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Identification of Uniparental Disomy Following Prenatal Detection of Robertsonian Translocations and Isochromosomes

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Rearrangements of the acrocentric chromosomes (Robertsonian translocations and isochromosomes) are associated with an increased risk of aneuploidy. Given this, and the large number of reported cases of uniparental disomy (UPD) associated with an acrocentric rearrangement, carriers are presumed to be at risk for UPD. However, an accurate risk estimate for UPD associated with these rearrangements is lacking. A total of 174 prenatally identified acrocentric rearrangements, including both Robertsonian translocations and isochromosomes, were studied prospectively to identify UPD for the chromosomes involved in the rearrangements. The overall goal of the study was to provide an estimate of the risk of UPD associated with nonhomologous Robertsonian translocations and homologous acrocentric rearrangements. Of the 168 nonhomologous Robertsonian translocations studied, one showed UPD for chromosome 13, providing a risk estimate of 0.6%. Four of the six homologous acrocentric rearrangements showed UPD, providing a risk estimate of 66%. These cases have also allowed delineation of the mechanisms involved in producing UPD unique to Robertsonian translocations. Given the relatively high risk for UPD in prenatally identified Robertsonian translocations and isochromosomes, UPD testing should be considered, especially for cases involving the acrocentric chromosomes 14 and 15, in which UPD is associated with adverse clinical outcomes.

Introduction

Uniparental disomy (UPD) is the abnormal inheritance of both homologous chromosomes from a single parent, with no contribution of that chromosome from the other parent (Engel 1980). UPD has been described for nearly every chromosome, with several showing phenotypic effects due to imprinting (Ledbetter and Engel 1995; Shaffer et al. 1998; Kotzot 1999). Mechanisms that may lead to UPD include trisomy rescue through loss of a chromosome, monosomy rescue through duplication of a chromosome, and gametic complementation through union of aneuploid gametes that complement one another (Spence et al. 1988).

Investigation leading to the identification of UPD may be initiated after presentation of a numerical or structural chromosome abnormality or recessive disease (Ledbetter and Engel 1995; Shaffer et al. 1998; Kotzot 1999). In a recent review of literature describing patients with UPD, the following structural chromosome abnormalities were identified: acrocentric isochromosomes, Robertsonian translocations, nonacrocentric isochromosomes, marker chromosomes, derivative chromosomes, and reciprocal translocations (Shaffer et al. 1998). Of the patients with both UPD and one of these structural anomalies, ~60% had acrocentric isochromosomes and ~21% had Robertsonian translocations between nonhomologous chromosomes.

Rearrangements of the acrocentric chromosomes are most often whole-arm exchanges of nonhomologous chromosomes resulting in Robertsonian translocations. The breakpoints usually occur in the short arms of the participating chromosomes, to result in dicentric translocations (Han et al. 1994; Page et al. 1996; Sullivan et al. 1996). Nonhomologous Robertsonian translocations are the most common, recurrent, constitutional chromosomal rearrangement in the human population, with an incidence of ~1/1,000 individuals (Hamerton et al. 1975). Compared with the general population, carrier individuals are at a higher risk of having aneuploid offspring, especially Down syndrome and trisomy 13 (table 1). Homologous rearrangements of the human acrocentric chromosomes can be the result of either isochromosome or Robertsonian translocation formation (Shaffer et al. 1993*a*, 1994). With the technological advances of molecular genetics, including the accessibility of highly polymorphic markers, homologous rearrangements can now be characterized as isochromosomes, both arms derived from a single parental chromosome, or true Robertsonian translocations, comprising two different, homologous chromosomes. The ability to

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Table 1

Empiric Risks for Pregnancy Outcome of Common Robertsonian Translocation (Rob) Carriers

	Carrier Parent[a]			
	Mother		Father	
Rob	SAB	Unbal	SAB	Unbal
13q14q	22%	1%	13%	1%
14q21q	24%	10%–14%[b]	33%	1%

Note.—Most SABs were not karyotyped. However, a proportion is presumed to be aneuploid. Data for rob(13q14q) and SAB derived from Harris et al. (1979); data for rob(14q21q) and SAB derived from Neri et al. (1983).

