

## ELECTRONIC LETTER

# Mosaicism for duplication 12q (12q13→12q21.2) accompanied by a pericentric inversion in a dysmorphic female infant

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*J Med Genet* 2002;39:e72(<http://www.jmedgenet.com/cgi/content/full/39/11/e72>)

While several case reports describe partial trisomy 12qter, reports of interstitial 12q duplications are extremely rare. We present here the clinical findings in a female infant with mosaicism for a duplication of chromosome 12q13.3→12q21.2 accompanied by a pericentric inversion (12)(p13.3q21.2). No other cases with an interstitial duplication for this region have been reported. The female infant has several dysmorphic anomalies but has no symptoms associated with the clinically distinguishable syndrome of 12q duplication.<sup>1</sup> Since the duplication is maternally isodisomic, the rearrangement is most likely of postzygotic origin.

## CASE REPORT

The index patient, a female, is the first child of healthy, non-consanguineous parents with normal family histories. At her birth, the father was 39 years and the mother 35 years old.

Pregnancy and term delivery were normal. Birth weight was 3200 g (75th centile), length 50 cm (50th centile), and OFC 32.5 cm (3rd centile is 33 cm). In addition to the microcephaly, a distinct craniofacial appearance was noted, including antimongoloid position of both eyes with shallow orbits and proptosis, periorbital oedema, trigonocephaly, and large, everted, and poorly lobulated ears (fig 1). Additional findings were accessory nipple on the right, deep sacral sulcus, hypertrophic clitoris with otherwise normal external genitalia, and bilateral metatarsus adductus. No internal malformations were present with normal cardiac and renal imaging. No perinatal or postnatal problems were noted. Now, at the age of 11 months, psychomotor development is mildly retarded (developmental age of 10 months on the Bayley Developmental scale). Weight is 8.7 kg (25th centile), length 75 cm (75th centile), and OFC 41.8 cm (3rd centile is 43 cm).

Cytogenetic studies were performed using PHA stimulated lymphocytes according to standard cytogenetic procedures. High resolution chromosome analysis of lymphocytes showed a mos46,XX/46,XX,der(12)(pter→p13::q22→p13::q21.2→qter). The der(12)(p13q21.2) chromosome was present in approximately 33% of the cells (fig 2). The mother and father have a normal karyotype.

Fluorescence in situ hybridisation (FISH) was performed following standard procedures. FISH studies using subtelomeric probes for 12p (PAC 9015) and 12q (PAC 221K18) confirmed the presence of the inversion (fig 3A).<sup>2</sup> YACs and PACs covering the breakpoint regions were used as FISH probes to



Figure 1 Front view of the face of the child.

delineate the breakpoints further (table 1). The inversion was localised between 12p13.3 (LL12NCO1 4H9A) and 12p13.2 (PAC 50F4 containing *ETV6*) (fig 3B) and between 12q21.1 (PAC 578A9) and 12q21.31 (PAC 530C5) on the q arm. Unexpectedly, in addition to the inversion, an inverted duplication of 12q13.3-12q21 (probes y850H3-PAC 578A9) was detected (fig 3C). The karyotype can thus be written as: mos46,XX/46,XX,der(12)(pter→p13::q13→q21.2::q21.2→p13::q21.2→qter).

DNA polymorphism studies for the duplicated region of chromosome 12 (table 2) were carried out on the patient and both parents. CA repeats, spaced along the chromosome, were amplified by PCR, using a fluorescein-isothiocyanate (FITC) label on one of the primers. The fragments were sized on an ALF DNA sequencer (Amersham Pharmacia Biotech). Primer sequences were as previously published.<sup>3</sup> For markers D12S1691, D12S1585, D12S1722, and D12S1684, the signal intensity was consistently higher for the maternal allele than

Table 1 Clones used in the FISH analysis

Probe location	Probe name	Der(12)
12p13.33 (12pter)	PAC 9015	Normal
12p13.3	LL12NCO1 4H9A	Normal
12p13.2	PAC 50F4 ( <i>ETV6</i> )	Pericentric inv
12q12	y918A6	Pericentric inv
12q13	y850H3	Inv duplicated
12q15	y788E12	Inv duplicated
12q21.1	RPC111-578A9	Inv duplicated
12q21.31	RPC111-530C5	Normal
12q22	y850A12	Normal
12q23.1	y886A6	Normal
12q23.3	y788F12	Normal
12q24.1	y856H2	Normal
12q24.33 (12qter)	PAC 221K18	Normal

## Key points

- We describe a unique case with a pericentric inversion and duplication of chromosome 12 in mosaic form.
- The possible origin is discussed.

