus on chromosome 15q26 (*IDDM3*) produces susceptibility to insulin-dependent diabetes mellitus. Nat Genet 8:189–194

Field LL, Tobias R, Thomson G, Plon S (1996) Susceptibility to insulin-dependent diabetes mellitus maps to a locus (*IDDM11*) on human chromosome 14q24.3-q31. Genomics 33:1–8

Gelb BD, Willner JP, Dunn TM, Kardon NB, Verloes A, Poncin J, Desnick RJ (1998) Paternal uniparental disomy for chromosome 1 revealed by molecular analysis of a patient with pycnodysostosis. Am J Hum Genet 62:848–854

Hahnemann JM, Vejerslev LO (1997) European Collaborative Research on Mosaicism in CVS (EUCROMIC): fetal and extrafetal cell lineages in 192 gestations with CVS mosaicism involving single autosomal trisomy. Am J Med Genet 70: 179–187

Hall JG (1990) Genomic imprinting: review and relevance to human diseases. Am J Hum Genet 46:857–873

Hanna JS, Shires P, Matile G (1997) Trisomy-1 in a clinically recognized pregnancy. Am J Med Genet 68:98

Hassold T, Abruzzo M, Adkins K, Griffin D, Merrill M, Millie E, Saker D, et al (1996) Human aneuploidy: incidence, origin, and etiology. Environ Mol Mutagen 28:167–175

Howard PJ, Cramp CE, Fryer AE (1995) Trisomy 1 mosaicism only detected on a direct chromosome preparation in a neonate. Clin Genet 48:313–316

Jones C, Booth C, Rita D, Jazmines L, Spiro R, McCulloch B, McCaskill C, et al (1995) Identification of a case of maternal uniparental disomy of chromosome 10 associated with confined placental mosaicism. Prenat Diagn 15:843–848

Koehler KE, Hawley RS, Sherman S, Hassold T (1996) Re-

combination and nondisjunction in humans and flies. Hum Mol Genet 5:1495–1504
Ledbetter DH, Engel D (1995) Uniparental disomy in humans: development of an imprinting map and its implications for prenatal diagnosis. Hum Mol Genet 4:1757–1764
Ledbetter DH, Zachary JM, Simpson JL, Golbus MS, Pergament E, Jackson L, Mahoney MJ, et al (1992) Cytogenetic results from the US Collaborative Study on CVS. Prenat Diagn 12:317–345
Martin RH, Ko E, Rademaker AW (1991) Distribution of aneuploidy in human gametes: comparison between human sperm and oocytes. Am J Med Genet 39:321–331
Martin RH, Spriggs E, Ko E, Rademaker AW (1995) The relationship between paternal age, sex ratios, and aneuploidy frequencies in human sperm, as assessed by multicolor FISH. Am J Hum Genet 57:1395–1399
Neu RL, Kouseff BG, Madan S, Essig Y-P, Miller K, Tedesco TA (1988) Monosomy, trisomy, fragile sites, and rearrangements of chromosome 1 in a mentally retarded male with multiple congenital anomalies. Clin Genet 33:73–77
Pulkkinen L, Bullrich F, Czarnecki P, Weiss L, Uitto J (1997) Maternal uniparental disomy of chromosome 1 with reduction to homozygosity of the LAMB3 locus in a patient with Herlitz junctional epidermolysis bullosa. Am J Hum Genet 61:611–619
Robinson WP, Bernasconi F, Mutirangura A, Ledbetter DH, Langlois S, Malcolm S, Morris MA, et al (1993) Nondisjunction of chromosome 15: origin and recombination. Am J Hum Genet 53:740–751
Spriggs EL, Rademaker AW, Martin RH (1996) Aneuploidy in human sperm: the use of multicolor FISH to test various theories of nondisjunction. Am J Hum Genet 58:356–362
Teshima IE, Kalousek DK, Vekemans MJ, Markovic V, Cox DM, Dallaire L, Gagne R, et al (1992) Canadian multicenter randomized clinical trial of chorion villus sampling and amniocentesis: chromosome mosaicism in CVS and amniocentesis samples. Prenat Diagn 12:443–466

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