

Mosaicism for duplication 12q (12q13→q24.2) in a dysmorphic male infant

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Abstract

We report the clinical findings in a boy with mosaicism for a duplication of chromosome 12q13.1→q24.2. His clinical characteristics are very similar to previously reported mosaic duplications of the distal long arm of 12, as well as several cases with non-mosaic duplications. It is proposed that this represents a clinically distinguishable syndrome for 12q duplication, in mosaic or non-mosaic form.

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Structural abnormalities involving the long arm of chromosome 12 and mosaicism for such arrangements have been reported very rarely. It has been proposed that significant alteration of the long arm is likely to be lethal.¹⁻³ We report here a case of mosaicism for the distal portion of 12q (46,XY,dir dup(12)(q13.1→q24.2)) in a male infant with distinct dysmorphic features and congenital heart disease.

Case report

The proband is the first born child of healthy, non-consanguineous parents. The mother has another child, a healthy boy. The mother was 22 years and the father 24 years at the time of the proband's birth.

The proband was delivered normally at term after an unremarkable pregnancy. The Apgar scores were 8 and 9 at one and five minutes. His postnatal course was complicated by poor feeding and the development of congestive heart failure. He was transferred to our hospital on day 4 of life.

On admission, he had a weight of 3660 g (75th centile), a head circumference of 34.5 cm (25th centile), and a length of 51 cm (50th centile). He had a flattened occiput and redundant nuchal skin, flattened facies with a broad, flat nasal bridge, hypertelorism, and upward slanting palpebral fissures. There were no Brushfield spots. His ears were low set and posteriorly rotated with abnormal helical folding. His mouth was down turned. He had widely spaced nipples and a shawl scrotum. He had bilateral single transverse palmar creases and bilateral wide spaces between the first and second toes (fig 1). On neurological examination, he was significantly hypertonic.

Cardiovascular examination showed a heart rate of 150/minute and a respiratory rate of 90/minute with subcostal indrawing and grunting. The blood pressure was 82/50 in the right arm and 55/30 in the right leg. No femoral

pulses were palpable but a good right radial pulse was present. The left radial pulse was diminished. Palpation of the precordium showed an active right ventricle; on auscultation, dual heart sounds and a harsh systolic murmur were heard. Both the liver and spleen were palpable below the costal margins. Clinically, he was in congestive heart failure.

On chest radiograph, there were signs of an enlarged heart and pulmonary venous congestion. The electrocardiogram showed right ventricular and right atrial hypertrophy. A two dimensional echocardiogram showed preductal coarctation of the aorta with a hypoplastic transverse arch, a large muscular apical ventricular septal defect, and a bicuspid aortic valve. The abdominal ultrasound was normal.

At 6 days of age, the child underwent a repair of his coarctation and pulmonary artery banding. His postoperative course was complicated by persistent congestive heart failure and failure to thrive. At 6 weeks of age, he underwent cardiac catheterisation which showed a large apical VSD with a pulmonary band in place and a patent foramen ovale. A large aneurysmal dilatation appeared to be at the site of the aortic patch repair. At 3 months of age, after discharge from hospital, his weight was 3705 g (less than the 3rd centile) and his head circumference was 35.5 cm (less than the 3rd centile). His heart failure was controlled by medication.

When he was examined in the Genetic Outpatient Clinic at 7½ months of age, he was physically well but developmentally delayed by at least two months. He was unable to sit unsupported, but did have good head control, and could roll over. He was smiling and babbling. He was able to grasp objects and transfer them to his mouth. On physical examination, his weight (6 kg) and head circumference (40.5 cm) were less than the 3rd centile, while his length (69 cm) was on the 25th centile. His dysmorphic features were unchanged and he remained hypertonic. On cardiovascular examination, he had a soft, blowing systolic murmur (softer than on previous examinations). The basal second sound was single. Right arm blood pressure was 105/60. He had good femoral pulses. Further cardiac surgery is pending.

CYTOGENETIC STUDIES

Chromosome analysis of cultured lymphocytes with GTG banding showed a 46,XY/46,XY,dir dup(12)(q13.1→q24.2) mosaic karyotype with the 12q+ chromosome in six out of 50 cells (fig 2). A repeat lymphocyte chromosome analysis confirmed these findings with

