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A Systematic Search for Uniparental Disomy in Carriers of Chromosome Translocations

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Abstract

A systematic search was made for uniparental disomy in carriers of apparently balanced chromosome translocations who also had unexplained abnormalities of mental or physical development. Of 65 families studied, biparental origin of both translocated chromosomes was demonstrated in 64, and only 1 case of maternal uniparental disomy of chromosome 14 was detected in the carrier of a Robertsonian t(13q14q). We conclude that uniparental disomy is a rare occurrence in this population.

Introduction

The term uniparental disomy was originally used by Eric Engel [1] in 1980. Under normal circumstances humans have 22 pairs of autosomes and 1 pair of sex chromosomes, one of each homologous pair originating from the father and one from the mother. In uniparental disomy, diploid offspring inherit both homologues of a chromosome pair from 1 parent. Unless there are obvious cytogenetic heteromorphisms to distinguish the parental origin of the homologues, uniparental disomy is cytogenetically undetectable.

There are a number of proposed mechanisms by which uniparental disomy might arise. Nondisjunctional events during meiosis may result in aneuploid gametes which, on fertilization, give rise to uniparental disomy in the zygote by one of three mechanisms:

(1) *Gamete complementation*: Engel's original suggestion was that fusion of a nullisomic

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Table 1. Uniparental disomy in humans

Chromosome	Parental origin	Reasons for investigating UPD	Phenotype	Ref.
4	maternal	inv(4)(p15;2:q12)inv(4)(p15;2:q12)mat	mental retardation	40
4	maternal	t(4;4)(4p4p;4q4q)de novo	not intellectually delayed, infertility	41
6	paternal	clinical	not intellectually delayed, C4 deficiency	14
7	maternal	clinical	short stature, cystic fibrosis	6
7	maternal	clinical	short stature, cystic fibrosis	7
7	maternal	clinical	short stature, connective tissue disorder	9
7	unknown	t(7;7)(7p7p;7q7q)de novo	short stature	42
9	maternal	46,XY,inv(9),inv(9)/47,XY,+9,inv(9),inv(9)	mental retardation	43
10	paternal	clinical	MEN 2A, premature, VSD, mental retardation, tracheo-oesophageal fistula	44
11	paternal	clinical	embryonic tumours, hemihypertrophy	45
11 (partial) (3 cases)	paternal	clinical	Beckwith-Wiedemann	46
11 (partial)	paternal	clinical	Beckwith-Wiedemann, thalassaemia	47
11 (partial) (2 cases)	paternal	clinical	Beckwith-Wiedemann	20
13	maternal	46,XX/47,XX,+13	mental retardation	48
14	maternal	t(13;14)mat	not intellectually delayed, scoliosis, hydrocephalus, premature puberty	35
14	paternal	t(13;14)pat/t(1;14)(q32;q32)mat	mental retardation, multiple congenital abnormalities	49
14	maternal	clinical/t(14;14)de novo	rod monochromacy, IQ 86 scoliosis, premature puberty	8
14	maternal	45,XX,t(13;14)/46,XX,+14,t(13;14)de novo	mental retardation, scoliosis, premature puberty	38
14	paternal	45,XX,t(14q14q)de novo	multiple congenital abnormalities	50
15 (2 cases)	maternal	clinical/t(13;15)mat (× 1)	Prader-Willi syndrome	51
15 (7 cases)	maternal	clinical	Prader-Willi syndrome	21
15 (2 cases)	maternal	clinical/t(15q15q)de novo (× 1)	Prader-Willi syndrome	52

Table 1 (continued)

