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A Somatic Origin of Homologous Robertsonian Translocations and Isochromosomes

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Summary

One t(14q14q), three t(15q15q), two t(21q21q), and two t(22q22q) nonmosaic, apparently balanced, de novo Robertsonian translocation cases were investigated with polymorphic markers to establish the origin of the translocated chromosomes. Four cases had results indicative of an isochromosome: one t(14q14q) case with mild mental retardation and maternal uniparental disomy (UPD) for chromosome 14, one t(15q15q) case with the Prader-Willi syndrome and UPD(15), a phenotypically normal carrier of t(22q22q) with maternal UPD(22), and a phenotypically normal t(21q21q) case of paternal UPD(21). All UPD cases showed complete homozygosity throughout the involved chromosome, which is supportive of a postmeiotic origin. In the remaining four cases, maternal and paternal inheritance of the involved chromosome was found, which unambiguously implies a somatic origin. One t(15q15q) female had a child with a ring chromosome 15, which was also of probable postmeiotic origin as recombination between grandparental haplotypes had occurred prior to ring formation. UPD might be expected to result from de novo Robertsonian translocations of meiotic origin; however, all de novo homologous translocation cases, so far reported, with UPD of chromosomes 14, 15, 21, or 22 have been isochromosomes. These data provide the first direct evidence that nonmosaic Robertsonian translocations, as well as isochromosomes, are commonly the result of a mitotic exchange.

Introduction

Robertsonian translocations are whole-arm exchanges between acrocentric or telocentric chromosomes, which, in humans, occur between chromosomes 13, 14, 15, 21, and 22. These are the most frequent chromosomal rearrangements in man, with an estimated frequency in newborns of about 1/900 (Gardner and Sutherland 1989). The majority of observed Robertsonian translocations involve two different chromosomes, whereas most homologous translocations are only rarely observed, except perhaps for t(21q21q), which is found in some Down syndrome patients. Isochromosomes are indistinguishable, by cytogenetic morphology, from a homologous Robertsonian translocation and result from either misdivision of the centromere or a U-type exchange in meiosis or mitosis (Van Dyke et al. 1987; Therman and Susman 1993).

In addition to a trisomic outcome, transmission of a Robertsonian translocation of meiotic or premeiotic origin could be associated with uniparental disomy (UPD) if the corresponding homologue from the other parent is lost prior to or after conception. De novo isochromosomes resulting in UPD have been reported for chromosome 14 (Pentao et al. 1992), chromosome 15 (Freeman et al. 1993), and chromosome 21 (Blouin et al. 1993). However, only one case of UPD due to a de novo Robertsonian translocation has been reported, and this involved the nonhomologous chromosomes 13 and 14 (Antonarakis et al. 1993).

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Table 1

Summary of Patients and Results

Case	Karyotype	Phenotype	Ascertainment	Molecular Result[a]
1	45XX,−15,−15,+t(15q15q)	Normal	Multiple abortions	Mat + pat
2	45XX,−15,−15,+t(15q15q)	Normal	Multiple abortions	Mat + pat
3	45XX,−15,−15,+t(15q15q)	PWS	PWS	Maternal UPD (15)
4	45XX,−21,−21,+t(21q21q)	Normal	Trisomy-21 child	Mat + pat
5	45XX,−21,−21,+t(21q21q)	Normal	Multiple abortions	Paternal UPD (21)
6	45XX,−22,−22,+t(22q22q)	Normal	Multiple abortions	Maternal UPD (22)
7	45XX,−22,−22,+t(22q22q)	Normal	Multiple abortions	Mat + pat
8	45XY,−14,−14,+t(14q14q)	Mild MR	Mild MR	Maternal UPD (14)

[a] Mat + pat = received an allele from both parents.

Balanced Robertsonian translocations are often ascertained in couples with repeated spontaneous abortions. As UPD(15) is always associated with the Prader-Willi syndrome (PWS; when maternal) or the Angelman syndrome (AS; when paternal) (Nicholls et al. 1989; Malcolm et al. 1991; Robinson et al. 1991; Mascari et al. 1992; Mutirangura et al. 1993), t(15q15q) carriers with a normal phenotype must show maternal and paternal inheritance of the involved chromosomes. UPD(14) has also been associated with an abnormal phenotype (Temple et al. 1991; Wang et al. 1991; Pentao et al. 1992). Individuals with maternal or paternal UPD(21) (Créau-Goldberg et al. 1987; Blouin et al. 1993) or with maternal UPD(22) (Kirkels et al. 1980; Palmer et al. 1980) have been normal, and therefore ascertainment of balanced t(21q21q) or t(22q22q) individuals should not be biased against UPD.