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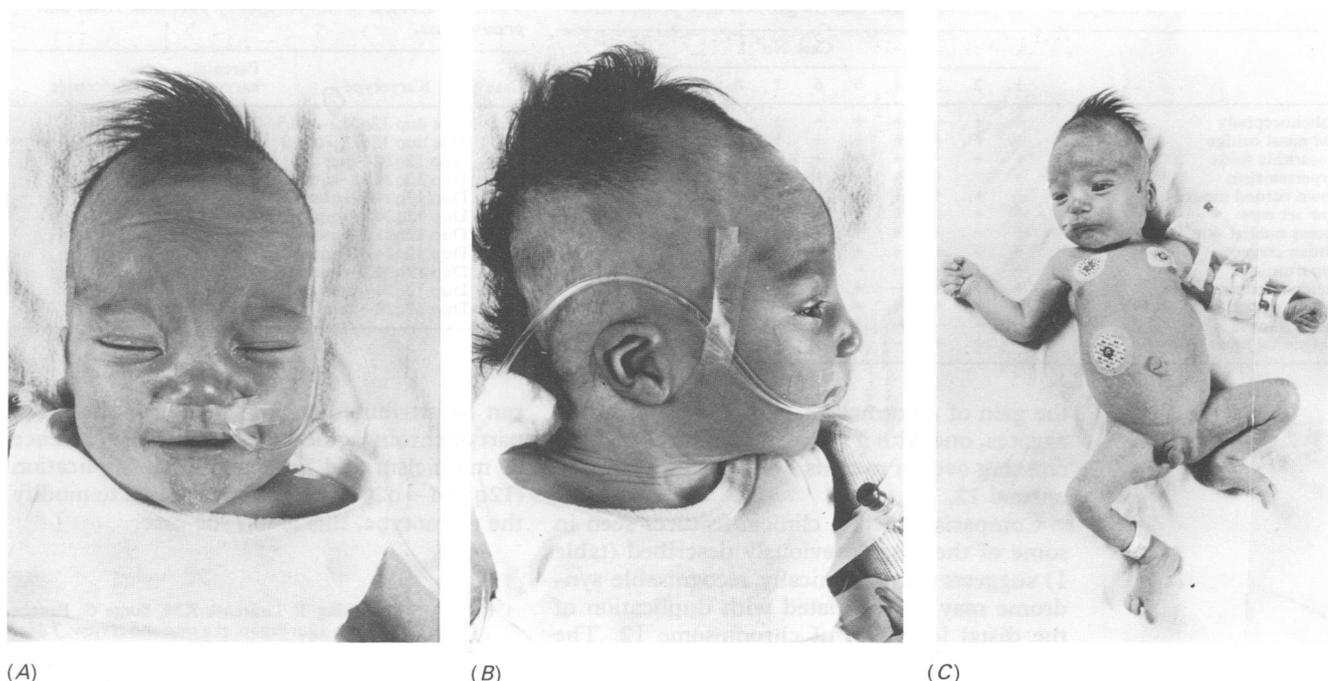


Figure 1 The proband at 5 days of age. (A) Facial view. Note upward slanting palpebral fissures, hypertelorism, broad, flat nasal bridge, and down turned mouth. (B) Lateral view of face. Note low set ears with abnormal helical folding and flattened occiput and forehead. (C) Whole body. Note clenched hands and toes, widely spaced nipples, and shawl scrotum. Toes 1 and 2 are widespread.

mosaicism for the 12q in seven out of 70 (10%) of cells examined. Parental karyotypes were normal.

Discussion

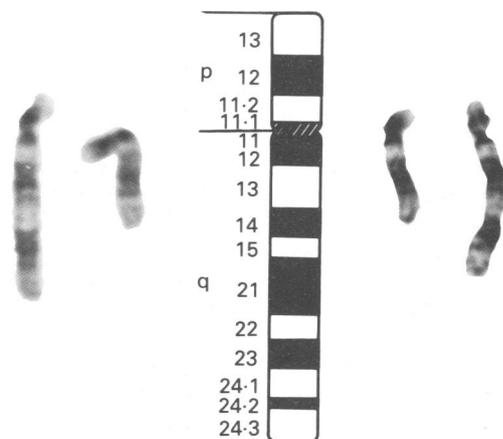
To our knowledge only two previous cases of mosaic duplication for the distal portion of chromosome 12 have been reported.⁴ These involved a breakpoint at 12q24.1. No previous case of mosaic duplication for the larger portion of 12q as represented by this case, that of 12q13.1→q24.2, has been reported.

There has been no report of trisomy 12 in a liveborn to our knowledge, but trisomy 12 has been observed in early embryos.⁵ Also, there are two reports of mosaic trisomy in live-borns.^{5,6} However, these are not entirely con-

vincing as they appear to be associated with a relatively mild phenotype. In one case,⁵ 7% mosaicism for trisomy 12 was associated with infertility in a 31 year old male, as well as situs inversus, chronic sinusitis, and bronchitis. In the second case,⁶ a 36 year old mentally retarded female with equinovarus foot deformity and scoliosis was found to have 13% of lymphocytes mosaic for trisomy 12.

In contrast, there are now several reports of non-mosaic partial duplication of 12q^{1-3,7-12} with the breakpoint most often at 12q24. This breakpoint presumably reflects the extent of deletions/duplications usually permitted and possibly relates to the presence of the heritable fragile site *FRA12C* at 12q24.3.¹³ In a complete review of published reports on translocations involving chromosome 12,¹⁴ 10 of 18 cases involved a breakpoint at or about 12q24, two at 12q21, one at 12q14, three at 12q13, and one each at 12q11 and 12q12.