Chromosome	Parental origin	Reasons for investigating UPD	Phenotype	Ref.
15 (18 cases[1])	maternal	clinical/t(8;18)(p24.1;q23)de novo (× 1) /marker chromosome (× 1)	Prader-Willi syndrome	22
15	maternal	mosaic trisomy 15 on chorionic villus sample	Prader-Willi syndrome	53
15	maternal	mosaic trisomy 15 on chorionic villus sample	Prader-Willi syndrome	54
15 (2 cases)	paternal	clinical	Angelman syndrome	55
15	paternal	clinical	Angelman syndrome	56
15	paternal	clinical/t(6;15)(p25.3;q11)pat	Angelman syndrome	57
15	paternal	clinical/t(15q15q)de novo	Angelman syndrome	37
16	maternal	mosaic trisomy 16 on chorionic villus sample	intrauterine growth retardation	10
16	maternal	mosaic trisomy 16 on chorionic villus sample	intrauterine growth retardation	11
16 (4 cases)	maternal	mosaic trisomy 16 on chorionic villus sample	intrauterine growth retardation, fetal death (× 1), anal atresia (× 1)	12
16	maternal	mosaic trisomy 16 on chorionic villus sample	intrauterine growth retardation, clubfoot	13
16	paternal	clinical	hydrops fetalis, α-thalassaemia-1	58
21	maternal	46,XX/46,XX,del(21)(q22.1 → qter)de novo	mental retardation	59
21	paternal	45,XX,–21/46,XX/46,XX,r(21)de novo	mental retardation	59
21	maternal	45,XX,t(21q21q)	not intellectually delayed, trisomic offspring	15
21	paternal	45,XX,t(21q21q)	not intellectually delayed, trisomic offspring	16
22	maternal	t(22q22q)mat	not intellectually delayed, infertility	17
22	maternal	t(22q22q)mat	not intellectually delayed, infertility	18
XY	paternal	clinical	not intellectually delayed, haemophilia A	19
XX	paternal	clinical/45,X/46,XX	short stature, gonadal dysfunction	60

Clinical = molecular investigations were instigated because of the clinical features of the patient. The karyotype is included only when abnormal.

[1] Includes 2 cases previously reported in Nicholls et al. [51].

gamete with a gamete disomic for the same chromosome would result in a diploid zygote.

(2) *Monosomy duplication:* A zygote resulting from the fusion of a monosomic gamete with a nullisomic gamete would be nonviable unless the single chromosome duplicated itself, resulting in isodisomy of that chromosome.

(3) *Trisomy rescue:* When a disomic gamete fuses with a normal monosomic gamete the resulting zygote is trisomic. If the zygote corrects the initial trisomy by loss of the supernumerary chromosome, random loss would result in a normal zygote in 2/3 of cases, and uniparental disomy in 1/3.

Postzygotic mitotic nondisjunction may also result in uniparental disomy, if one homologue of a chromosome pair is lost and the other duplicated to retain euploidy. Mitotic events would result in mosaicism for uniparental disomy unless they occur very early on in embryogenesis.

Uniparental disomy may affect development if an autosomal recessive gene mutation is unmasked by autozygosity, or if the chromosome involved bears regions subject to imprinting. Imprinting is defined as the differential expression of a gene dependent upon the parent of origin. Studies in mice have demonstrated that uniparental disomy of certain chromosomes appears to have no phenotypic effect, presumably because they do not bear imprinted regions. However, some chromosomes demonstrate different phenotypic effects dependent upon the parent of origin, while uniparental disomy of others appears to be nonviable [2–4]. Situations analogous to those caused by imprinting in mice are also evident in humans, indicating that similar imprinting mechanisms exist, and from mouse studies it would be predicted that imprinted regions are present on human chromosomes 2, 5, 6, 7, 9, 11, 15, 16, 19, 20, 21 and 22 [4, 5]. Thus uniparental disomy can provide a tool for the determination of both imprinted regions in the human genome and the mapping of autosomal recessive genes.

Relatively few cases of uniparental disomy in humans have yet been described in the literature (for summary, see table 1). This could be a true reflection of their rarity, or result from the lack of a simple screening test. In some patients the clinical features associated with uniparental disomy are clearly due to an autosomal recessive disease such as cystic fibrosis [6, 7] or rod monochromacy [8]. In others, the clinical features common to all patients with uniparental disomy of the same chromosome may result from the presence of imprinted regions on the chromosome. Three cases of maternal uniparental disomy of chromosome 7 have been described, and short stature is a feature in each case [6, 7, 9]. Maternal uniparental disomy of chromosome 16 has now been described on seven occasions [10–13] and may result in intrauterine growth retardation. However, each case has been associated with a trisomic cell line for chromosome 16 which may have been the cause of the poor placental function. Uniparental disomy for chromosomes 6 (paternal), 21 (both maternal and paternal), 22 (maternal) and XY (paternal) have all been reported to be associated with normal development [14–19].

