Mosaicism for a tandem duplication dup(1)(q11q22) in an 18 year old female

Deepthi de Silva, Doreen Massie, John Drummond, David Couzin, John C S Dean

Abstract
The clinical features and cytogenetic results of an 18 year old mentally handicapped female found to be a mosaic for a tandem duplication of chromosome 1 (46,XX,dup(1)(q12q22)/46,XX) are reported. The case is compared with the three previously described cases and possible mechanisms for the origin of the duplication are discussed. This patient was not found to have features of Proteus syndrome which was previously reported in a subject mosaic for a tandem duplication involving chromosome 1 (q11q25).

Keywords: tandem duplication; dup(1)(q12q22); mosaicism

Duplications involving chromosome 1 (q11q22) are rare, only three cases having been published. The previously reported cases consist of an 11 month old male infant with an inverted duplication of chromosome (1)q22q11,1 a 3 year old female with mosaicism of a direct duplication of chromosome (1)(q11q25),2 and a child with mosaicism for a direct duplication of chromosome (1)(q12q23).3 We report the case of an 18 year old mentally handicapped woman with dysmorphic features who was found to be chromosomally mosaic in blood for a de novo tandem duplication of part of the long arm of chromosome 1 (46,XX,dup(1)(q12q22)).

Case report
The proband was the first child of healthy, unrelated, Scottish parents, the father aged 28 years and the mother aged 30 years. The pregnancy was complicated by intrauterine growth retardation and breech presentation. She was born at term by elective caesarean section. Apgar scores were 2, 8, and 9 at one, five, and 10 minutes respectively. At birth she weighed 2480 g (3rd centile), occipitofrontal circumference (OFC) was 33.3 cm (25th-50th centile), and the crown-heel length was 46 cm (3rd centile). Medical records from the neonatal period indicate that she was noted to have micrognathia, microphthalmia, and a high palate. Feeding was poor and at the age of 6 months a gastrostomy was formed and feeding continued through this route until the age of 13 months, when the proband was able to take semi-solid foods. A barium meal performed before the gastrostomy had suggested neuromuscular incoordination of the oesophagus. A CT scan of the brain also performed at the age of 6 months showed slight atrophy of the brain, enlargement of the ventricles, and prominent basal cisterns. Aged 6 months, she underwent tenotomies for treatment of bilateral dislocation of the hips.

Developmental assessment performed at the age of 2.5 years confirmed severe development delay with gross and fine motor function at the 1 year level and verbal comprehension at the 9 month level. She had very poor expressive language. Aged 3 years 11 months, she developed febrile convulsions for which she was initially started on phenobarbital and later this was changed to carbamazepine. An EEG performed at the age of 5 months was reported as being normal but a repeat examination at 6 years indicated early bilateral paroxysmal discharges associated with right sided slow spike discharges. At reassessment aged 15 years, she was found have an advanced bone age associated with short stature.

She was referred to the Genetic Clinic at the parents’ request for further information regarding the possible aetiology of her mental handicap. On examination at the age of 18 years 5 months, she was found to be a placid, friendly girl. Her height was 143.5 cm (<<3rd centile), weight 35.6 kg (<<3rd centile), and OFC 52.1 cm (3rd centile). She had a rounded, puffy face and a prominent nose with thickened nostrils and broad nasal tip (fig 1A, B). She had narrow palpebral fissures associated with epicanthic folds. The skull shape was normal and her hair was thick and curly. The fingers were thin, spindly, and hyperextensible and both hands and feet were cold in spite of normal peripheral pulses (fig 1C, D). The feet were small and pes cavus was noted bilaterally (fig 1D). She also had a thoracic scoliosis, fixed flexion deformities of both knees, and a short neck. Cardiovascular and abdominal examination were normal and no focal neurological deficit was noted. She was able to comprehend simple commands and communicate to a limited extent using a combination of makaton and signs. Her carers report that she was continent during the day and that she had a tendency to be constipated. Her menarche was at the age of 17 years.

