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. Since the duplication is maternal 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 → p13.3::q13 → q21.2::q21.2 → 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 90I5) and 12q (PAC 221K18) confirmed the presence of the inversion (fig 3A). YACs and PACs covering the breakpoint regions were used as FISH probes to 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→p13.3::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.

### Table 1 Clones used in the FISH analysis

<table>
<thead>
<tr>
<th>Probe location</th>
<th>Probe name</th>
<th>Der(12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12p13.33 (12ppter)</td>
<td>PAC 90I5</td>
<td>Normal</td>
</tr>
<tr>
<td>12p13.3</td>
<td>LL12NCO1 4H9A</td>
<td>Normal</td>
</tr>
<tr>
<td>12p13.2</td>
<td>PAC 50F4 (ETV6)</td>
<td>Pericentric inv</td>
</tr>
<tr>
<td>12q12</td>
<td>y918A6</td>
<td>Pericentric inv</td>
</tr>
<tr>
<td>12q13</td>
<td>y850H3</td>
<td>Inv duplicated</td>
</tr>
<tr>
<td>12q15</td>
<td>y788E12</td>
<td>Inv duplicated</td>
</tr>
<tr>
<td>12q21.1</td>
<td>RPC11-578A9</td>
<td>Inv duplicated</td>
</tr>
<tr>
<td>12q21.31</td>
<td>RPC11-530C5</td>
<td>Normal</td>
</tr>
<tr>
<td>12q22</td>
<td>y850A12</td>
<td>Normal</td>
</tr>
<tr>
<td>12q23.1</td>
<td>y886A6</td>
<td>Normal</td>
</tr>
<tr>
<td>12q23.3</td>
<td>y788F12</td>
<td>Normal</td>
</tr>
<tr>
<td>12q24.1</td>
<td>y850H2</td>
<td>Normal</td>
</tr>
<tr>
<td>12q24.33 (12qter)</td>
<td>PAC 221K18</td>
<td>Normal</td>
</tr>
</tbody>
</table>
for the paternal allele, while for the other markers about simi-
lar signal intensities were obtained. The results of this analy-
sis are shown for D12S1684 (fig 4). In general, the amplifica-
tion 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 D12S1581, 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 12q13.3–12q15 in the patient and both
parents.

### Table 2

DNA polymorphic marker alleles for chromosome 12q13.3–12q15 in the patient and both parents

<table>
<thead>
<tr>
<th>Marker</th>
<th>Father</th>
<th>Patient</th>
<th>Mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>D12S347</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>D12S1618</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>D12S1586</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>D12S1691</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>D12S1585</td>
<td>3</td>
<td>3</td>
<td>2.2</td>
</tr>
<tr>
<td>D12S1722</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>D12S1684</td>
<td>3</td>
<td>1</td>
<td>2.2</td>
</tr>
<tr>
<td>D12S1710</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

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 dupli-
cation of 12q13–12q21.2.

Dixon et al. 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 karyo-
types 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 gen-
eral, trisomy 12q may be characterised by the following clini-
ical 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, crypto-
orchidism, 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. 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. 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 altera-
tion of the long arm would be lethal, especially duplications of
the 12q13→12q21.2 region. 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 chro-
mosome 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. In three
others, simple duplications were isodisomic and were
suggested to be postzygotic in origin. To investigate the

![Figure 2](image-url)
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. Possibly, the unequal sister chromatid exchange was accompanied by the pericentromeric inversion in a single event.

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

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