Few syndromes associated with imprinted regions are well recognized. An exception is uniparental disomy of chromosome 15 which, when it is maternal, results in Prader-Willi syndrome and, when paternal, in Angelman syndrome. Another well-characterized condition in which imprinting is known to play a part is Beckwith-Wiedemann syndrome. Henry et al. [20] have demonstrated that 20% of sporadic cases of Beckwith-Wiedemann syndrome have paternal uniparental isodisomy (autozygosity) for 11p15.5. In some cases the loss of maternal alleles was shown to be a

mitotic event as evidenced by somatic mosaicism for the uniparental disomy.

It has been shown in Prader-Willi syndrome that the maternal age is greater in patients with maternal uniparental disomy compared with those with a paternal deletion of 15q12–13 [21, 22]. This is consistent with the fact that the incidence of oocyte aneuploidy increases with maternal age, and supports the three mechanisms proposed for uniparental disomy. It would be anticipated that gamete complementation is the least likely mechanism, since errors in both maternal and paternal meiosis are required. Evidence of trisomy 15 in chorionic villus samples from 2 Prader-Willi patients indicates that trisomy correction is the mechanism by which they have arisen. Table 1 shows that in a total of 30 patients, excluding those ascertained for Prader-Willi, Angelman and Beckwith-Wiedemann syndromes, maternal uniparental disomy (21 cases) is more common than paternal (9 cases).

In order to gain further insight into uniparental disomy in humans, we have studied a population which we reasoned should be at increased risk of uniparental disomy. Since any situation that predisposes to the production of aneuploid gametes would be expected to predispose to uniparental disomy, our systematic search began with the selection of a population of individuals who should be at increased risk of uniparental disomy because their parents were at increased risk of meiotic nondisjunction.

Carriers of Robertsonian and certain reciprocal translocations have been identified as a high risk group, since the incidence of nondisjunction is increased for those chromosomes involved in the translocation. Under normal circumstances, during meiosis I, homologous chromosomes pair and recombination occurs before the homologues separate and move to the two daughter cells. In cells with structural rearrangements of the chromosomes the homologues are unable to pair in the usual way (fig. 1).

In Robertsonian heterozygotes the translocation chromosome and the two normal homologues usually synapse as a trivalent. Alternate segregation results in balanced/normal gametes. Adjacent segregation results in disomic and nullisomic gametes [23]. In reciprocal translocations the two translocation and the two normal homologues form a quadrivalent at pachytene. They can then segregate in a number of ways. Alternate segregation results in normal/balanced daughter cells, adjacent 2:2 segregation results in unbalanced daughter cells and adjacent 3:1 segregation can lead to aneuploid daughter cells. Recent studies using fluorescence in situ hybridization on human meiotic preparations have demonstrated that the segregation patterns in carriers of reciprocal translocations vary between individuals, and that the presence of interstitial chiasmata can influence the products of meiosis [24, 25]. A number of studies have demonstrated that carriers of Robertsonian and reciprocal translocations are at increased risk of producing unbalanced offspring [e.g. 26, 27].

A beneficial feature of searching for uniparental disomy in carriers of a translocation is that the chromosomes at risk of being uniparentally disomic can be targeted since they are those involved in the translocation. Thus, for each proband, only two chromosomes need to be studied, whereas it is difficult to screen for uniparental disomy in the general population since all the chromosomes must be tested for parental origin. Our postulate that translocation carriers are at increased risk of uniparental disomy is born out by a search of the literature which reveals that there have been 14 cases of uniparental disomy associated with translocations. Of the 14, 8 are associated with homologous translocations, 4 with