[a] SAB = spontaneous abortion; Unbal = documented aneuploid offspring.

[b] Risk for aneuploidy depends on the gestational age at the time of ascertainment.

distinguish these distinct rearrangements aids in the understanding of the mechanisms leading to their formation.

The presence of a Robertsonian translocation or an isochromosome ascertained through chromosome analysis, either prenatally or postnatally, appears to increase the likelihood of UPD for the chromosome or chromosomes involved. The association of acrocentric rearrangements and UPD is likely due to the increased risk for aneuploidy. However, an accurate estimate of the actual risk of UPD associated with these rearrangements is currently unknown. Our prospective investigation screened prenatally identified, acrocentric rearrangements, including both familial and de novo Robertsonian translocations and isochromosomes, and has allowed for an estimate of the risk for UPD when an acrocentric rearrangement is identified prenatally.

Material and Methods

Ascertainment of the Study Population

Prenatal specimens were studied by routine cytogenetics at many referral centers in the United States and abroad; those found to contain an acrocentric rearrangement were referred to our laboratory to exclude UPD for the chromosomes involved. A total of 174 specimens were sent for UPD studies. The distribution of the rearrangements is shown in table 2. Parental chromosomes from available parents (171 of 174 cases) were analyzed to determine whether the rearrangement was de novo or familial in origin. For three cases, paternal samples were unavailable. Informed consent was obtained from each family included in this study, and the study protocol was approved by the Baylor College of Medicine Institutional Review Board.

Molecular Analysis

DNA was isolated from amniocytes or chorionic villi derived from the fetus and peripheral blood from available parents by standard methods. All markers were obtained from Research Genetics. PCR-based polymorphic markers for the chromosomes involved in each of the rearrangements were analyzed. All loci were analyzed according to Shaffer et al. (1993*b*), with the following modifications in PCR conditions: initial 30 s at 94°C, annealing for 1 min at 56°C, and extension for 1 min at 72°C.

Confirmation of Marker Location

A PCR-based marker referred to as "NA" (assay number AFM079XD11; Genome Database accession number 1222803; Research Genetics) was used to exclude UPD 14 for many of the cases included in this study. It was presumed to be mapped to chromosome 14; however, we were informed late in the study that the map assignment had been changed to chromosome 16. Monochromosomal hybrids GM11535 (Mares et al. 1991) and CP43 (Lai et al. 1983) each contain a single human chromosome 14 as the only human genetic material. FISH studies using α-satellite probes specific for chromosome 14 (obtained labeled with digoxigenin; Vysis) and chromosome 16 (obtained labeled with biotin; Vysis) confirmed that these hybrids contained only a human chromosome 14 and not human chromosome 16. PCR of the two monochromosomal hybrids and their corresponding rodent cell lines (RJK88 and CHO-K1) showed amplification in both monochromosomal hybrids, using two different lot numbers of the primer pairs corresponding to NA, and no amplification in the

Table 2

Distribution of the Prenatally Identified Acrocentric Rearrangements (Der) Studied

	Translocation Origin				
Der	Maternal	Paternal	De novo	Unknown	Total
13q13q	0	0	2[a]	0	2
13q14q	51[b]	36	26[b]	3	116
13q15q	4	2	0	0	6
13q22q	0	1	0	0	1
14q14q	0	0	2[c]	0	2
14q15q	5	7	4[b]	0	16
14q21q	10	2	7	0	19
14q22q	5	2	1	0	8
15q15q	0	0	1[d]	0	1
15q22q	0	1	1	0	2
22q22q	0	0	1	0	1
Total	75	51	45	3	174

[a] Both cases previously reported in Berend et al. (1999).

[b] One mosaic case in this category.

[c] One case previously reported in Klein et al. (1999).

[d] Previously reported in Cheung et al. (1997).

