Partial trisomy 12q: a clinically recognisable syndrome. Genetic risks associated with translocations of chromosome 12q

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SUMMARY A newborn child with an unusual facial appearance and multiple abnormalities was found to be trisomic for a large part of 12q as a result of adjacent 1 segregation of a familial translocation, t(9;12) (p24;q21·2). A combination of cytogenetic analysis, clinical features, and enzyme marker studies allows an accurate assessment of the breakpoints. Although trisomic for a considerably larger area of 12q than other reported cases, there are many similar features suggesting that trisomy 12q is a clinically recognisable syndrome. The frequency and mode of segregation of 12q translocations and their implications for genetic counselling are discussed.

Case report

The proband (fig 1) was the third child of healthy, unrelated parents. Pregnancy and delivery were uneventful, gestation was about 37 weeks, birth weight was 2·15 kg, and head circumference was 34 cm. The head was dolichocephalic with frontal bossing and the ears were low set and poorly lobulated. Hypertelorism, macrostomia, and micrognathia were observed, and the bridge of the nose was broad and depressed and the tip turned down-

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wards. The neck was short with loose skin and there was a low hairline and excessive body hair. The nipples were wide set. All four extremities showed peripheral cyanosis and there was a valgus deformity of the feet and a dimple at the base of the spine. ECG showed right ventricular hypertrophy. At 14 days hydrocephalus was observed which developed rapidly after 25 days. At 37 days the proband died. Necropsy revealed a gap of about 5 mm in the interventricular septum, the lungs were hypoplastic with poor lobe formation, and there was some evidence of brain malformation. Cause of death was

FIG 1 Proband at 12 days.

thought to be a combination of severe obstructive hydrocephalus and congenital heart defect.

CYTOGENETIC STUDIES

G banding of peripheral blood lymphocytes of the proband revealed a 46,XX,der(9) karyotype (fig 2B). Analysis of methotrexate treated chromosomes of the proband's parents showed this to be the result of adjacent 1 segregation of a balanced translocation in the mother, 46,XX,t(9;12) (p24;q21·2) (fig 2A). The father's karyotype was normal. Further family studies showed the balanced translocation to be present in the mother's father, her brother, and a sister (fig 3).

ENZYMES MARKER STUDIES

The locus of the structural gene for the conversion of galactose-1-phosphate to uridine diphosphate

galactose has been assigned to 9p, though the exact position is under dispute. Benn *et al*¹ suggested a position of 9pter→p24, but others support a more proximal position. The proband's value of 76 nmol/h/mg protein (normal homozygous range 61 to 100) indicates that the Galt locus is proximal to the breakpoint in the proband. This supports the cytogenetic evidence of the breakpoint of the translocation being very close to 9pter.

Discussion

PARTIAL TRISOMY 12q: A CLINICALLY RECOGNISABLE SYNDROME

As far as we are aware, there are eight reported cases of partial trisomy 12q in newborns (table 1). Six of these have arisen as a result of a familial translocation and two as a result of duplication of 12q24→qter. The remarkable similarity between them suggests that trisomy 12q is a clinically recognisable syndrome (table 1).

Trisomy 12q is characterised by a dysmorphic head, usually dolichocephalic or brachycephalic, which is large relative to length and weight, widely spaced eyes, a flat nasal bridge, down-turned angles of the mouth, low set poorly lobulated ears, a small chin, a short neck with loose skin, a low hairline, widely spaced nipples, a sacral dimple, a simian palmar crease, skeletal abnormalities, cardiopathy, and psychomotor retardation. A sacral dimple has been reported in six cases and a seventh had a hairy patch at the same position. This may be an indication of a neural tube defect. The presence of a sacral dimple in conjunction with the above features could be a useful clinical marker in the diagnosis of future cases of partial trisomy 12q. Five of the above cases had a break at 12q24·1 suggesting that there may be a predisposition for breaks at this point.⁸ However, they do not form a subgroup clinically. The three remaining cases had breakpoints at 12q21·2 (present case) and 12q24·3.^{4,6} The similarity of the case of Zabel and Baumann⁴ to the present case suggests that the genes responsible for the clinical features of partial 12q trisomy are distal to 12q24·3. There has been one further report⁹ of two adult sisters who were trisomic for 12q24→qter. They were mentally retarded and had a similar craniofacial dysmorphism. Unfortunately no data were available for the newborn period. The case of Muelenaere *et al*⁹ does indicate that there is a possibility of extended postnatal survival for trisomies distal to 12q24. This is not surprising as only the present case, trisomic for a larger amount of 12q than the others, showed a lethal developmental defect.

