J Med Genet 1991; 28: 511–514

Maternal uniparental disomy for chromosome 14

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Abstract

We report the first case of maternal uniparental disomy of chromosome 14 in humans. The male proband inherited a balanced 13;14 Robertsonian translocation from his mother. Molecular studies showed that neither chromosome 14 was of paternal origin. The proband is of above average intelligence, but he has hydrocephalus, a bifid uvula, premature puberty, short stature, and small testes. It is not known if the clinical findings are related or coincidental to the uniparental disomy.

In 1980 Engel[1] recognised that, because of the relatively large proportion of human gametes that have an additional or missing chromosome, there was a possibility of fertilisation involving two complementary aneuploid gametes resulting in a euploid conceptus in which both members of one chromosome pair came from the same parent. He called this phenomenon uniparental disomy. Later in the same year the first two examples of uniparental disomy were described.[2 3] Both were women referred for recurrent abortions who were found to have a Robertsonian translocation t(22;22) that had been inherited from their phenotypically normal mother. These exceptional women must have arisen by the fertilisation of an egg carrying the translocation by either a sperm nullisomic for chromosome 22 or by a normal sperm, the resulting trisomy 22 conceptus losing the paternal 22 very early in development. Both women were phenotypically normal and it can therefore be concluded that maternal uniparental disomy for chromosome 22 is not associated with any major developmental disability. Carpenter *et al*[4] described a child with developmental and language delay who was homozygous for a pericentric inversion of chromosome 4 for which the mother was heterozygous. This child may also be a uniparental disomic. More recently Nicholls *et al*[5] reported six cases of maternal uniparental disomy for chromosome 15 in patients with Prader–Willi syndrome and in at least one case the mother had a 13;15 Robertsonian translocation and her affected child had inherited both the translocation and the normal chromosome 15 from his mother. Malcolm *et al*[6] reported two cases of paternal uniparental disomy for chromosome 15 among 26 chromosomally normal patients with Angelman's syndrome. Wang *et al*[7] reported a mentally retarded girl who had multiple congenital abnormalities and was a paternal uniparental disomic for chromosome 14, her father having a Robertsonian translocation involving chromosomes 13 and 14 and her mother a reciprocal translocation between chromosomes 1 and 14. Two isolated cases of cystic fibrosis who also had growth retardation have both been shown to be maternal uniparental disomics for chromosome 7.[8 9]

In a series of experiments with mice carrying translocations, Cattanach and his colleagues[10 11] showed that uniparental disomy for different chromosomes had quite different effects. Both maternal and paternal uniparental disomics for chromosomes 1, 4, 5, 9, 13, 14, and 15 of the mouse appear normal, whereas uniparental disomics for chromosomes 2, 6, 7, 8, 11, and 17 do not. Chromosomes or chromosome regions containing genes whose expression differs depending on whether they are maternally or paternally derived are said to be imprinted. The phenotypic effect of such imprinting covers a wide spectrum. For example, paternal uniparental disomy for chromosome 6 in the mouse has no phenotypic effect whereas maternal uniparental disomy is lethal. Both maternal and paternal disomy for chromosome 2 in the mouse are associated with developmental abnormality, but the abnormal phenotypes depart from normal in opposite directions.

Uniparental disomy can result from fertilisation of a gamete disomic for a chromosome by a gamete nullisomic for the same chromosome ('gamete complementation') or by a loss or gain of a chromosome from a trisomic or monosomic conceptus ('aneuploid correction').[12] Therefore, any situation

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Received for publication 26 March 1991.
Accepted for publication 15 April 1991.

that predisposes to the formation of aneuploid gametes will also predispose to uniparental disomy. One population that is known to be at a high risk of producing gametes with an additional or missing chromosome are carriers of Robertsonian translocations. We have therefore instituted a systematic search for uniparental disomy among patients with unexplained developmental abnormalities who have an apparently balanced Robertsonian translocation. Twenty-two such patients have been identified by the Wessex Regional Genetics Laboratory and to date we have reinvestigated only two and found one, the subject of this report, to be a maternal uniparental disomic for chromosome 14.

Case report

The proband was the first child of unrelated Caucasian parents. The pregnancy progressed uneventfully until the onset of spontaneous labour at 32 weeks. Delivery was by caesarian section for fetal distress. At birth his weight was 1430 g (25th centile) and his head circumference 28 cm (10th centile). Apgar score was 7. He had a cyanotic episode within a few hours of birth and was given antibiotics. Cultures were all negative. He did not require ventilation but his head circumference increased rapidly in size and by 10 days was 31 cm (50th centile) and by 2 months was 36·3 cm (>97th centile). The hydrocephalus arrested spontaneously and a shunt was unnecessary. Early motor milestones were delayed. He sat at 12 months and took his first steps at 17 months and now has poor motor coordination. His speech, however, was advanced with several words by the age of 12 months. His intellectual development has remained good. He attends a normal school and is likely to go on to university education.

At the age of 4 years he had bilateral orchidopexy for undescended testes. A scoliosis (concave to the right) was noted in the first year of life which progressed rapidly and required the insertion of Harrington rods at the age of 12 years. Spinal *x* rays showed block vertebrae at T5/6.

