Maternal translocation (9;18) with two abnormal offspring each with different chromosome derivatives

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SUMMARY We report a phenotypically normal woman with an apparently balanced reciprocal translocation between chromosomes 9 and 18 [46,XX,t(9;18)(p22;p11.2)], giving rise to unbalanced chromosome complements in two of her children, each of whom received a different derivative chromosome. The proband's karyotype is 46,XY,-18,+der(18),t(9;18)(p22;p11.2)mat, which results in a duplication of the distal portion of the short arm of chromosome 9 with a concomitant deletion of much of the short arm of chromosome 18. The karyotype of the proband's brother is 46,XY,-9,+der(9),t(9;18)(p22;p11.2)mat, which results in a deletion of the distal short arm of chromosome 9 and a duplication of most of the short arm of chromosome 18. The phenotype of each child is significantly different from that of his sib and is not consistent with any previously reported chromosome abnormality.

35 year old, G7P2A4 mother and her 32 year old husband. The pregnancy was complicated by uterine compression of the mother's inferior vena cava which was treated with intermittent bed rest for five months. Delivery was vaginal, vertex presentation with a birth weight of 2495 g (3rd centile) and length of 45 cm (3rd centile). At birth, he was noted to have a right sided cleft lip and palate. At seven days of age he developed respiratory difficulties secondary to chylothorax which required mechanical ventilation and responded well to thoracentesis and the parental introduction of medium chain triglycerides.

At seven months of age, the child was referred for evaluation of possible glycogen storage disease. Hepatosplenomegaly had been noted with abnormalities in liver function. Alpha₁ antitrypsin activity, cystic fibrosis testing, TORCH titres, liver ultrasound, radioisotope scan, and amino acid analysis were all within normal limits. A liver biopsy showed evidence of glycogen excess.

Physical examination showed a frail appearing, hypotonic, seven month old white male (fig 1) with a weight of 4.5 kg (<<3rd centile), height of 57.8 cm (<<3rd centile), and head circumference of 40.5 cm (<2nd centile). He had dolichocephaly with a prominent, high forehead and fine, sparse, red blond hair with normal patterning. The palpebral fissures were upward slanting with epicanthic folds, thickened eyelids, bilateral ptosis, and blue irides (fig 1). Inner canthal distance was 2.2 cm (25th centile), outer canthal distance 5.7 cm (<3rd centile), and interpupillary distance 3.6 cm (<3rd centile). The ears were borderline low set and posteriorly rotated with upturned lobules. The nose had a prominent nasal root and a small tip with some nostril deformation secondary to the cleft lip. Right cleft lip and palate were evident. The chin was small. The neck was short without any excess skin. Examination of the hands showed a Sydney line on the right palm and normal flexion creases on the left palm. The fingers had slightly blunt tips with normal nails. There was proximal placement of the second and fourth toes bilaterally. The abdomen was prominent with a mild umbilical hernia, bilateral inguinal hernias, hepatomegaly, and a palpable spleen tip. His penis was 1.5 cm (<10th centile). Skin was thin with a prominent underlying venous

In this report we describe a family with an inherited translocation between chromosomes 9 and 18. After the birth of the second child with multiple congenital anomalies, the mother was found to have a balanced reciprocal translocation between chromosomes 9 and 18 [46,XX,t(9;18)(p22;p11.2)]. She has had a total of seven pregnancies, of which four resulted in spontaneous abortion. One resulted in a karyotypically and phenotypically normal daughter and two resulted in sons with different unbalanced chromosome complements. The proband's karyotype is essentially trisomy 9p/monosomy 18p, and his brother's karyotype is essentially monosomy 9p/trisomy 18p.

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CASE 1

The proband was born at 38 weeks' gestation to a

FIG 1 Facial appearance of the proband (case 1).

pattern particularly in the temples and over the abdomen.

CASE 2

Case 2 is the older brother of the proband. He was born to the then 27 year old G5P0A4 mother and her 23 year old husband. The pregnancy was uncomplicated and delivery was vaginal after 15 hours of labour with forceps extraction. Apgar scores were 8 and 9 at one and five minutes respectively. At birth he was noted to be floppy with strabismus, micropenis, and left club foot.

At three months of age, he had no voluntary movement. EEG, EKG, EMG, and muscle biopsy were within normal limits. Based on these results, a diagnosis of benign congenital hypotonia was made. He sat without support at two years, walked at three years, and spoke his first word at four years.

Chromosome analysis was performed elsewhere when the patient was two years old and was reported as normal.

The patient has had significant behavioural problems including autism, aggression, and cruelty to animals and other children. However, he has no

FIG 2 Case 2, brother of the proband.

Case reports

self-mutilative behaviour. He has no sensation of smell, taste, or touch. He has hyperacute hearing and good peripheral vision with no central vision.

Physical examination showed a well developed, well nourished, nine year nine month old, white male (fig 2) who was friendly and cooperative. Height was 140 cm (75th to 90th centile), weight 35.8 kg (90th centile), and head circumference 52 cm (2nd to 50th centile). He had brachycephaly with a prominent metopic suture and narrowing at the temples, giving him mild trigonocephaly. His hair was brown with a double posterior hair whorl. Palpebral fissures were level, with strabismus, brown irides, and synophrys. Inner canthal distance was 2.3 cm (<3rd centile), outer canthal distance 7.2 cm (<3rd centile), and interpupillary distance 5.0 cm (3rd to 25th centile). The ears were low set with small lobes and a prominent antehelix. The nose had a prominent root and bridge and low septum. The mouth had wide vermilion peaks to the lips, poorly grooved philtrum, high narrow palate, and an overbite with opalescent teeth and a space between the upper central incisors. The midface was flat. Examination of his extremities showed normal palmar flexion creases bilaterally, a good range of motion, normal nails, long toes with broad big toes, and flat feet. He had a mild pectus excavatum with the left side of the chest being slightly more prominent than the right side. The right shoulder was raised above the left shoulder and there was mild scoliosis. Genitalia were unremarkable.