To assess accurately the risk to translocation families of an abnormal child it is necessary to study previously reported cases of 12q translocations.

FIG 2 *G* banded partial karyotype of (A) balanced translocation in mother and (B) partial trisomy 12q in proband.

FIG 3 *Family pedigree.*

THE FREQUENCY, SEGREGATION, AND RISK ASSOCIATED WITH TRANSLOCATIONS OF 12q

Until recently cases of partial trisomy 12q have been extremely rare. Roberts *et al*³ suggested that this could be the result of a high level of alternate segregation with a low level of interstitial chiasma. In the last 3 years, however, there have been five cases of partial trisomy 12q reported. Furthermore, Ford *et al*⁸ recorded ten cases of unbalanced products out of 18 12q translocations. Based on the unusual segregation pattern of 12q translocations we believe that the comparatively low frequency of trisomy 12q in the newborn population is the result of non-viability of 12q13→q21·2 in an unbalanced form. This is the only region for which there is no liveborn trisomy. Trisomies distal to 12q21·2 resulted from adjacent 1 segregation and had a partial trisomy 12q phenotype (table 1). Trisomies proximal to 12q13 resulted from 3:1 or adjacent 2 segregation and consequently had a trisomy 12p phenotype (table 2).

Only three of the seven cases in table 2 involve acrocentric chromosomes, suggesting that it is not

simply the configuration of the meiotic quadrivalent that has led to 3:1 segregation. The absence of adjacent 1 segregation may be the result of non-viability of its products. There are a further 18 reports of balanced translocations involving 12q0→q15 which are not associated with abnormal offspring.^{8 17 18} In these cases and those of table 2 it is clear that there is selection against the products of adjacent 1 segregation. If this were because of nonviability of these products then a history of spontaneous abortion might be expected in affected families. The case of Savary *et al*¹⁴ is interesting in this respect. The proband presented with a trisomy 12p phenotype resulting from a postzygotic non-disjunction of a familial translocation (table 2). There were no other abnormal children in the family but in two generations 12 spontaneous abortions out of 31 conceptions occurred; these may well be the result of adjacent 1 segregation products.

Abnormal translocation products of chromosome 12q leading to liveborn offspring occur either from adjacent 1 segregation for breakpoints distal to 12q21·2 or from 3:1 segregation for breakpoints proximal to 12q13. The frequency, however, of

TABLE 1 Cytogenetic and clinical details in cases of partial trisomy 12q.