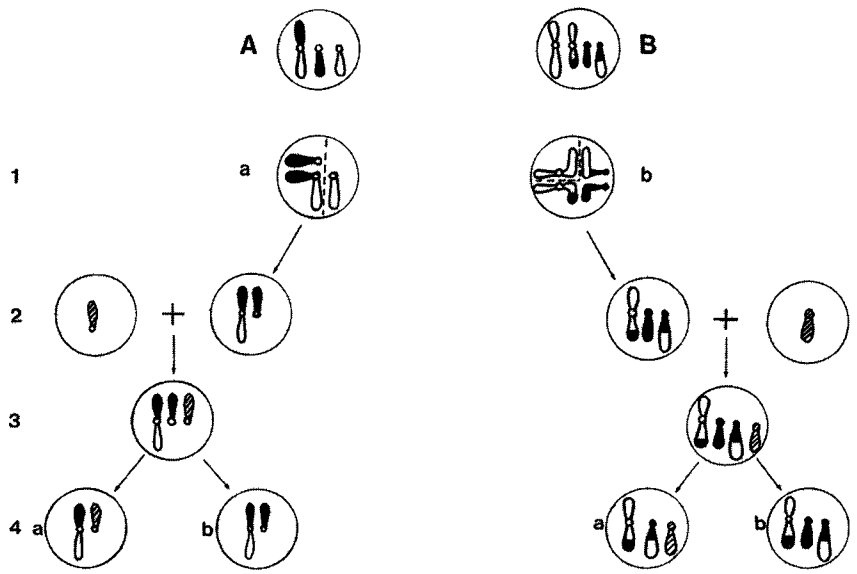

Fig. 1. Mechanisms resulting in uniparental disomy in carriers of (A) Robertsonian and (B) reciprocal translocations. 1. At meiosis, (a) adjacent segregation and (b) 3:1 segregation. 2. Fusion of gamete disomic for the black chromosome with a normal monosomic gamete (hatched chromosome). 3. Zygote trisomic for the black/hatched chromosome. 4. Trisomy correction results in either (a) a normal zygote or (b) uniparental disomy of the black chromosome.

nonhomologous Robertsonian translocations and 2 with reciprocal translocations. In addition, there are 2 cases associated with isochromosomes (table 1).

The Study Population

Individuals were identified initially from the Wessex Regional Genetics Laboratory. A systematic search was made for those who presented with an unexplained abnormality of mental or physical development including infertility and who were subsequently found to have an apparently balanced Robertsonian or reciprocal translocation. The clinical criteria for inclusion were wide, as, for the majority of chromosomes, it is not known how, or if, uniparental disomy affects development.

All families were contacted via a letter to the physician who initially referred the patient for chromosome analysis. An attempt was made to contact all families although, as our records went back 15 years, it was often impossible to trace the patients. In those families who agreed to participate, 10–20 ml of blood was obtained from the proband and both parents. As we had no idea what proportion would show uniparental disomy, a thorough clinical examination was only proposed for those subsequently found to have uniparental disomy.

Following this initial approach, collaboration with a second Regional Genetics Unit, North West Thames Health Authority, was initiated and an identical search was made. Clinical geneticists in the UK and Europe were also invited to collaborate.

Methods

Cytogenetic Analysis

Chromosome analysis was carried out on peripheral blood lymphocytes from each proband and both parents where possible. Translocation breakpoints were determined after G-banding of metaphase chromosomes [28].

Molecular Techniques

DNA was extracted from whole blood by a salt precipitation technique [29]. Parental origin of the chromosomes involved in the translocations was determined using two molecular techniques: (1) analysis by standard Southern blot methods and hybridization with radioactive probes [30, 31] and (2) amplification of polymorphic microsatellite repeat sequences [32, 33] using standard PCR amplification [34]. PCR products were visualized using a 6% denaturing polyacrylamide gel followed by autoradiography. Details of the probes and primers used may be obtained on request from the authors.

Since we were searching for uniparental disomy of whole chromosomes, a single biparental result, or two results, one demonstrating a maternal contribution and one demonstrating a paternal contribution, was sufficient to exclude uniparental disomy for each chromosome.

Results

A total of 94 families were contacted via the Wessex Genetics Service, and 22 families via the North West Thames Genetics Service. To date we have tested 44 complete families (proband and both parents) and 12 partial families (proband and 1 parent). We have also tested 9 further families supplied by other centres. In total, a search for uniparental disomy was made in 65 probands. Details of each case are given in tables 2 and 3.

Our study population represented a total of 130 target chromosomes and uniparental disomy was excluded for 129 of these, i.e. biparental origin was determined for both translocated chromosomes in 64 probands. Only a single case of uniparental disomy was detected (family No. Z57). The proband was the carrier of a Robertsonian t(13;14)mat and was found to have maternal uniparental disomy of chromosome 14. This patient was one of the first three studied and full details have been published [35].

Discussion

The main conclusion that can be drawn from this study is that uniparental disomy is a relatively rare event among balanced translocation carriers, when they have been ascertained because of clinical abnormality. In this series of 65 cases, uniparental disomy was found only in patient Z57, and its relationship to his clinical condition is not yet clear (see below).

Of the 72 cases of uniparental disomy reported in the literature and included in table 1, 14 were associated with a translocation showing that uniparental disomy does occur in balanced chromosome translocations. Only 2 of the 14 were associated with reciprocal translocations, of which 1 involved chromosomes unrelated to the uniparental disomy, suggesting that uniparental disomy may well be rare in carriers of reciprocal translocations. However, prior to this study the incidence of uniparental disomy in translocation carriers was unknown.