In the present study, eight individuals with de novo, nonmosaic, apparently balanced Robertsonian translocations between homologous chromosomes were ascertained. Molecular polymorphisms were used to determine the parental and meiotic or mitotic stage of origin of the translocated chromosomes.

Patients and Methods

Patients

All probands in this study showed de novo, nonmosaic, apparently balanced isochromosomes or Robertsonian translocations involving homologous chromosomes (see table 1). Most of the cases in this study were ascertained because of repeated abortions in the proband (cases 1, 2, 5, and 7) or his wife (case 6) (see table 1). Case 3 had typical features of PWS, case 4 gave birth to a female with Down syndrome, and case 8 showed mild mental retardation (MR).

Cytogenetic and clinical findings in both case 1, a balanced t(15q15q) carrier female, and her son with a ring chromosome 15 have been reported elsewhere (Neri et al. 1983). C-banding in the phenotypically normal mother showed a single centromere, and silver staining showed absence of nucleolar organizing regions. No mosaicism was found among the more than 50 metaphases analyzed. She had four spontaneous abortions, followed by birth of a son carrying a ring chromosome 15 derived from the translocation chromosome. Case 2 was also previously reported and is a normal healthy woman who, by age 25 years, had four spontaneous abortions, which ended after about 12 wk gestation (Zizka et al. 1977). C- and G-banding results were supportive of a probable dicentric t(15q15q), which was found in all of 200 metaphases examined. The t(15q15q) chromosome of case 3, with the PWS, was found in all of 20 metaphases examined.

Case 4, a phenotypically normal t(21q21q) carrier, gave birth to two offspring, both with Down syndrome. No mosaicism of the t(21q21q) chromosome in the proband was seen in 100 metaphases. The mother of the proband did not carry the translocation chromosome. The father was not examined; however, the patient had seven healthy siblings, making it rather unlikely that the father carried the translocation, either. Similarly, case 5 is a phenotypically normal t(21q21q) carrier born to a 31-year-old mother and 35-year-old father. She was the last of eight children born, all healthy. Three pregnancies in the proband ended in spontaneous abortion after approximately 6, 14, and 14 wk gestation. A fourth pregnancy was interrupted when cytogenetic analysis (CBG- and GTG-banding) of 100 metaphases in the mother disclosed an apparently monocentric t(21q21q) chromosome.

Clinical details of case 6 (45,XY,-22,-22,+i(22q)), a

Table 2

Molecular Results for All Patients

Locus (probe)	Location	Case			
		Case 1			
		Proband	Son, r(15)	Mother	Father
D15S11	15q12	ab	ab	b	ab
D15S13 (189-1)	15q12	11	11	11	11
D15S10 (3-21)	15q12	11	11	11	11
GABRB3	15q12	ab	bc	a	bc
GABRB3 (28β3-H3)	15q12	22	12	12	12
D15S24	15q13	ab	a	ab	ab
CYP19	15q21	c	bc	ac	ac
D15S108	15q21	a	a	ab	...
D15S38	15q22	12	11	22	12
D15S99	15q24	bc	ab	b	bc
D15S86 (ms-620)	15q26	ab	a	ab	ab
		Case 2			
		Proband	Sib 1	Sib 2	Sib 3
D15S9 (ML34)	15q12	12	12	1	1
D15S11	15q12	a	a	ab	ab
D15S13	15q12	ab	ab	b	b
D15S113	15q12	a	...	...	...
GABRB3	15q12	b	b	a	a
ACTC	15q14	ab	ab	a	a
CYP19	15q21	a	...	...	...
D15S108	15q21	ab	ab	aa	aa
D15S99	15q22–24	a	...	...	...
		Case 3			
		Proband	Mother		Father
D15S18 (p39)	15q11–12	22	22		12
D15S11	15q12	a	a		a
D15S13	15q12	a	ab		b
GABRB3	15q12	a	a		a
GABRA5	15q12	b	ab		bc
D15S24 (CMW-1)	15q13	a	ab		bc
CYP19	15q21	b	b		ab
D15S108	15q21	a	ab		ab
IPM15M9	15q24	a	ab		cd
D15S86	15q26	a	ab		b
		Case 4			
		Proband	Mother		Father
D21S258	21q11.2	bc	bd		ac
D21S11	21q21	b	b		ab
D21S167	21q22.2	bc	bc		ac
D21S267	21q	bc	c		ab
D21S268	21q	ab	a		b
D21S270	21q	ac	ab		bc