**Table 2** DNA polymorphic marker alleles for chromosome 12q13.3-12q15 in the patient and both parents

Marker	Father	Patient	Mother
D12S347	2 1	1 3	3 2
D12S1618	2 3	3 1	1 4
D12S1586	1 3	3 2	2 3
D12S1691	3 4	4 1 1	1 2
D12S1585	2 3	3 2 2	2 1
D12S1722	2 3	3 2 2	2 1
D12S1684	3 1	1 2 2	2 3
D12S1710	2 1	1 3	3 1

for the paternal allele, while for the other markers about similar signal intensities were obtained. The results of this analysis are shown for D12S1684 (fig 4). In general, the amplification of the larger allele is less than the amplification of the shorter allele. However, for D12S1684 the ratio of the peak intensities of the second allele over the first allele is 1.43 in the patient while it is 0.86 in an unrelated control sample with similar haplotype. For markers D12S1691, D12S1585, and D12S1722, the shorter allele was maternal. In markers D12S1585 and D12S1722, the ratio of the shorter allele over the larger was respectively 1.88 and 1.72 in the proband while a ratio of 1.11 and 1.16 was recorded for the father. For marker D12S1691, no accurate ratio could be determined because of the presence of stutter peaks. Hence, the combined results for these markers give evidence for a maternal isodisomy for the duplicated chromosome 12q13→12q21.1 region.

## DISCUSSION

While several reports have described the duplication of the terminal portion of 12q with breakpoint in the 12q21-12q24 region, only two reports have described chromosomal duplication of 12q13-12q21.2.

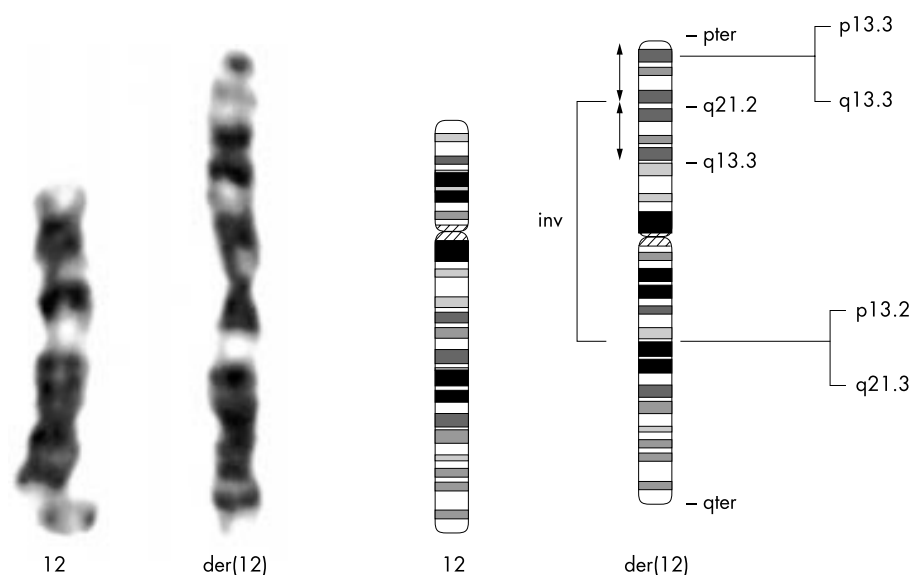
Dixon *et al*<sup>1</sup> described a boy with mosaicism for a duplication of chromosome 12q13.1→12q24.2. The *de novo* direct duplication in mosaic state was assumed from banded karyotypes in a 7 month old male with multiple minor anomalies, a complex cardiac malformation, and developmental delay. The

12q+ chromosome was present in about 10% of the cells. The clinical characteristics of this patient were very similar to other published cases with terminal 12q duplications. In general, trisomy 12q may be characterised by the following clinical features: psychomotor retardation, growth retardation, dolichocephaly, hypertelorism, flat nasal bridge, downturned mouth, micrognathia, low set ears, poor lobulation of the ears, short neck, hypertonia, widely set nipples, sacral dimple, cryptorchidism, and simian crease. These characteristic features are well observed in infants or young cases, but gradually become less noticeable with age in adult cases. Skeletal abnormalities of the extremities may be a characteristic feature in trisomy 12q syndrome also.<sup>4-6</sup> In contrast, our patient shows barely any signs of the 12q duplication syndrome phenotype. Probably the genes causing the 12q duplication phenotype reside at the telomeric end of 12q.