The only significant series of patients with uniparental disomy ascertained for clinical reasons are those with Prader-Willi syndrome where uniparental disomy accounts for 15–20% of cases. It is of interest that from two studies investigating a total of 25 cases of maternal uniparental disomy of chromosome 15, one was associated with a t(13;15) Robertsonian translocation, and one with a reciprocal translocation involving nonrelated chromosomes (t(8;18)) [21, 22].

The association between clinical anomalies and balanced chromosomal rearrange-

Table 2. Carriers of Robertsonian translocations studied for uniparental disomy

Family No.	Translocation	Parental origin of translocation	Clinical features
001	t(13q14q)	paternal	undescended testes, hypospadias
002	t(13q14q)	paternal	mental retardation
006	t(13q22q)	maternal	failure to thrive
007	t(13q14q)	maternal	mental retardation
009	t(13q14q)	paternal	hypotonia
008	dic(13;14)(p11;p11)	maternal	recurrent abortion
010	t(13q14q)	unknown	infertility
012	t(13q14q)	maternal	mental retardation
013	dic(13;14)(p11;p11)	unknown	recurrent abortion
019	t(13q14q)	unknown	recurrent abortion
021	t(14q21q)	unknown	infertility, recurrent abortion
022	dic(22;22)(p11;p11)	de novo	short stature
025	t(21q22q)	de novo	failure to thrive
029	t(15q21q)	de novo	acute lymphoblastic leukaemia
038	dic(13;14)(p11;p11)	maternal	infertility
042	dic(14;21)(p11;p11)	paternal	amenorrhoea
044	t(14q22q)	maternal	mental retardation
045	dic(13;14)(p11;p11)	maternal	recurrent abortion
053	t(13q14q)	maternal	recurrent abortion
055	dic(13;14)(p11;p11)	unknown	infertility
Z57	t(13q14q)	maternal	see Temple et al. [35]
061	t(13q14q)	de novo	mental retardation
062	t(14q21q)	de novo	mental retardation
063	t(14q21q)	maternal	recurrent abortion
068	t(13q14q)	paternal	mental retardation
069	t(13q14q)	paternal	recurrent abortion
070	t(13q14q)	paternal	infertility
073	t(14q21q)	paternal	craniosynostosis

ments is documented but contentious [36]. There is, however, generally considered to be an empiric risk of 5–10% for a developmental anomaly in de novo reciprocal balanced translocation carriers when detected prenatally [23]. We would suggest that few of these developmental anomalies are caused by uniparental disomy, and, on the basis of our results, the search for uniparental disomy in translocation carriers is unlikely to be very productive. An exception may be the rare examples of balanced translocations involving homologous chromosomes, particularly where the chromosome involved has a high

