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INVITED EDITORIAL
Uniparental Disomies in Unselected Populations

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Introduction

Uniparental disomy (UPD) is the presence, in a diploid individual, of a chromosome pair that derives from only one parent (Engel 1980). The first clinical case of UPD was reported by Beaudet's group and involved a girl with cystic fibrosis and unusually short stature who carried two copies of maternal chromosome 7, presumably resulting from a monosomy 7 duplication (Spence et al. 1988). At the time, the frequency of such an occurrence could only be guessed but was deemed to be low (Warburton 1988). Yet, only a few months later, another, very similar case was recognized, raising the possibility that UPD might be common in humans (Voss et al. 1989). In this issue of the *Journal,* Field et al. (1998) report a case of UPD for maternal chromosome 1. This chromosomal abnormality causes no evident phenotype and was ascertained inadvertently during the course of a genomic screen of families in which two or more children exhibit type 1 diabetes. This serendipitous finding raises the question of how many people in a normal unselected population carry an unequal share of paternal and maternal chromosomes in their cells—namely, 24 from one parent and 22 from the other parent.

Known Cases of UPD

During the past decade, 29 of the 47 possible uniparental chromosome pairs (including the XY pair) have been identified among individuals ascertained for medical reasons (Ledbetter and Engel 1995; Engel 1998). Pairs derived from a single parent, observed to date in one to several cases, include maternal chromosomes 1, 2, 4, 6, 7, 9, 10, 13–16, 21, 22, and X and paternal chromosomes 1, 5–8, 11, 13–16, 20–22, X, and XY. Evidence for UPD in these cases arose from the observation of imprinting disturbances, non-Mendelian inheritance of recessive genes, or anomalous chromosome patterns.

Distinct and recurrent phenotypes have been observed for some homologous pairs, depending on their maternal or paternal origin. Thus, some recognizable conditions became instrumental in the identification of chromosomal domains in which gene expression is a function of the parental sex. As a result, uniparentally inherited pairs have been identified as the basis of some well-known and some novel imprinting syndromes. Five such known conditions include Prader-Willi syndrome, from maternal UPD 15 (Nicholls et al. 1989); Angelman syndrome, from paternal UPD 15 (Malcolm et al. 1991; Bottani et al. 1994); Beckwith-Wiedemann syndrome, from paternal UPD 11 (Henry et al. 1991); Silver-Russell syndrome, from maternal UPD 7 (Kotzot et al. 1995); and transient neonatal diabetes mellitus, from paternal UPD 6 (Temple et al. 1995). The newly recognized conditions occur with maternal UPD 14 (Antonarakis et al. 1993), which leads to short stature and precocious puberty; paternal UPD 14 (Cotter et al. 1997) causes dwarfism, skeletal dysplasia, and thoracic narrowing. Less well established is the phenotype of stunted growth and congenital heart and digestive-tract anomalies, which is associated with maternal UPD 16 (Vaughan et al. 1994; Schneider et al. 1996) and that of growth restriction and pulmonary dysplasia apparently seen with maternal UPD 2 (Bernasconi et al. 1996; Harrison et al. 1995; Johnston et al. 1996; Shaffer et al. 1997).

Another subset of UPD cases has been recognized because of anomalous patterns of transmission of recessive genes (Spence et al. 1988; Voss et al. 1989). In such cases, UPD would have gone unnoticed, but for molecular analyses that can show that homozygous alleles can originate from a single duplicated chromosome that was present in one biological parent but absent was in the other (a condition known as "uniparental isodisomy"). The 18 recessive disorders shown in table 1 occur in some of the cases because of this unusual non-Mendelian form of inheritance.

Cytogenetic anomalies have also led to the unmasking of UPD cases. These anomalies include cases of trisomy/euploid mosaicism with confined placental aneuploidy, as originally described by Cassidy et al. (1992) and oth-

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Table 1

Recessive Disorders

Condition	UPD Type	Reference(s)
Pycnodysostosis	1 pat	Gelb et al. (1998)
Junctional epidermolysis bullosa, Herlitz type	1 mat	Pulkkinen et al. (1997)
Spinal muscular atrophy III (juvenile type)	5 pat	Brzustowicz et al. (1994)
Complement (C4A+C4B) deficiency	6 pat	Welch et al. (1990)
Methylmalonic acidemia	6 pat	Abramowicz et al. (1994)
Cystic fibrosis	7 mat	Spence et al. (1988), Voss et al. (1989)
Osteogenesis imperfecta (COL1A2 mutation)	7 mat	Spotila et al. (1992)
Cystic fibrosis and Kartagener syndrome	7 pat	Pan et al. (1998)
Congenital chloride diarrhea	7 pat	Höglund et al. (1994)
Chylomicronemia, familial	8 pat	Benlian et al. (1996)
Cartilage/hair hypoplasia	9 mat	Sulisalo et al. (1997)
Beta-thalassemia major	11 pat	Beldjord et al. (1992)
Complete congenital achromatopsia (rod monochromacy)	14 mat	Pentao et al. (1992)
Bloom syndrome (with Prader-Willi syndrome)	15 mat	Woodage et al. (1994)
Hydrops fetalis alpha-thalassemia	16 pat	Ngo et al. (1993)
Familial Mediterranean fever	16 mat	Korenstein et al. (1994)
Duchenne muscular dystrophy	X mat	Quan et al. (1997)
Hemophilia A	XY	Vidaud et al. (1989)