His growth was initially normal. His height at 7 years (117 cm) and 8 years (122 cm) was between the 10th and 25th centiles. He went into puberty at the age of 10 and had a corresponding growth spurt, but there has been little growth since the age of 12 years and at 15 years his standing height was 154·7 cm (<3rd centile), sitting height 79·3 cm (−3·5 SD below the mean), and subischial leg length 75·4 cm (−1·0 SD below the mean). A hand *x* ray at this time showed complete fusion of epiphyses. He was reinvestigated neurologically at 15 years of age because he developed a fine resting tremor. A CT scan confirmed hydrocephalus affecting the lateral and third ventricles. The fourth ventricle was within normal limits.

On examination at age 17 his appearance was dominated by the discrepancy between his height and the size of his head. He had a prominent forehead and supraorbital ridges. His philtrum was short and his mouth downturned (fig 1). His teeth were normal but the palate was high and short with a bifid uvula. Speech was high pitched and nasal in quality. Hair growth on the head and face was normal. Examination of the eyes and ears was normal, as were hearing and vision.

His hands and feet were small and slender with fifth finger clinodactyly and normal nails. He had a mild scoliosis. There was truncal obesity but his arms and legs were thin. The nipples were widely spaced and pigmented. Secondary sexual hair had developed normally. Pubic hair was Tanner stage 5 and his genitalia were relatively small. His penile length was 10 cm (10th centile) and testicular volume on both the left and right sides was 8 ml (<3rd centile). Neurological examination showed normal cranial nerves but a mild, right sided hemiplegia. In addition, he had a fine tremor more marked in the left hand. Testosterone, thyroxine, TSH, and LH/FSH levels were normal as were his electrolytes.

The proband has a normal brother. His mother's height is 160 cm and his father's height 190 cm. There is no other family history of relevance and no history of miscarriages.

Laboratory investigations and results

Chromosome studies of peripheral blood leucocytes showed the father to have a normal chromosome

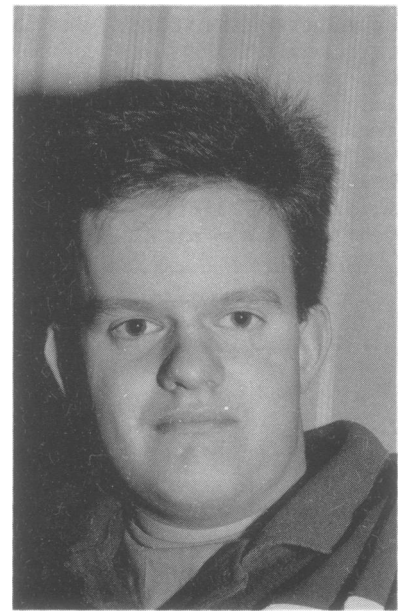

Figure 1 Photograph of the proband at 17 years. Note the prominent forehead, short philtrum, and downturned mouth.

The inheritance of chromosome 13 and 14 polymorphic markers.

Locus	Probe	Location	Enzyme	Proband	Father	Mother
	Cytogenetic polymorphisms	cen/p		a,t(13q14q)	a,b	c,t(13q14q)
D13Z1	αR1680	cen	*Taq*I	1,1	1,1	1,2
D13S1	p7F12	q12–14	*Msp*I	1,1	1,2	1,2
D13S3	p9A7	q21–34	*Hin*dIII	1,1	1,1	1,1
D13S11	p9A7	q21–34	*Msp*I	2,2	2,2	2,2
D13S5	pHUB8	q22–34	*Hin*dIII	1,2	1,2	1,1
D13S2	p9D11	q22	*Taq*I	1,2	2,2	1,2
D13S2	p9D11	q22	*Msp*I	1,1	1,1	1,1
D13S7	pHU26	q22	*Bgl*II	1,1	1,2	1,1
D13S49	pCMI40	q	*Taq*I	A,B	A,A	A,B
D13S39	pTH162	q	*Bgl*II	2,3	2,3	2,3
	Cytogenetic polymorphisms	cen/p		c,t(13q14q)*	a,b	c,t(13q14q)
D14S1	pAW101	q32.32–32.33	*Eco*RI	A,A	A,B	A,B
D14S23	cKKA39	q32.33–32.33	*Msp*I	C,C*	A,B	A,C
D14S20	pMCOC12	q32.33	*Msp*I	B,B*	A,A	B,B
D14S22	pCMM66	q	*Pst*I	A,A	A,B	A,A
D14S19	pHHH208	q	*Bam*HI	3,3	1,3	3,3
D14S16	pTHH37	q	*Pst*I	2,2	1,2	2,2

*No paternal alleles present.