Table 3. Carriers of reciprocal translocations studied for uniparental disomy

Family No.	Translocation	Parental origin of translocation	Clinical features
003	t(4;5)(q21.1;q35.1)	paternal	mental retardation, large
004	t(11;14)	de novo	overgrowth, mental retardation
005	t(2;13)(q21;q32.3)	de novo	dysmorphic
011	t(8;15)(q22;q15)	de novo	diaphragmatic hernia
014	t(1;13)(p22;q32)	paternal	mental retardation
015	t(4;9)(q25;q22.3)	de novo	mental retardation, hypotonia
016	t(1;2)(2;14)(p22;q31)(p16;q22)	unknown	mental retardation, short
017	t(3;8)(p11.1;q13.2)	paternal	recurrent abortion
018	t(17;22)(q21.1;q12.2)	de novo	autism
020	t(2;5)(q33;q12)	de novo	mental retardation
023	t(15;20)(q22.3;q13.3)	paternal	mental retardation
024	t(6;10)(q13;q21.2)	de novo	mental retardation, hypotonia
026	t(12;22)(12p22p;12q22q)	maternal	recurrent abortion
028	t(4;8)(q34.2;q24.13)	paternal	mental retardation, autism
030	t(11;13)(p13;q12.3)	maternal	recurrent abortion
032	t(9;15)(q22;q13)	maternal	congenital malformations
033	t(3;10)(p24.2;q25.2)	maternal	recurrent abortion
035	t(2;12)(q37;q24.1)	maternal	mental retardation
037	t(8;16)(q22.1;q13)	paternal	delayed puberty, short
039	t(3;13)(q13.2;q32.3)	de novo	mental retardation
040	t(12;17)(q24.31;q25.3)	maternal	mental retardation, autism
041	t(7;12)(p15;q13)	paternal	ambiguous genitalia
046	t(8;14)(q13;q24)	unknown	recurrent abortion
047	t(3;6)(p21.33;p21.33)	maternal	delayed puberty
048	t(4;16)(q27;p13.3)	maternal	recurrent abortion
049	t(1;19)(p34.3;q13.3)	maternal	dysmorphic
050	t(8;13)(q22.3;q22.1)	maternal	diaphragmatic hernia
051	t(18;20)(q21.2;p12.2)	paternal	dyslexic
052	t(3;20)(q13.2;p12.2)	de novo	delayed puberty, short
054	t(5;15)(q13.1;q21.1)	paternal	mental retardation
056	t(3;10)(p23;q21.2)	maternal	mental retardation
058	t(11;17)(p13;p13.1)	maternal	undescended testes
072	t(13;14)(q12;q24)	maternal	dysmorphic, short
075	t(2;16)(p13;q22)	maternal	mental retardation
076	t(6;16)(p21.1;q22.1)	paternal	speech delay
077	t(5;18)	paternal	short stature
078	t(5;6)(q22;q13)	paternal	mental retardation, dysmorphic

Table 4. A comparison of clinical features of maternal uniparental disomy for chromosome 14 and mosaic trisomy 14

	Maternal uniparental disomy of chromosome 14			Mosaic trisomy 14
	Temple et al., 1991 [35]	Pentao et al., 1992 [8]	Antonarakis et al., 1993 [38]	Fujimoto et al., 1992 [39]
Sex	male	female	female	9× female, 6× male
Gestation	32/40	40/40	32–33/40	12 > 37/40 3 < 36/40
Birth weight centiles	1.43 kg 10th centile	2.216 kg <5th centile	1.759 kg 10th–25th centile	10 > 3rd centile 5 < 3rd centile
Postnatal hydrocephalus	+	–	+	0/15
Kyphoscoliosis	+	+	+	0/15
Premature puberty	+ 10 years	+ 8½ years	+ 9 years	not recorded
Prepubertal short stature	–	+ –1.5 SD at 9 months	+ <5th centile	15/15
Postpubertal short stature	+ <3rd centile	+ <5th centile	not applicable	1/1
Cryptorchidism	+ small testes as adult	not recorded	not recorded	6/6
Intellectual development	normal	IQ 86–78 mild delay	IQ 86 mild delay	9/9 mentally retarded
Palate cleft/ high arched	+ bifid uvula	–	+	10/14
Other features	–	× 3 miscarriages rod monochromacy	absent patellae hypercholesterolaemia	microphthalmia 2/15

probability of having an imprinted region [37].

Since the publication of the 1 case of maternal uniparental disomy of chromosome 14 detected in our study [35], 2 other cases have been described [8, 38]. There are clinical similarities among these patients which might help in the recognition of further cases (table 4). Affected individuals had short stature, scoliosis, hydrocephalus and premature puberty. It is of interest that the patient described by Antonarakis et al. [38] was shown to have a trisomy 14 cell line in 5% of blood lymphocytes. Features described in mosaic trisomy 14 [39] show similarities to the 3 cases of maternal uniparental disomy of 14 (table 4) and it could be that it is mosaicism for trisomy 14 that accounts for the clinical picture. From mouse studies it is not yet clear whether imprinted regions would be predicted on human chromosome 14 [5].

This is the first study which has searched systematically for uniparental disomy for chromosomes other than for chromosome 15 in Prader-Willi and Angelman syndromes, and chromosome 11 in Beckwith-Wiedemann syndrome. Uniparental disomy for some chromosomes may be lethal, while for other chromosomes, for example paternal chromosome 6, chromosome 21 and maternal chromosome 22, uniparental disomy is associated with a normal phenotype. Our study was designed to answer the question of the incidence of uniparental disomy in phenotypically abnormal carriers of apparently balanced translocations, and does not provide information on the total incidence of uniparental disomy in translocation carriers. We did not detect many cases of uniparental disomy, thus showing that uniparental disomy is not a common cause of phenotypic abnormality in this population.

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