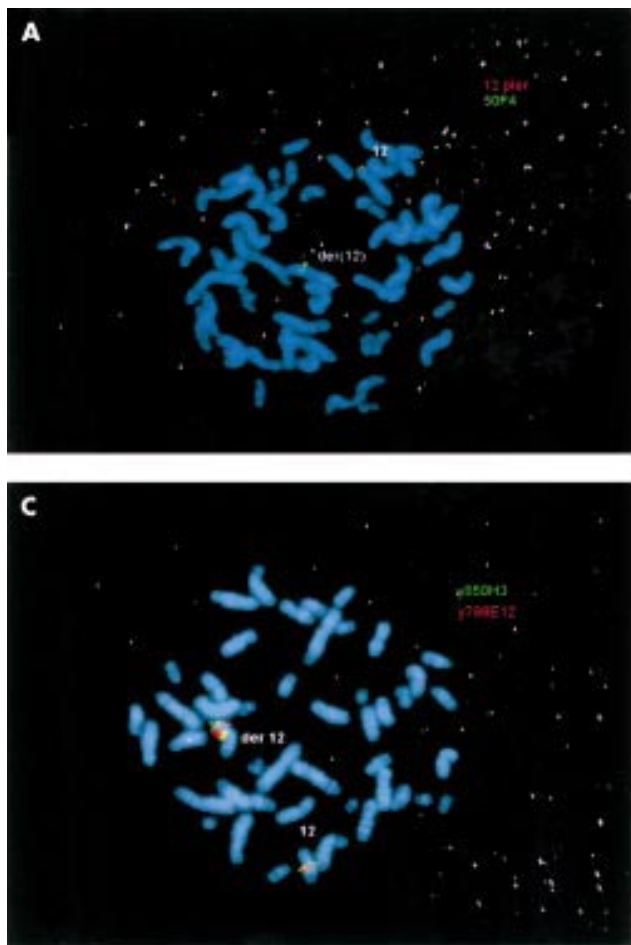
A possible direct duplication dup(12)(q14→12q21) was found in a moderately mentally retarded girl with minor anomalies who developed a malignant intramedullary ependymoma causing death at 12 years 8 months of age.<sup>7</sup> Since none of these dysmorphic features observed in this girl overlaps with the features observed in our patient, we believe that this extra material in 12q might be derived from another chromosomal region.

The 12q duplication syndrome is mainly characterised by duplications in the 12q21-12q24 region. Owing to the rarity of 12q duplications, it has been suggested that significant alteration of the long arm would be lethal, especially duplications of the 12q13→12q21.2 region.<sup>4-6</sup> Both cases with duplication of this region are mosaics. It thus is likely that the duplication of 12q13-21 is viable only in mosaic form and that gene dosage effects of genes in this region cause embryonic lethality.

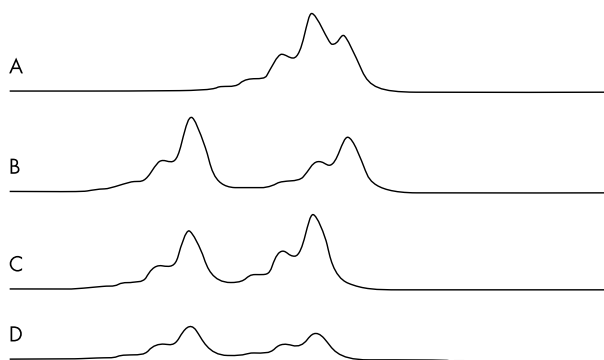
Intuitively, it is often assumed that a single derivative chromosome in mosaics containing a normal cell line and a cell line containing 46 chromosomes with a single rearranged chromosome originated by a postzygotic rearrangement. However, to our knowledge, only six reports have investigated the origin of such chromosomal rearrangements. Contrary to expectation, in three cases the rearrangement was meiotic in origin and was followed by at least two consecutive non-disjunction events, thus generating a normal and an abnormal cell line each containing 46 chromosomes.<sup>8-10</sup> In three others, simple duplications were isodisomic and were suggested to be postzygotic in origin.<sup>11-13</sup> To investigate the



**Figure 2** Partial G banded karyotype showing the normal chromosome 12 (on the left) and the derivative chromosome 12 (on the right). An ideogram of the normal and the derivative chromosome 12 is also shown. The location of the breakpoints is indicated on the right. The bracket represents the inversion. The arrow indicates the inverted duplication.



**Figure 3** FISH analysis showing (A) the inversion with probes from 12pter (PAC 90I5) and qter (PAC 221K18), (B) the pericentric inversion with breakpoints between 12p13.33 (LL12NCO1 4H9A) and 12p13.32 (PAC 50F4), and (C) the inverted duplication with probes from 12q13 (y850H3) and 12q15 (y788E12).