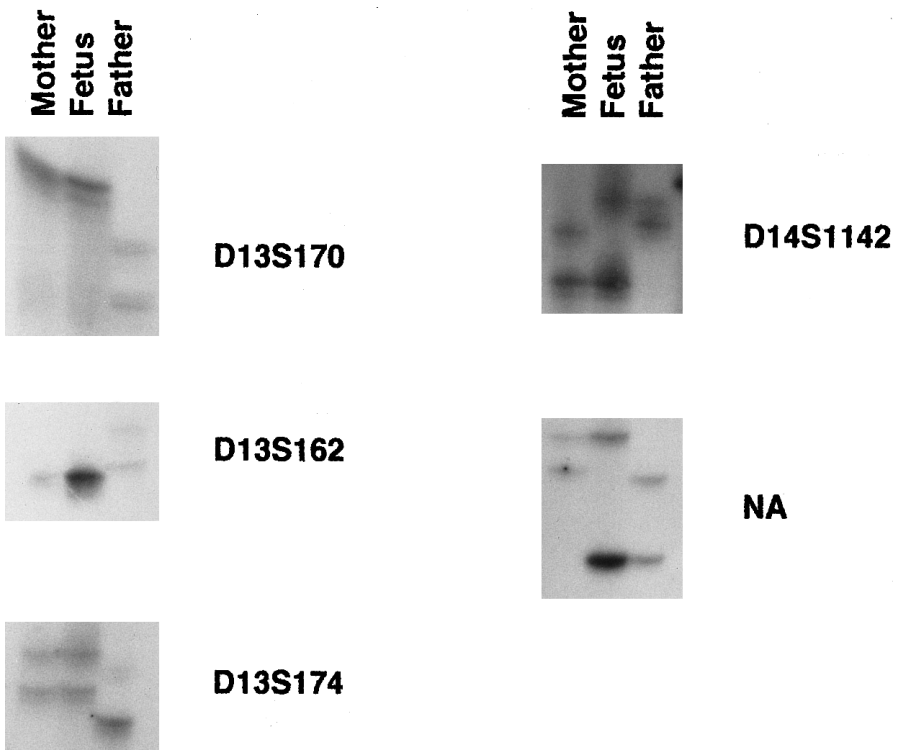

Figure 1. Molecular results for a case of maternal disomy 13. For each marker, the DNA samples are shown in the lanes as indicated. For the chromosome 13 markers, the fetus inherited alleles only from the mother and failed to inherit a paternal allele, consistent with maternal disomy 13. For the chromosome 14 markers, the fetus inherited an allele from each parent, demonstrating biparental inheritance for chromosome 14 and results consistent with correct paternity. Locus NA refers to assay number AFM079XD11 and Genome Database accession number 1222803.

control rodent DNA. This result confirms that this marker maps to human chromosome 14.

Interpretation of the Data

At least two informative markers were used to exclude UPD for each chromosome. For nonhomologous Robertsonian translocations, UPD was assessed for both chromosomes involved in the translocation. UPD was evident when the fetus failed to inherit an allele from one parent for multiple markers for a single chromosome. For cases exhibiting UPD, polymorphic markers for an additional chromosome were analyzed to exclude nonpaternity, sample mix-up, or amplification failure. For three cases (table 2, column labeled "Unknown"), paternal samples were unavailable. Thus, only limited conclusions could be drawn from these analyses. The confidence intervals (CIs) for the empiric risk estimates for UPD were determined by means of the statistical program EPISTAT.

Results

Of the 168 nonhomologous Robertsonian translocations studied, one case of a 45,XX,rob(13;14)(q10;q10)mat[48]/46,XX,+13,rob(13;14)(q10;q10)mat[2] was found to have upd(13)mat (fig. 1). No UPD was evident among the remaining 167 cases, including two other mosaic cases.

Four of the six prenatal cases with homologous acrocentric rearrangements referred to our laboratory for UPD studies showed paternal UPD: two upd(13)pat and two upd(14)pat. These included two der(13q13q) and two der(14q14q) (Berend et al. 1999; Klein et al. 1999). Reduction to homozygosity in the fetal sample from heterozygosity in the father at proximal (pericentromeric) markers is consistent with each of these four rearrangements being isochromosomes [i(13)(q10) and i(14)(q10)]. Three of the rearrangements showed homozygosity at all informative loci tested along the length of the chromosome involved, consistent with isodisomy. One der(13q13q) showed homozygosity (isodisomy) for proximal markers and heterozygosity (heterodisomy) for distal markers (Berend et al. 1999).