(*continued*)

Table 2 (continued)

Locus (probe)	Location	Case		
		Case 5		
		Proband	Mother	Father
D21S258	21q11.2	a	–	ab
D21S11	21q21	b	a	ab
D21S167	21q22.2	b	ab	b
D21S265	21q	a	bd	ac
D21S267	21q	b	c	ab
D21S268	21q	c	a	bc
D21S270	21q	c	ab	ac
		Case 6		
		Proband	Mother	Father
D22S9 (p22/34)	21q11	1.9	1.9	1.9
D22S1 (pms3–18)	21q11.2–13	5.8	5.8	5.8/3.2
D22S163 (p607)	22	a	a	a
D22S156	22q11.2–12.2	a	a	bc
D22S264	22q11.2	b	bc	ab
D22S258	22q11.2	a	ab	cd
CYP2D	22q13	b	ab	bc
D22S315	22	a	ab	bc
D22S283	22	c	cd	ab
D15S114	15q	ac	c	ab
IP15M9	15q	ad	ab	cd
D15S99	15q	ab	ab	ab
D14S49	14q	ab	ac	ab
		Case 7		
		Proband	Mother	Father
D22S156	22q11.2–12.2	ab	b	a
D22S264	22q11.2	a	–	a
D22S258	22q11.2	a	ac	ab
CYP2D	22q13	bc	bc	ab
D22S315	22	ab	ac	b
D22S274	22	ab	ab	b
D22S283	22	ab	ab	a
		Case 8		
		Proband	Mother	Father
TCRA	14q11.1–11.2	a	a	a
D14S49	14q11	b	ab	cd
MYH6	14q11.2–13	b	ab	cd
D14S43	14q24.3	b	b	ab
D14S48	14q24.3–32.1	a	ab	bc
D14S51	14q32.1	a	a	b
D14S65	14q	d	ad	bc
D14S67	14q	a	ab	ab
D15S99	15q	ab	ab	ab
IP15M9	15q	ab	ac	b