CYTOGENETIC STUDIES

Chromosome studies on the proband were performed on fibroblasts cultured from a skin biopsy. Fibroblasts were cultured for six weeks in a flask and subsequently harvested using the *in situ* method.¹ Initial GTG banded chromosome analysis showed a 46,XY,t(18;?)(p11;?) chromosome complement with an abnormal banding pattern on the short (p) arm of chromosome 18.

To investigate the proband's karyotype further, chromosome studies were performed on peripheral blood samples from both parents. Lymphocytes were cultured and harvested for high resolution chromosome analysis using routine methods.² The mother's karyotype showed an apparently balanced reciprocal translocation: 46,XX,t(9;18)(p22;p11.2) (fig 3). The proband's karyotype can therefore be designated 46,XY,-18,+der(18),t(9;18)(p22;p11.2)mat (fig 3). The father's karyotype was normal.

Subsequent studies using blood lymphocytes on the proband's phenotypically abnormal brother and phenotypically normal sister showed 46,XY,-9,+der(9),t(9;18)(p22;p11.2)mat (fig 3) and 46,XX chromosome complements, respectively. The

FIG 3 (a) Ideogram of $t(9;18)(p22;p11.2)$.

(b) Chromosomes of the proband's mother; arrows indicate the derivative chromosomes. (c) Chromosomes of the proband; arrow indicates the derivative 18.

(d) Chromosomes of the proband's brother; arrow indicates the derivative 9.

mother's translocation appears to be *de novo*. Chromosome studies on her parents showed normal chromosome complements.

Discussion

Trisomy 9p, monosomy 9p, and monosomy 18p are each well recognised syndromes. Trisomy 18p has only rarely been reported, most likely because it has very little influence on the phenotype.³ Case reports involving a translocation between chromosomes 9 and 18 resulting in an unbalanced chromosome complement are extremely rare. Our review of published reports found only four such reports.⁴⁻⁷ In each of these cases, the chromosome complement was essentially trisomy 9p/monosomy 18p. Although our proband has a similar karyotype, he is phenotypically quite different from these cases. A comparison of our patient with the trisomy 9p syndrome^{8,9} and the monosomy 18p syndrome¹⁰ is shown in table 1. Our proband has several phenotypic features that are not consistent with either syndrome. These may have occurred either through the interaction of the two karyotypic abnormalities, or they may reflect the amount of deletion or addition of genetic material present in our patient.

To the best of our knowledge, our second patient has a previously undescribed chromosome abnormality. We compared his phenotype with the monosomy 9p syndrome^{11 12} and the trisomy 18p syndrome³ in table 2. Our patient 2 has very few

abnormal phenotypic features. The paucity of features of the monosomy 9p syndrome in this male may reflect the amount of 9p which is deleted in this case.

Unfortunately, cytogenetic analysis was not performed on the products of conception from this woman's first four pregnancies which spontaneously miscarried. Theoretically, this woman can produce 14 different types of gamete of which one is normal, one is balanced, and 12 are unbalanced. Since she has two living sons with different derivative chromosome complements, we know that at least two of the 12 unbalanced gametes are compatible with viable offspring. It is interesting to speculate that her first four pregnancies were the products of fertilisation of one or more of the other 10 unbalanced gametes resulting in non-viable pregnancies.

TABLE 1 Phenotypic features of case 1 in comparison to trisomy 9p and monosomy 18p syndromes.

Feature	Case 1	9p+	18p-
Growth deficiency	+	+	+
Mental deficiency	+	+	+
Microcephaly	+	+	+
Rounded facies	+	+	+
Hypertelorism	-	+	+
Palpebral fissure slant	↑	↑	↑↓
Deep set eyes	-	+	+
Ptosis	+	+	+
Epicanthic folds	+	+	+
Prominent nose	+	+	+
Low nasal bridge	+	+	+
Cup shaped ears	+	+	+
Large, protruding ears	+	+	+
Downturned corners of mouth	-	+	+
Wide mouth	-	+	+
Micrognathia	+	+	+
Cleft lip/palate	+	+	+
Short digits	-	+	+
Clinodactyly	-	+	+
Single flexion crease	+	+	+
Dystrophic nails	-	+	+
Micropenis	+	+	+
Inguinal hernia	+	+	+
Hypopigmentation	+	+	+
Hypotonia	+	+	+

*Too early to determine.

TABLE 2 Phenotypic features of case 2 in comparison to monosomy 9p and trisomy 18p syndromes.

Feature	Case 2	9p-	18p+
Normal growth	+	+	+
Mental deficiency	+	+	+
Trigonocephaly	+	+	+
Upward slanting palpebral fissures	-	+	+
Prominent eyes	-	+	+
Short nose	+	+	+
Depressed nasal bridge	-	+	+
Anteverted nares	+	+	+
Abnormal ears	+	+	+
Posteriorly rotated ears	-	+	+
Long philtrum	-	+	+
Narrow palate	+	+	+
Midfacial hypoplasia	+	+	+
Micrognathia	-	+	+
Short neck	-	+	+
Excess whorl patterns	-	+	+
Foot positioning defects	+	+	+
Cardiac defects	+	+	+
Micropenis/cryptorchidism	+	+	+
Inguinal or umbilical hernias	-	+	+
Scoliosis	+	+	+

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