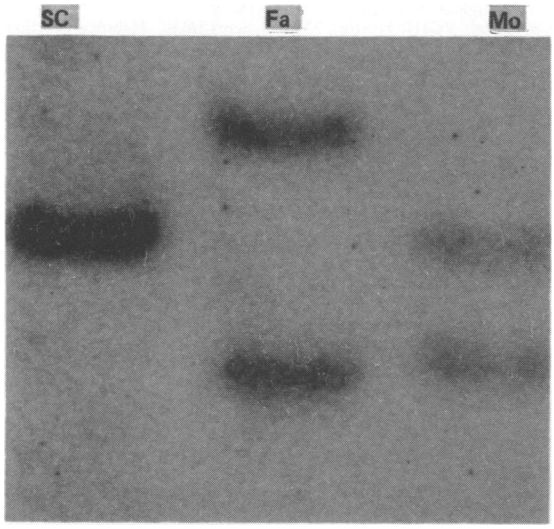

Figure 2 Southern blot of probe cKKA39 (recognising locus D14S23), showing absence of a paternally derived allele.

constitution while both the proband and his mother had 45 chromosomes and a Robertsonian translocation involving chromosomes 13 and 14. Fluorescent polymorphisms were examined and the results suggested that the proband had inherited his single free chromosome 13 from his father, but his single free chromosome 14, as well as the translocation, from his mother (table).

The inheritance of 10 probes that recognise loci on chromosome 13 and six probes that recognise loci on chromosome 14 were studied.[13 14] As can be seen from the table, given that the proband has inherited his 13;14 translocation from his mother, he must have inherited his free chromosome 13 from his father because at locus *D13S5* he has inherited a paternal allele that is not present in his mother. The situation is different for chromosome 14 where he has not inherited paternal alleles for loci *D14S20* or *D14S23*. Furthermore, the results of all four other chromosome 14 loci tested are compatible with the proband having inherited both the translocation and the free chromosome 14 from his mother, there being no paternal chromosome 14. We also considered the possibility that he might have inherited a paternally derived chromosome 14 with a microdeletion. However, dosage studies of the same filters sequentially hybridised to chromosome 14 and chromosome 21 probes indicated that he had two copies of the chromosome 14 loci studied.

The proband appeared to be homozygous for all six chromosome 14 probes tested, including the only two for which his mother was heterozygous. Both these latter probes recognise loci at the distal tip of the long arm. Their reduction to homozygosity suggests that the free maternal chromosome 14 paired with the translocation chromosome during pachytene and underwent at least one exchange between the centromere and the loci *D14S1* and *D14S23*. Thus, nondisjunction in this patient was not associated with failure of pairing or exchange.

Paternity was checked using multiallelic probes that recognise loci *D16S7* and *D21S112* and the results were consistent with the legal father being the biological father.

Discussion

The most plausible interpretation of our results is that the proband is a maternal uniparental disomic for chromosome 14. What is less clear is whether his present clinical problems of short stature, hydrocephalus, scoliosis, nasal speech, bifid uvula, and small testes are caused by this finding or are coincidental to it. Abnormalities of growth have been recognised in other examples of uniparental disomy in both humans[8 9] and in mice.[10] However, the proband's short stature might be the result of premature puberty complicated by a progressive scoliosis further reducing truncal height. This suggestion is supported by two prepubertal height recordings within the normal range. Early puberty itself may be related to uniparental disomy of chromosome 14, but in the proband this could be secondary to hydrocephalus. Similarly, a bifid uvula may be significant or coincidental. One unexplained finding was his small testicular volume despite normal genital and secondary sexual hair development. Both testes were well positioned in the scrotal sac after an orchidopexy at 4 years. It is unlikely that the subsequent failure of testicular enlargement is related to the operation, which could also not explain the failure of the testes to descend initially. What is clear, however, is that despite prematurity, a stormy neonatal course, and subsequent hydrocephalus, the proband is of normal intelligence which suggests that maternal uniparental disomy for chromosome 14 is compatible with normal intellectual development.

We are currently looking at persons with maternally inherited Robertsonian translocations involving chromosome 14, both phenotypically normal and abnormal, in order to determine whether or not chromosome 14 shows an imprinting effect. The only previously described patient with uniparental disomy for chromosome 14 was a paternal uniparental disomic and she had mental retardation and multiple congenital abnormalities.[7] Again, it is impossible to know whether her phenotypic abnormalities are causal or coincidental to her paternal uniparental disomy.

The proximal part of chromosome 14 in man is homologous to chromosome 14 in the mouse, while the more distal part is homologous to mouse chromosome 12.[15] Both maternal and paternal uniparental disomies for mouse chromosome 14 are known and neither is associated with any phenotypic effect. However, the status of both maternal and paternal uniparental disomies for mouse chromosome 12 is not known. If the abnormal phenotypes described by Wang *et al*[7] and by ourselves are found to be caused by uniparental disomy, chromosome 14 must, like chromosome 15, show an imprinting effect for both paternally and maternally inherited chromosomes, the effect being very different for the two types of disomy. If, however, the phenotypes turn out to be coincidental to the disomy it will indicate that human chromosome 14 is not imprinted, at least not in a way that interferes with normal growth and development.

We are grateful to Dr P Betts for referring the patient to us and to Dr N Dennis for his help and encouragement. This work was supported in part (TH, DP) by grant HD.21341 from the National Institutes of Health.

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