ers (Kalousek et al. 1993; DeLozier-Blanchet et al. 1997; Van Opstal et al. 1998), as well as Robertsonian translocations (James et al. 1994), isochromosomes (Freeman et al. 1993; Eggerding et al. 1994; Bernasconi et al. 1996), small marker chromosomes (Robinson et al. 1993; James et al. 1995), and heteromorphic duplications (Willatt et al. 1992).

UPD for a given chromosome may also cause the unusual association of two clinical disorders (Nicholls 1991; Schinzel 1991), either through imprinting imbalance and reduction to recessive homozygosity (Spence et al. 1988; Voss et al. 1989; Pentao et al. 1992; Woodage et al. 1994) or through the combination of two recessive traits in an isodisomic segment (Pan et al. 1998).

UPD in the General Population?

Even after the aforementioned guidelines have been used in the search for singly derived pairs, an unknown proportion of UPD cases will remain undetected in the population at large. However, by knowing the frequency of a syndrome and the proportion of specific cases of it that are caused by UPD, one can, in some cases, derive an approximate frequency of this aberration of chromosome transmission. Robinson et al. (1996) have estimated the population frequency of maternal and paternal UPD 15 at ~1/80,000 and ~10^{-6} viable births, respectively. They derived these values by assuming the frequency of Prader-Willi syndrome and Angelman syndrome to be 1/20,000 each (Bottani et al. 1994), with, respectively, 25% and 2% of UPD cases contributing to their etiology. Similarly, if the frequency of Beckwith-Wiedemann syndrome is 1/15,000 (Wiedemann 1997) and paternal UPD 11p (of somatic origin) is the cause of some 20% of the cases (Henry et al. 1993), then the population frequency approaches 1/75,000. At a population frequency of 1/500,000 for transient neonatal diabetes mellitus (Temple et al. 1996) and with 40% of the cases stemming from paternal UPD 6 (Temple et al. 1998), an exclusively paternal derivation of chromosome 6 should occur at a frequency of 1/1,250,000 births. Unfortunately, the frequency of Silver-Russel syndrome is not established, and the cause of the syndrome may be very heterogeneous, so that the frequency of maternal UPD 7 cannot be approached from this angle.

What, then, if we attempt an ascertainment of UPD cases through the bias of Mendelian recessive disorders, by looking among them for exceptions stemming from isodisomy and reduction to homozygosity? By this approach, maternal UPD 7 has been documented, by molecular means, in 1/55 cystic fibrosis families tested (Voss et al. 1989), whereas 2/54 individuals with cartilage/hair hypoplasia examined exhibit maternal UPD 9 (Sulisalo et al. 1997), and 1/61 junctional epidermolysis bullosa cases, Herlitz type (Pulkkinen et al. 1997), are disomic for maternal chromosome 1. Similar findings, of paternal UPD 5 in spinal muscular atrophy III (juvenile type) (Brzustowicz et al. 1994) and of paternal UPD 8 in chylomicronemia cases (Benlian et al. 1996), support the generality of this effect, although the frequency of these events is not known. It is possible, then, that 1%–2% of typically recessive traits result from UPD and primary or secondary isodisomy of the type discussed by Field et al. (1998), although it is difficult to regard this estimate with any confidence. Naturally, this approach cannot be used to estimate the frequency of uniparental heterodisomy.

The serendipitous finding by Field et al. (1998), in the course of their genomewide linkage study, is not without precedent. Recently, maternal (Van den Berg–Loonen et al. 1996) and paternal (Bittencourt et al. 1997) isodisomy 6 have been observed in, respectively, a thalassemic individual and a renal patient who were being studied by HLA typing for organ transplantation. The maternal UPD 6 finding was made among some 700 tests performed during 10 years.

These findings, as well as that by Field et al. (1998), should motivate a genomewide analysis of randomly ascertained healthy families. With present-day genomic tools, it should be possible to enlarge and improve on earlier, broad-based cytogenetic studies, which investigated the overall frequency of chromosome anomalies within normal populations and among cohorts of spontaneously aborted fetuses. Once we have learned how many of us carry unequal numbers of maternal and paternal chromosomes, we can begin in earnest to investigate the possibly subtle behavioral or developmental effects of the various classes of UPD.

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