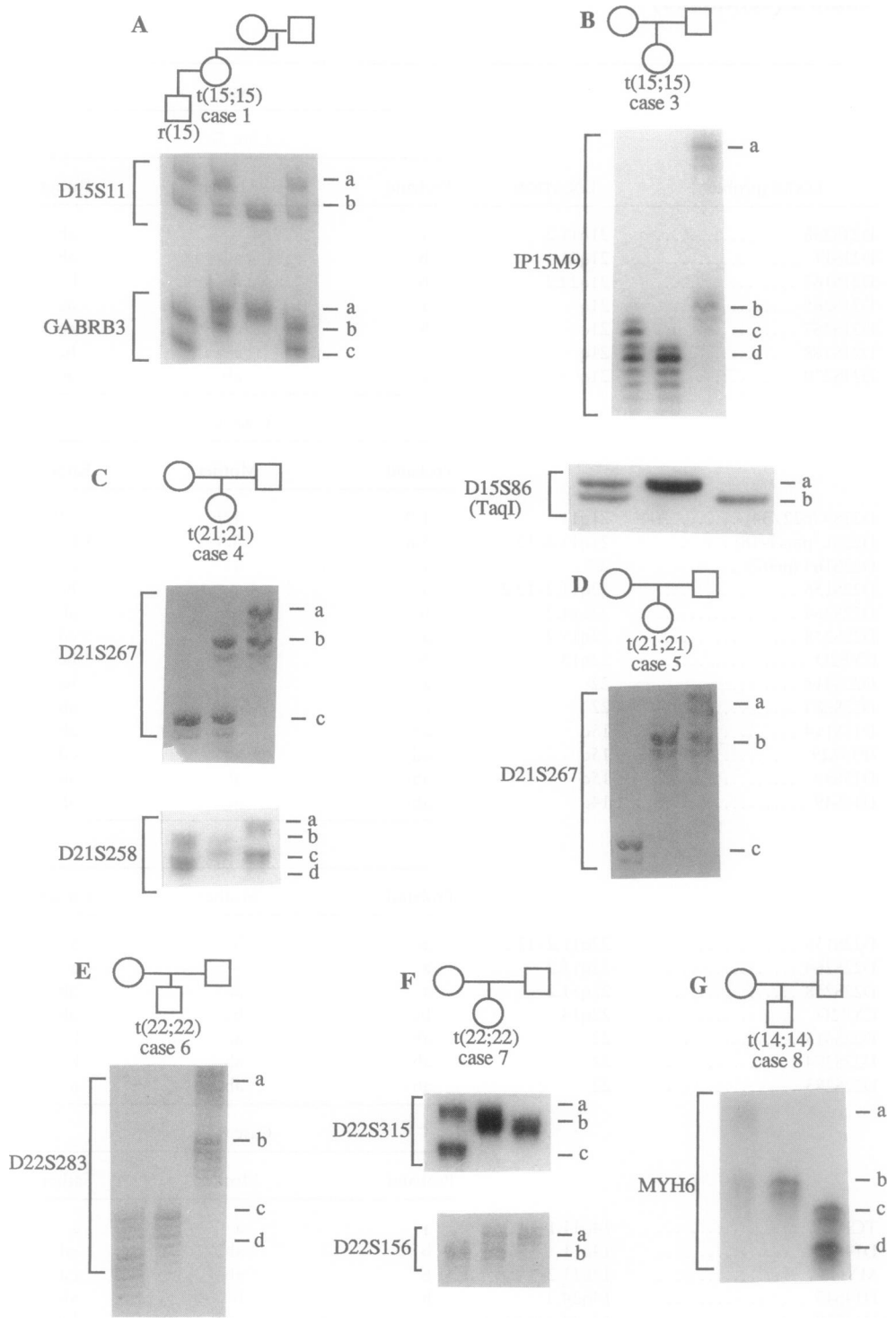

Figure 1 Molecular results. *A*, Case 1, who inherited, at GABRB3, allele a from her mother and allele b from her father. Her ring chromosome 15 son, labeled "r(15)," inherited the grandpaternal allele b and allele c from his father. *B*, Case 3, who, both at the IP15M9 microsatellite and at the VNTR locus D15S86, failed to inherit a paternal allele and is homozygous for a single maternal allele. *C*, Case 4, who shows maternal and paternal inheritance at D21S267 (silver-stained gel) and D21S258. *D*, Paternal UPD(21), which is evident in case 5 by lack of

healthy and normal male whose wife had six spontaneous abortions, will be published elsewhere (Schinzel et al. 1994). At least 20 metaphases were examined, and CBG-banding showed a monocentric translocation chromosome. Cytogenetic results of case 7 (45,XX,-22,-22,+t(22q22q)) have also been published elsewhere (Farah et al. 1975). In brief, this phenotypically normal female of average height and intelligence has had 24 spontaneous abortions but no healthy child. No mosaicism was seen in 120 metaphases examined.

Case 8 (45,XY,-14,-14,+t(14q14q)) was referred for chromosome examination at the age of 2 years 9 mo because of motor retardation and MR. He was the second child born to healthy parents. Breech delivery following an uneventful pregnancy was at 36 wk, with birthweight 1,900 g (below the 3d percentile). At 9 mo of age, length (63 cm), weight (4.9 kg), and head circumference (41 cm) were below the 3d percentile. At 2 years 9 mo of age, the following minor anomalies were observed: microcephaly (occipitofrontal circumference 44.5 cm), a hypotonic facies with large and protruding ears, pseudo exophthalmos probably due to shallow orbits, depressed nasal bridge, narrow and upturned nose, constantly open mouth, and irregular position of the upper and lower incisors; normal hearing; right undescended testis; and broad and short fingernails, transverse palmar crease on the right, flat arches of feet, and prominent calcanei. Hand length was 9.5 cm (3d percentile), foot length 14 cm (~10th percentile). Developmentally, he corresponded to an age of about 20 mo. At least 20 metaphases were examined, and CBG-banding in this case showed a single centromere on the translocation chromosome.

Methods

Molecular analysis in all patients and their parents was performed using PCR amplification of microsatellite polymorphisms. The primers used and their location are given in table 2. Information on primers and probes is available from the Genome Data Base, with the exception of D15S13 (Mutirangura et al., in press). Additional information on map location is available from Bowcock et al. (1992), NIH/CEPH Collaborative Mapping Group (1992), Weissenbach et al. (1992), and McInnis et al. (1993). All primers were obtained from Research Genetics, with the exception of those located in 15q11-q13, which were synthesized elsewhere.

PCR amplification was performed on a Perkin-Elmer Thermocycler with 30 cycles of 1 min at 94°C-denaturation, 1 min at 55°C–57°C-annealing, and 1.5 min at 72°C-extension temperatures. Then, 0.5–3 ml of reaction product was mixed with an equal volume of urea loading buffer (42% urea, 0.1% xylene cyanol, 0.1% bromophenol blue, and 0.1% 0.5-M EDTA) and was directly loaded onto a 0.4-mm thick 6% polyacrylamide/50% urea gel. Visualization of bands was done either by including ^{32}P-labeled cytosine in the PCR and exposure of the gel to X-ray film or, usually, by silver staining of the gels. In addition, several probes detectable by conventional Southern blotting of *Taq*I-digested DNA were also analyzed.