Two of the homologous acrocentric rearrangements studied showed normal, biparental inheritance, indicating that these rearrangements comprised one paternal chromosome and one maternal chromosome; thus,

they represent Robertsonian translocations, between two different homologous chromosomes and not isochromosomes, derived from a single parental chromosome [rob(15;15)(q10;q10) (Cheung et al. 1997) and rob(22;22)(q10;q10)].

Discussion

UPD has been described for all of the acrocentric chromosomes. An apparently normal phenotype is associated with maternal or paternal UPD for chromosomes 13, 21, and 22 (Ledbetter and Engel 1995; Shaffer et al. 1998; Kotzot 1999), and an abnormal phenotype is associated with both maternal and paternal disomy of chromosomes 14 (reviewed in Ledbetter and Engel 1995; Shaffer et al. 1998; Kotzot 1999) and 15 (resulting in Prader-Willi and Angelman syndromes, respectively). Although UPD for only chromosomes 14 and 15 would be of clinical concern, all possible types of acrocentric rearrangements, familial and de novo, were screened in this investigation, since presumably the risk of UPD is small (<1%; see "Nonhomologous Robertsonian Translocations" subsection, below) and sufficient numbers of translocations needed to be studied to identify cases of UPD. In addition, all chromosomes involved in the rearrangements were analyzed, regardless of the potential clinical outcome, since this was necessary to ascertain the overall occurrence of UPD associated with these rearrangements.

Nonhomologous Robertsonian Translocations

A theoretical estimate of the risk of UPD in Robertsonian translocation carriers may be calculated as the risk of malsegregation of the translocation and its corresponding homologues (resulting in trisomy), multiplied by the chance that the trisomy would resolve by loss of a chromosome, multiplied by the chance that the remaining chromosomes would result in UPD. It is difficult to generalize a risk among all Robertsonian translocations, since the risk of malsegregation for some Robertsonian translocations depends on the chromosomes involved and the sex of the carrier. Table 1 shows some of the known risks for aneuploidy for the more common Robertsonian translocations, rob(13q14q) and rob(14q21q). These two Robertsonian translocations constitute >80% of all Robertsonian translocations in the population (Therman et al. 1989); thus, empiric risk figures are available for these translocations but are largely unavailable for the remaining possible types of Robertsonian translocations. For rob(13q14q), for example, the risk of UPD may be the risk of aneuploidy (~1%), multiplied by the chance of "rescue" (unknown, but presumably small), multiplied by the chance of UPD (50%). Thus, the theoretical risk of UPD for a rob(13q14q) carrier is something less than 1%, perhaps ~0.5%. Of the 168 nonhomologous Robertsonian translocations studied, one showed UPD. Thus, the empiric risk for finding UPD for any nonhomologous Robertsonian translocation can be estimated to be 1/168, ~0.6% (95% CI 0.01%–3.3%). This estimate is not significantly different from the theoretical calculation of 0.5%. For rob(13q14q), our largest study group, UPD is estimated to occur in ~0.9% (1/116; 95% CI 0.01%–4.7%) of carrier fetuses. Although three cases in this study showed a mosaic chromosome pattern and one of these resulted in UPD, we cannot conclude that only individuals with identified mosaicism are at risk for UPD. For most cases, 15–20 cells were analyzed, and, thus, mosaicism at levels <11% (Hook 1977) cannot be excluded. The finding of mosaicism for a trisomic cell line in the one UPD case lends support to the "trisomy rescue" mechanism (Cassidy et al. 1992) in Robertsonian translocation carriers with UPD. Figure 2*a* illustrates the trisomy rescue mechanism leading to UPD in nonhomologous Robertsonian translocation carriers.