Reports of direct intrachromosomal duplications are rare but reports of mosaicism for such structural alterations are rarer still.¹⁵ Mosaicism for the direct intrachromosomal duplication found in the patient reported here is thought to have arisen by unequal mitotic crossing over between the near terminal portion of one 12q and the proximal portion of another 12q and the subsequent segregation of the duplicated 12q with a normal chromosome 12.¹⁶⁻¹⁹ The occurrence of mitotic crossing over is well documented in man^{20,21} and unequal crossing over is thought to arise through asymmetry in chromosome pairing involving tandem repeats.²² Other possible mechanisms to explain the chromosomal finding in our patient are as follows: (1) unequal sister chromatid exchange, (2) unequal crossing over at meiosis I with the normal cell line arising postzygotically from the loss of the duplicated 12q and



dir dup (12) (q13-1 → q24-2)

Figure 2 Ideogram of normal chromosome 12 with normal and abnormal (duplicated) chromosomes 12.

Table 1 Review of clinical features of published cases and comparison with present case.

	Case No											
	1	2	3	4	5	6	7	8	9	10	11	12
Dolichocephaly	+	+	-	+	+	-	+	+	+	-	-	-
Flat nasal bridge	+	+	+	+	+	+	+	+	+	+	+	+
Epicanthic folds	+	-	-	+	+	-	-	-	-	+	-	-
Hypertelorism	+	-	+	+	-	+	-	+	+	+	-	-
Down turned mouth	+	+	+	+	+	+	+	+	+	+	+	-
Low set ears	+	+	+	+	+	+	+	+	+	+	+	+
Excess nuchal skin	+	-	+	+	+	+	+	+	-	+	+	+
Simian creases	+	+	+	+	+	+	+	-	+	+	+	+
Hypertonia	+	+	+	-	-	+	-	-	-	-	-	-
Skeletal abnormalities	+	+	-	-	+	+	+	+	+	+	+	+
Widely spaced nipples	-	+	+	+	+	+	-	+	-	+	+	+
Sacral dimple	-	-	-	+	+	+	+	+	+	+	+	+
Congenital heart disease	-	+	+	-	-	+	+	+	+	+	-	-

the gain of a normal 12, and (3) fusion of two zygotes, one with a segregant from an unequal crossing over at meiosis I and the other with a normal 12.

Comparison of the clinical features seen in some of the cases previously described (table 1) suggests that a clinically recognisable syndrome may be associated with duplication of the distal long arm of chromosome 12. The similarity between the mosaic and non-mosaic cases, despite the length of the duplication, would also support this. A review of published photographs of mosaic and non-mosaic cases also confirms the similarities between these patients.^{1-4,6-9,11}

The prominent features seen in the cases with a duplication from 12q24→12qter in a mosaic line⁴ are summarised in table 1. Features in common with our case include the following: a flat nasal bridge, epicanthic folds, hypertelorism, a down turned mouth, low set ears, excess nuchal skin, simian creases, widely spaced nipples, hypertonia, and congenital heart disease (patent ductus arteriosus in one case, coarctation and VSD in our case). However, skeletal deformities (ulnar deviation of the hands in both cases) were not observed in our patient. Parental karyotypes were normal in all parents tested.

When the comparison is extended to cases that are non-mosaic for a 12q duplication,^{1-3,7-12} the clinical similarities persist. Nine recent reports^{3,12} are also presented in table 1. All of these cases were secondary to a parental translocation involving 12q and the last band of another chromosome. The cases, therefore, have a duplication/deletion syndrome (table 2). The deleted portions are very small, and their contribution to the phenotype may be minor. In fact, the features noted are similar: a flat nasal bridge, epicanthic folds, hypertelorism, a down turned mouth, low set ears, excess nuchal skin, simian creases, hypertonia, and widely spaced nipples. In addition, other congenital anomalies in the cardiac, renal, gastrointestinal, skeletal, and central nervous systems have been noted in other cases described.^{1-3,7-12}

In conclusion, there is considerable phenotypic overlap between reported cases and, therefore, a clinically distinct multiple congenital anomalies/mental retardation syndrome

Table 2 Review of karyotypes of published cases and present case.

Case	Karyotype	Parental karyotypes	Reference
1&2	Mos dup 12q24.1→24.5	Normal	4
3	Mos dup 12q13→q24.2	Normal	Present case
4	Dup 12q24→qter	t(11;12)mat	12
5	Dup 12q24.13→qter	t(2;12)pat	3
6	Dup 12q24.3→qter	t(9;12)mat	7
7	Dup 12q24.1→qter	t(2;12)pat	1
8	Dup 12q21.2→qter	t(9;12)mat	2
9	Dup 12q24.31→qter	t(4;12)mat	8
10	Dup 12q24.1→qter	t(4;12)mat	9
11	Dup 12q24→qter	t(12;18)pat	10
12	Dup 12q24→qter	t(12;21)mat	11

can be attributed to duplication of the distal part of chromosome 12. Although the presence of mosaicism and the size of the duplication (12q13.1→q24.2) might be expected to modify the phenotype, this is not the case.

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