Parental origin of chromosome 15 could also be determined using either of two probes that detect parent-of-origin–specific methylation sites within 15q12, as described elsewhere (Dittrich et al. 1992; Driscoll et al. 1992). In brief, genomic DNA digested with *Hpa*II+*Hind*III was run on 1% agarose gels, blotted by Southern transfer to nylon membranes, and hybridized with either ML34 (D15S9) or PW71 (D15S63). A "maternal" (unmethylated) band and a "paternal" (methylated) band can be detected with both probes. Individuals with uniparental inheritance in this region (due to UPD or a deletion) will show only one or the other parental band.

Results

Molecular results for all cases are presented in table 2. As UPD(15) is known to be associated with either PWS or AS, it was suspected a priori that both normal females with a t(15q15q) chromosome (cases 1 and 2) would show maternal and paternal inheritance and that the PWS patient (case 3) would show either maternal UPD(15) or a deletion in the proximal arm of one chromosome. As expected, case 1 showed maternal and paternal inheritance for several chromosome 15 loci, indicating that the t(15q15q) chromosome formed subsequent to zygote formation (fig. 1*A*). Parent-of-origin–specific methylation patterns for PW71 and ML34, in both the mother and the ring-chromosome child, showed maternal and paternal bands, confirming biparental inheritance of proximal 15q. It could also be inferred that the grandpaternal allele at loci GABRB3 (15q12) and D15S38 (15q22) was transmitted in the ring

inheritance of the maternal allele c for D21S267 (silver-stained gel). Only one paternal allele is transmitted. *E*, Maternal UPD(22), illustrated by lack of paternal transmission to case 6 at D22S283 (silver-stained gel). *F*, Maternal and paternal inheritance, seen for D22S315 and D22S156 (silver-stained gel) in case 7. *G*, Case 8, who has only inherited maternal allele b for MYH6 (the mother is heterozygous, having alleles a and b).

chromosome 15 but that the grandmaternal allele was transmitted for D15S99 (15q24). Thus, the ring formation in the child occurred subsequent to maternal recombination in the first meiotic division and may also have been an early somatic event that served to "rescue" a trisomic fertilization product.

Parents were not available for case 2; however, this female was heterozygous for several loci along the chromosome (excluding an isochromosome), and maternal and paternal methylation-specific bands were detectable using both ML34 and PW71 (excluding UPD). Marker information from three sisters of the proband showed that the proband was identical in genotype to one sib, at all loci tested. In addition, it could be inferred that, at GABRB3, both parents must have been heterozygous, whereas the proband was homozygous, which excludes uniparental heterodisomy. This translocation, therefore, also must have formed between the maternal and paternal chromosomes soon after zygote formation.

Case 3, a t(15q15q) carrier with PWS, showed maternal only methylation bands in proximal 15q. Nonpaternal inheritance and reduction of maternal heterozygosity to homozygosity were seen throughout the chromosome (fig. 1*B*). Thus, this patient is inferred to have an isochromosome 15. The lack of recombination along the two arms indicates that the isochromosome formation may have resulted from misdivision at the centromere in a zygote or early embryo that was monosomic for chromosome 15. Alternatively, the isochromosome may have formed during or prior to meiosis in the mother and may have been associated with lack of pairing with the other normal homologue (e.g., centromere misdivision in a univalent).

Case 4, with a t(21q21q), showed maternal and paternal inheritance along the entire chromosome (fig. 1C). As UPD(21) is not associated with an abnormal phenotype and as the carrier was nonmosaic, there was no ascertainment bias that would have excluded a meiotic mechanism in forming the Robertsonian translocation of this case.

Case 5, also with a t(21q21q), showed lack of maternal inheritance for several loci on chromosome 21: D21S267, D21S279, and D21S11 (fig. 1*D*). Reduction of paternal heterozygosity to homozygosity was also observed along the chromosome, for these loci as well as for D21S258, the most centromeric locus. These results imply isochromosome formation from the paternally inherited chromosome 21; this is the second case of paternal UPD reported for this chromosome.