**Figure 4** Polymorphism analysis on D12S1684 in (A) the mother, (B) father, (C) the proband, and (D) an unrelated control patient with the same haplotype as the proband.

mechanism of the rearrangement, we investigated the parental origin of the duplication. We show that the rearrangement in this patient is also most likely a postzygotic event since the duplication is maternally isodisomic. The duplication might have arisen by unequal mitotic crossing over and subsequent segregation of the duplicated 12q with a normal chromosome. The cell line with a deletion of this 12q region would have been eliminated. The duplication event would then be followed by a pericentric inversion. However, it is difficult to envisage how the duplication during a mitotic crossing over would be accompanied by a pericentric inversion. The other possible mechanism to explain the chromosomal finding in this patient is by an unequal sister chromatid exchange. Pos-

sibly, the unequal sister chromatid exchange was accompanied by the pericentromeric inversion in a single event.

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#### REFERENCES

- Dixon JW, Costa T, Teshima IE. Mosaicism for duplication 12q (12q13→q24.2) in a dysmorphic male infant. *J Med Genet* 1993;**30**:70-2.
- Flint J, Wilkie AO, Buckle VJ, Winter RM, Holland AJ, McDermid HE. The detection of subtelomeric chromosomal rearrangements in idiopathic mental retardation. *Nat Genet* 1995;**9**:132-40.
- Dib C, Faure S, Fizames C, Samson D, Drouot N, Vignal A, Millasseau P, Marc S, Hazan J, Seboun E, Lathrop M, Gyapay G, Morissette J, Weissenbach J. A comprehensive genetic map of the human genome based on 5,264 microsatellites. *Nature* 1996;**380**:152-4.
- Roberts SH, Mattina T, Laurence KM, Sorge G, Pavone L. Partial trisomy 12q: report of a case and review. *J Med Genet* 1981;**18**:470-3.
- Pratt NR, Bulugahapitiya DT. Partial trisomy 12q: a clinically recognisable syndrome. Genetic risks associated with translocations of chromosome 12q. *J Med Genet* 1983;**20**:86-9.
- Tengstrom C, Wilska M, Kahkonen M, Autio S, Leisti J. Partial trisomy 12q: clinical and cytogenetic observations. *Clin Genet* 1985;**28**:112-17.
- Neville BGR, Berry AC, Stoddart Y. A case of malignant spinal cord ependymoma in association with a duplication of part of the long arm of chromosome 12. *J Med Genet* 1985;**22**:154.
- Blouin JL, Aurias A, Creau-Goldberg N, Apiou F, Alcaide-Loridan C, Bruel A, Prieur M, Kraus J, Delabar JM, Sinet PM. Cytogenetic and molecular analysis of a de novo tandem duplication of chromosome 21. *Hum Genet* 1991;**88**:167-74.
- Gratacos M, Nadal M, Martin-Santos R, Pujana MA, Gago J, Peral B, Armengol L, Ponsa I, Miro R, Bulbena A, Estivill X. A polymorphic

- genomic duplication on human chromosome 15 is a susceptibility factor for panic and phobic disorders. *Cell* 2001;**106**:367-79.
- 10 **Schinzel A**, Kotzot D, Brecevic L, Robinson WP, Dutly F, Dauwerse H, Binkert F, Baumer A, Ausserer B. Trisomy first, translocation second, uniparental disomy and partial trisomy third: a new mechanism for complex chromosomal aneuploidy. *Eur J Hum Genet* 1997;**5**:308-14.
  - 11 **Kotzot D**, Schinzel A. Paternal meiotic origin of der(21;21)(q10;q10) mosaicism [46,XX/46,XX,der(21;21)(q10;q10),+21] in a girl with mild Down syndrome. *Eur J Hum Genet* 2000;**8**:709-12.
  - 12 **Faivre L**, Viot G, Prieur M, Turleau C, Gosset P, Romana S, Munnich A, Vekemans M, Cormier-Daire V. Apparent Sotos syndrome (cerebral gigantism) in a child with trisomy 20p11.2-p12.1 mosaicism. *Am J Med Genet* 2000;**91**:273-6.
  - 13 **Rauen KA**, Cotter PD, Bitts SM, Cox VA, Golabi M. Cardio-facio-cutaneous syndrome phenotype in an individual with an interstitial deletion of 12q: identification of a candidate region for CFC syndrome. *Am J Med Genet* 2000;**93**:219-22.