	<i>Present case</i> 46,XX,der(9), t(9;12) (p24;q21·2) mat	<i>Melnyk et al</i> ² 46,XY,der(4), t(4;12) (p16;q24·1) mat	<i>Roberts et al</i> ³ 46,XY,der(2), t(2;12) (q37;q24·1) pat	<i>Zabel and</i> <i>Baumann</i> ⁴ 46,XY,der(9), t(9;12) (p24·3;q24·3) mat	<i>Hemmings</i> <i>and Brown</i> ⁵ 46,XX,der(18), t(12;18) (q24;qter) pat	<i>Holborth</i> <i>et al</i> ⁶ 46,XY,der(21), t(12;21) (q24;p11) mat	<i>Harrod et al</i> ⁷ 46, dup(12), (q24·1→q24·5) Female Male
Gestation (wk)	37	40	36	41	36	44	— —
Weight (g)	2150	2863	2650 (5 wk)	3060	2680	3500	3035 1330
Length (cm)	48	—	46	47	44	54	51 30
Head circumference (cm)	34	36	34	34	35	—	37 30
Head shape	D/C	F/A	D/C	B/C	B/C	B/C	D/C D/C
Hypertelorism	+	+	—	+	+	+	+
Flat nasal bridge	+	+	+	+	+	—	+
Low set ears	+	+	+	+	—	+	+
Poor lobulation	+	—	+	+	+	+	+
Down-turned mouth	+	+	—	+	+	—	+
Micrognathia	+	+	+	+	—	+	+
Low hairline	+	—	+	+	—	—	—
Short neck	+	+	+	+	+	—	+
Loose skin at nape	+	+	+	+	+	—	+
Wide set nipples	+	+	—	+	+	—	+
Simian palmar crease	—	+	+	+	+	+	+
Planovalgus feet	+	+	—	—	—	+	—
Subluxation of hips	—	+	—	+	+	—	+
Sacral dimple	+	+	+	+	+	—	+
Cryptorchidism	N/A	+	+	+	N/A	+	N/A
Heart defect	+	+	+	+	—	+	+
Psychomotor retardation	N/A	+	+	+	N/A	+	+
Other repeated features	Large mouth, down-turned tip of nose, excessive body hair, brain malformation, hydrocephalus	Epicanthal folds, brain malformation	High arched palate, clinodactyly, hammer toes	Large mouth, high arched palate, short proximal arms, ulnar deviation of hands, hydrocephalus	Short proximal arms, brain malformation	Excessive hair, down-turned tip of nose, hammer toes	Epicanthal folds, prominent nasal tip, ulnar deviation of hands, clinodactyly
Survival	Died 37 d	Alive 16 mth	Alive 10 mth	Died 2½ mth	Died 6 d	Alive 2 yr	Alive 3 yr Alive 1 yr

D/C=dolichocephalic, B/C=brachycephalic, F/A=frontal asymmetry, N/A=not applicable.

TABLE 2 Abnormal products of proximal 12q translocations.

	Break on 12q	Break on other	Product	Disjunction	Phenotype	Reference
1	11	5p14	47,der(12),t(5;12)(p14;q11)mat	3:1	Trisomy 12p	10
2	12	14p11	47,der(12),t(12;14)(q12;p11)mat	3:1	Trisomy 12p	11
3	12	21q11	46,-21,der(12),t(12;21)(q12;q11)mat	2:2	Trisomy 12p	12
4	12	8p24	47,der(12),t(8;12)(p24;q12)pat	3:1	Trisomy 12p	13
5	13	8p21	47,der(12),t(8;12)(p21;q13)mat	Post-zygotic	Trisomy 12p	14
6	13	5p15	47,der(12),t(5;12)(p15;q13)mat	3:1	Trisomy 12p	15
7	14	21q22	47,+21,t(12;21)(q14;q22)mat	3:1	Trisomy 21	16

adjacent 1 segregation is far higher than that of 3:1 segregation and, therefore, of great importance when assessing risks to translocation families. Balanced translocation carriers whose breakpoints are distal to 12q21.2 are at high risk (greater than 1 in 10) of an abnormal child surviving to term. Translocations whose breakpoints are proximal to 12q13 are at much lower risk. Stene and Stengel-Rutkowski¹² calculated that for chromosomes 9, 10, and 12 the risk of unbalanced offspring through 3:1 disjunction was about 1 in 50. As there is considerable variation between translocations this figure is likely to be a conservative estimate for most 12q translocations. By considering the factors affecting 3:1 disjunction,^{12,19} that is, the parental origin of the translocation, the reciprocal chromosome involved, the configuration of the meiotic quadrivalent, and the resultant genetic imbalance, a more accurate assessment of risk can be made.

Balanced translocations of chromosome 12q may produce either trisomy 12p or trisomy 12q offspring. Both are clinically recognisable syndromes of congenital abnormalities and mental retardation compatible with an extended postnatal survival. The risk of a trisomy 12p infant associated with proximal 12q translocations may be a fraction of that for trisomy 12q infants from distal 12q translocations. A similar situation is likely to apply to other translocations and demonstrates the importance of assessing risk with reference to the particular translocation involved. Further studies of existing translocation families will allow increasingly accurate counselling of new reciprocal translocations.

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