Case 7, with a t(22q22q) chromosome, also showed maternal and paternal inheritance of chromosome 22 markers (fig. 1*F*). In contrast, the molecular data from case 6, with the same cytogenetic karyotype, showed nonpaternal inheritance and complete homozygosity for maternal alleles along the chromosome (fig. 1*E*). The mechanism of formation would be as for case 4, but maternal UPD(22) apparently had no abnormal phenotypic consequences (Schinzel et al. 1994). Paternity was confirmed with chromosome 14 and chromosome 15 polymorphisms.

Case 8, with a t(14q14q), showed no paternal inheritance for multiple chromosome 14 markers: MYH6, D14S49, D14S51, D14S48, and D14S65 (fig. 1*G*). Reduction of maternal heterozygosity to homozygosity was found at five loci and indicates that the translocation chromosome is a maternally derived isochromosome. Paternity was confirmed using chromosome 15 polymorphisms.

Discussion

UPD

An association of UPD(15) with PWS is well known (Nicholls et al. 1989; Robinson et al. 1991; Mascari et al. 1992), and de novo balanced t(15q15q) karyotypes are not an uncommon finding in PWS patients (Ledbetter et al. 1987; Butler 1990). The present case and one other previously analyzed with molecular probes were found to be isochromosomes (Hamabe et al. 1991). In addition, a case of AS with an iso(15q) resulting in paternal UPD(15) has been reported (Freeman et al. 1993).

Only one individual with paternal UPD(21) (Blouin et al. 1993) and two cases (neither confirmed molecularly) inferred to be maternal UPD(22) (Kirkels et al. 1980; Palmer et al. 1980) have previously been identified. The two similar cases in the present study provide independent confirmation that paternal UPD(21) and maternal UPD(22) have no apparent phenotypic effect. Infertility in these cases is presumably not due to imprinting but is a consequence of the rearrangement that would result in primarily monosomic or trisomic conceptions.

The maternal UPD(14) case of this study is the fourth such case identified, and the second due to an isochromosome. There does not, however, appear to be a clear phenotype associated with this aberration, possibly because of these cases' relatively mild clinical pictures, undetected mosaicism, and/or differences in homozygosity for recessive alleles. Common findings among these cases are developmental delay, growth retardation, and short hands and fingers (Temple et al. 1991; Pentao et al. 1992; Antonarakis et al. 1993). The pres-

ence of premature puberty found in two previous cases could not be evaluated in the patient in the present study, as he was only 3 years of age.

Ring Chromosome 15

Rearrangement of the t(15q15q) chromosome in case 2 led to a ring chromosome 15 in her son. Molecular analysis showed that the ring had formed after meiotic recombination, either during meiosis II or postmeiotically. Similar cases involving chromosome 13 (13;13 translocation mother, ring chromosome 13 child) (de Almeida et al. 1983) and chromosome 21 (21;21 translocation mother, ring chromosome 21 child) (Orye and Craen 1974) have been reported. Molecular studies were not performed in these cases. Evidence for a postmeiotic origin of such rings comes from other observations of mosaicism between a Robertsonian translocation and a ring chromosome. Such mosaic cases involving chromosome 13 (Schinzel 1984; Jalal et al. 1990; Duckett et al. 1992), chromosome 14 (Pangalos et al. 1984; Cantu et al. 1989; Thomas et al. 1989), chromosome 21 (Dallapiccola et al. 1982), and chromosome 22 (Fryns and Van den Berghe 1979) have been reported.

Origin of Robertsonian Translocations and Isochromosomes

Of the eight translocation cases analyzed here, four showed maternal and paternal inheritance of the involved chromosomes, while the remaining four were isochromosomes. Although none of the cases showed mosaicism in lymphocytes, none proved to be compatible with a Robertsonian translocation formation in meiosis. It appears, therefore, that such rearrangements are normally the result of a somatic event occurring in one of the early cell divisions after fertilization.

The hypothesis that most Robertsonian translocations occur by mitotic recombination events is supported by much indirect evidence. In situ hybridization indicates that the majority of Robertsonian translocations are dicentric and involve breaks within the satellite III DNA (Gravholt et al. 1992; Wolff and Schwartz 1992). Associations between the satellite regions of acrocentric chromosomes in somatic cells are well known and involve the fusion of nucleoli and the pairing of repeated pericentric DNA sequences (Jacobs et al. 1976; Therman et al. 1989). It is probably not coincidental that these translocations are the most frequent chromosomal rearrangement in man and that they also involve the only region that is known to be frequently "paired" in somatic cells.