Homologous Acrocentric Rearrangements

Of the six homologous acrocentric rearrangements studied, four were found to exhibit paternal UPD, indicating a high risk for UPD (~66%; 95% CI 22%–96%) when a homologous acrocentric rearrangement is identified prenatally. This risk is consistent with what would be expected for these types of rearrangements, since previous studies have shown that the majority of homologous rearrangements are isochromosomes (Shaffer et al. 1993*a*, 1994; Robinson et al. 1996*a*). Given that isochromosomes are derived from a single parental chromosome, individuals with an isochromosome and an otherwise balanced karyotype would necessarily exhibit UPD. Only one previous study addressed a theoretical risk of UPD associated with homologous rearrangements. Robinson et al. (1996*b*) reported a theoretical risk of 1/7 (14%) for UPD 15 associated with der(15q15q). Their risk was calculated by use of an estimate of the population frequencies of der(15q15q) and UPD 15 (resulting in either Prader-Willi or Angelman syndrome). The discrepancy between our empiric risk estimate of ~66% and their theoretical risk of ~14% (Robinson et al. 1996*b*) is likely due to (i) an inflated estimate of the population frequency of der(15q15q) and (ii) no consideration that most homologous acrocentric rearrangements are isochromosomes. These factors likely resulted in an underestimate of the risk for UPD when a der(15q15q) is encountered. However, we cannot exclude the possibility that specific homologous rearrangements may each have their own risk for UPD, since our data are based on a small number of cases. All cases in our study were ascertained prospectively as pre-