Robertsonian fusions have also been induced at a high rate in mammalian cell cultures by treatment with various DNA-damaging agents (Hsu et al. 1978). The frequency of translocations was found to be dose dependent and duration dependent and resulted in both apparent monocentric and dicentric chromosomes. Frequent mitotic exchange between heterochromatic regions of acrocentrics is also commonly observed in Bloom syndrome (Kuhn 1976; Therman et al. 1981).

Direct evidence that Robertsonian translocations may occur in human mitosis comes from reports of mosaicism with a normal cell line. Mosaic Robertsonian translocations involving nonhomologous chromosomes have been reported (e.g., see Hsu and Perlis 1984; Ledbetter et al. 1992; Lippman et al. 1992) but are more often observed for homologous chromosomes (table 3). The distinction between an isochromosome and a homologous Robertsonian translocation may also be inferred from mosaic cases: if the translocation cell line has 46 chromosomes (trisomic for the involved chromosome), then this is presumably an isochromosome; if the translocation cell line is balanced with 45 chromosomes, then this is more likely to be a Robertsonian translocation (Therman and Susman 1993). Of the mosaic cases ascertained from the literature, the vast majority appear to be isochromosomes (table 3). However, there is a strong bias toward ascertaining isochromosomes, as most were ascertained through a mosaic trisomy 21 or mosaic trisomy 13 phenotype. A Robertsonian translocation would have a balanced outcome and should not result in an abnormal phenotype. A high level of mosaicism would also reduce the probability of infertility, precluding ascertainment of mosaic cases through repeated spontaneous abortions.

Similarly, studies on the origin of t(21q21q) chromosomes acertained through trisomy 21 indicate that these are usually isochromosomes (Grasso et al. 1989; Antonarakis et al. 1990; Shaffer et al. 1991). An approximately equal ratio of maternally derived cases to paternally derived cases was found, and most isochromosomes showed no evidence of recombination, consistent with a postmeiotic origin. Complete homo zygosity of an isochromosome could occur if isochromosome formation occurred in meiosis II, following an achiasmate meiosis I. However, these two events are expected to be independent, and so this is unlikely to be a mechanism that would account for the majority of such isochromosomes. Analysis of grandparental markers from de novo isochromosome cases has been used to confirm a postmeiotic origin: in a molecular study of X isochromosomes, the observation of meiotic

Table 3

Reported Mosaicism Involving Homologous Robertsonian Translocations or Isochromosomes (Including Confined Placental Mosaicism)

Karyotype	Probable Origin	Reference
46/45,-21,-21,+t(21q21q)	Robertsonian translocation, mitotic	Therman and Susman 1993
46/46,-13,+t(13q13q)	Isochromosome, mitotic	Ledbetter et al. 1992
46/46,-13,+t(13q13q)	Isochromosome, mitotic	Ledbetter et al. 1992
46/46,-13,+t(13q13q)	Isochromosome, mitotic	Lippman et al. 1992
46/46,-13,+t(13q13q)	Isochromosome, mitotic	Emberger et al. 1972
46/46,-13,+t(14q14q)	Isochromosome, mitotic	Schinzel 1984
46/46,-15,+t(15q15q)	Isochromosome, mitotic	Ledbetter et al. 1992
46/46,-21,+t(21q21q)	Isochromosome, mitotic	Der Kaloustian et al. 1987
46/46,-21,+t(21q21q)	Isochromosome, mitotic	Mark et al. 1977
46/46,-21,+t(21q21q)	Isochromosome, mitotic	Priest et al. 1977
46/46,-21,+t(21q21q)	Isochromosome, mitotic	Breed et al. 1990
46/46,-21,+t(21q21q)	Isochromosome, mitotic	Miny et al. 1991
46/46,-21,+t(21q21q)	Isochromosome, mitotic	Hornstein and Soukup 1976
46/46,-22,+t(22q22q)	Isochromosome, mitotic	Spinner et al. 1992
46,13p-/46,t(13q13q)/45,t(13q21q)	Isochromosome, mitotic[a]	Anderson et al. 1979
46,13p-/46,-13,+t(13q13q)	Isochromosome, mitotic[a]	Fryns et al. 1979
46,13p-/46,-13,+t(13q13q)	Isochromosome, mitotic[a]	Fryns et al. 1989
46,21p-/46,-21,+t(21q21q)	Isochromosome, mitotic[a]	Guanti 1978
46,21p-/46,-21,+t(21q21q)	Isochromosome, mitotic[a]	Del Pol et al. 1979
45,t(15;21)/46,+t(21q21q)	?	Vianna-Morgante and Nunesmaia 1978
45,t(15;21)/46,+t(21q21q)	?	Atkins and Bartsocas 1974
46/47,+t(21q21q)	?	Hsu and Perlis 1984
46,-13,+t(13q13q)/45,-13	?	Punnett and Pleasure 1981
46,-13,+t(13q13q)/46,r13(p11q34)	?	Schinzel 1984
46,-21,+t(21q21q)/46,r(21q21q)	?	Dallapiccola et al. 1982

[a] See Schinzel (1990) for an explanation.

recombination between both maternal X chromosomes in a completely homozygous, nonmosaic isochromosome evidenced formation at an early postmeiotic stage (Lorda-Sanchez et al. 1991).

A Robertsonian translocation between two homologous chromosomes that occurs prior to or during meiosis could lead to UPD if the corresponding homologue from the other parent is lost or not transmitted. However, molecular analysis of most cases of UPD due to a de novo Robertsonian translocation has shown them to be homozygous throughout the chromosome and therefore also isochromosomes (table 4). Only a single case of maternal UPD(14), involving a de novo Robertsonian t(13q14q), is of probable meiotic origin (Antonarakis et al. 1993). It is probable, however, that a Robertsonian translocation occurring between homologous chromosomes during meiosis I (after replication) would have much greater segregation problems than it would if nonhomologous chromosomes were involved: the homologously translocated chromatids would be paired with and would have recombined with their two other sister chromatids, and unless all four chromatids segregated to one pole, chromosome breakage would ensue.

Although it is frequently inferred that lack of mosaicism must be an indication of a meiotic origin, this is clearly not a correct assumption. We suggest several reasons why Robertsonian translocations, or other rearrangements that are clearly of mitotic origin, may show no evidence for mosaicism. First, it is possible that, during the zygote formation or during the early cell divisions, the chromatin is more unstable (perhaps because of methylation changes that occur at this time) and more prone to rearrangements than at later cell stages. It is also quite likely that chromosomal mosaicism in humans occurs at a manyfold higher rate than is detectable by studying only lymphocytes (Pagon et al. 1979; Hall 1988; Thomas et al. 1989). It is well documented that mosaic cell lines found at chorionic villus sampling may not be detectable in the fetus, and this discrepancy could be a result of uneven distribution of cells, between fetus and placenta, and/or a result of selection against aneuploid cell lines in the fetus. Cell

Table 4

UPD Associated with De Novo Robertsonian Translocations or Isochromosomes

UPD	Translocation	Molecular Result	Reference
Maternal UPD (14)	i(14q)	Isodisomy	Pentao et al. 1992
Maternal UPD (14)	i(14q)	Isodisomy	Present study
Maternal UPD (14)	rob(13q14q)	Iso/heterodisomy	Antonarakis et al. 1993
Maternal UPD (15)	i(15q)	Proximal isodisomy	Hamabe et al. 1991
Paternal UPD (15)	i(15q)	Isodisomy	Freeman et al. 1992
Maternal UPD (15)	i(15q)	Isodisomy	Present study
Maternal UPD (21)	t(21q21q)	Uninformative	Créau-Goldberg et al. 1987
Paternal UPD (21)	i(21q)	Isodisomy	Blouin et al. 1993
Paternal UPD (21)	i(21q)	Isodisomy	Present study
Maternal UPD (22)	i(22q)	Isodisomy	Present study

selection or random cell loss can also explain observations of a mosaic abnormality in lymphocytes at birth but no evidence of mosaicism later in life. For example, two families were reported with abnormal karyotypes involving chromosome 21 at birth, with a somatic loss followed by duplication of the normal chromosome 21 (Petersen et al. 1992). Although no karyotypically normal cell line was found in lymphocytes at birth, the UPD(21) cell line predominated later in life (in one case, the replacement of abnormal with normal lymphocytes was found after only 12 mo).

In summary, four de novo nonmosaic cases with a homologous Robertsonian translocation were found to be due to a translocation between the maternally derived and paternally derived homologues. The lack of mosaicism indicates that these were due to an exchange occurring shortly after zygote formation. Although it has previously been believed that Robertsonian translocations are the result of a mitotic event, these cases provide the first molecular proof that a Robertsonian translocation may frequently occur in the absence of detectable mosaicism. In addition, three cases of maternal UPD (for chromosomes 14, 15, and 22) and the second case of paternal UPD(21) resulting from an isochromosome were found. No case has yet been observed of a de novo Robertsonian translocation between homologous chromosomes that leads to UPD, either because they do not normally occur in meiosis or because they are rare relative to isochromosome formation.

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