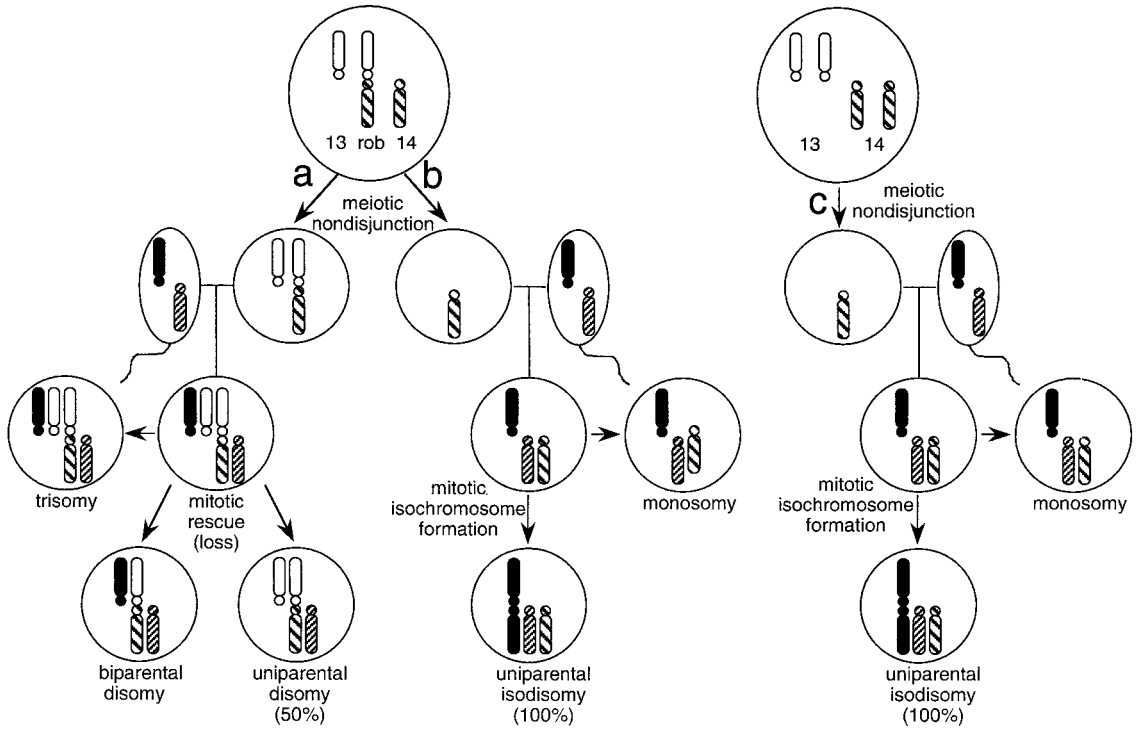

Figure 2. Mechanisms of uniparental disomy in prenatally identified Robertsonian translocation carriers. In this example, nondisjunction in meiosis I in a rob(13q14q) translocation carrier mother would result in (a) disomic and (b) nullisomic gametes. *a,* Union of a normal sperm and an ovum disomic for chromosome 13 results in a trisomy 13 conceptus. If the trisomy is rescued through postzygotic loss of one chromosome 13, 50% would show biparental inheritance and 50% would show uniparental inheritance (maternal heterodisomy) for chromosome 13. *b,* Union of a normal sperm with an ovum nullisomic for chromosome 13 results in a monosomy 13 conceptus. The monosomy may be rescued through postzygotic isochromosome formation, and, through this mechanism, 100% would show isodisomy. *c,* An alternative route for the monosomy rescue: maternal meiosis I nondisjunction in a chromosomally normal female. The resulting nullisomic ovum, fertilized by a normal sperm, would produce a monosomic conceptus, which could also be rescued by isochromosome formation. The monosomy rescue model predicts that the majority of resultant UPD would be paternal in origin.

natal samples with indications for prenatal testing, including advanced maternal age ($n = 2$), known translocation-carrier parent ($n = 1$), abnormal maternal serum triple screen ($n = 1$), and abnormalities seen on ultrasound ($n = 2$). Even excluding the two upd(14)pat cases that were ascertained for abnormal ultrasound findings, in our study the risk for UPD in homologous rearrangements ascertained prenatally would be 50% (95% CI 6.4%–93.6%).

In the present study, analysis of additional markers along the length of the four isochromosomes showed complete isodisomy in three, indicating a likely mitotic duplication. The finding of complete isodisomy (homozygosity) along the length of these isochromosomes and also the paternal origin of the UPD suggest that postzygotic "monosomy rescue" is the most likely mechanism resulting in UPD. Since nondisjunction occurs more often during maternal meiosis (Koehler et al. 1996), a maternal nondisjunction in meiosis I would result in a nullisomic ovum 50% of the time (fig. 2*b* and *c*). Subsequent fertilization by a normal sperm would result in a monosomic conceptus. Autosomal monosomies are presumably lethal early in embryogenesis and could be rescued by postzygotic duplication of the monosomic chromosome. In the case of these three isochromosomes, duplication of the paternal chromosome through isochromosome formation would rescue the monosomy, resulting in paternal UPD.

If monosomy rescue is the predominant mechanism for UPD associated with isochromosomes, more rearrangements of paternal origin would be expected, since aneuploidy occurs more frequently during maternal meiosis (Koehler et al. 1996) and the duplication event would occur for the only available, paternally inherited monosomic chromosome. Our data are in agreement with this expectation.

One isochromosome exhibited recombination, indicating that the isochromosome must have occurred prior to or during meiosis I. As previously reported by Berend et al. (1999), the mother carried a rob(13q14q). Nondisjunction in the mother likely resulted in a nullisomic ovum. Coincident meiotic formation of an isochromo-

some in the father and the union of these aneuploid, complementing gametes resulted in UPD. Thus, gametic complementation was shown to be the most likely mechanism for UPD in this case (Berend et al. 1999).

In summary, prospective studies of acrocentric rearrangements provide an excellent system for the estimation of the risk of UPD associated with these rearrangements. Since all cases were ascertained prenatally, this represents a relatively random sample. Given the risk of 0.6%–0.9% for UPD in prenatally identified Robertsonian translocations, molecular analysis should be considered for cases involving chromosomes 14 and 15, which are associated with adverse clinical outcomes. Molecular analysis should be considered in all cases of homologous acrocentric rearrangements, since there is a very high risk of UPD (~66%), and UPD in these cases is likely to be isodisomy and would carry a small, yet-to-be-defined risk for recessive disease.

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Electronic-Database Information

Accession number and URL for data in this article are as follows:

Genome Database, The, http://www.gdb.org/ (for marker "NA," accession number 1222803)

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