Karyotype analysis as a neonate was initially reported as normal but at the age of 6 months a repeat analysis showed additional chromosome material on chromosome 1. Repeat karyotype at the age of 8 years confirmed this. Aged 18, lymphocyte chromosomes were reanalysed and the extra material was confirmed to be a direct duplication of chromosome 1 (dup(1)(q12q22)) based on G and C banding (fig 2). Whole chromosome painting confirmed that the duplication consisted only...
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Figure 1 (A, B) Anterior and lateral view of the proband (photographs reproduced with permission). Note round face, prominent nose, and narrow palpebral fissures. (C, D) Hands and feet of the proband. Note thin fingers and toes and pes cavus.

of chromosome 1 material. This karyotype also showed around 10% of the cells to have a normal 46,XX karyotype, which had not been noted previously. The parental karyotypes were normal.

Discussion

Consistent clinical features of patients with duplications involving chromosome (1) (q11q22) are difficult to assess in view of the rarity of the findings, the mosaicism noted in 3/4 reported cases, the variation in ages of the reported cases, and the lack of photographs in two of the publications. In spite of this, some features appear to be present in more than one of the patients described (table 1) and are likely to be features associated with the duplication. Severe psychomotor retardation was noted in all four cases and three had postnatal growth retardation. Other reported features included micrognathia and cleft or high arched palate (4/4), scoliosis (3/4), narrow shoulders, and thin fingers (2/4). Two of the cases had required gastrostomy feeding related to oesophageal reflux and neuromuscular incoordination. Central nervous system anomalies were present in all four cases, although these
### Table 1  Summary of features

<table>
<thead>
<tr>
<th>Feature Type</th>
<th>Merens et al(^\text{1}) (male, 11 mth)</th>
<th>Say and Carpenter(^\text{2}) (female, 18 y)</th>
<th>Germain-Lee et al(^\text{3}) (female, 11 y)</th>
<th>Present case(^\text{4}) (female, 18 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotype</td>
<td>inv dup 1(q22q11)</td>
<td>dir dup 1(q12q23)</td>
<td>dir dup 1(q12q23)</td>
<td>dir dup 1(q12q23)</td>
</tr>
<tr>
<td></td>
<td>100% in lymphocytes and fibroblasts</td>
<td>78% lymphocytes</td>
<td>90% lymphocytes</td>
<td></td>
</tr>
<tr>
<td>Perinatal asphyxia</td>
<td>Mild asphyxia</td>
<td>Mild asphyxia</td>
<td>Mild asphyxia</td>
<td></td>
</tr>
<tr>
<td>Growth parameters</td>
<td>Normal</td>
<td>Not recorded</td>
<td>Not recorded</td>
<td></td>
</tr>
<tr>
<td>(birth)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeding problems</td>
<td>Not recorded</td>
<td>Severe</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>Omphalocele</td>
<td>Optic nerve bilateral coloboma</td>
<td>Intestinal malrotation</td>
<td></td>
</tr>
<tr>
<td>Dysmorphic features</td>
<td>Cleft soft palate</td>
<td>Cavernous haemangioma</td>
<td>Cleft palate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Micrognathia</td>
<td>Micrognathia</td>
<td>Micrognathia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Narrow palpebral fissures</td>
<td>Depressed nasal bridge</td>
<td>Narrow palpebral fissures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prominent nose</td>
<td>Hemihypertrophy of face and forehead</td>
<td>Prominent nose with broad tip</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low set ears</td>
<td>Left leg short</td>
<td>Pes cavus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Excess skin folds in ears</td>
<td>Long neck</td>
<td>Short neck</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thin fingers</td>
<td>Thoracolumbar kyphoscoliosis</td>
<td></td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>Asymmetry of pos fossa</td>
<td>Increased OFC; weight and length normal</td>
<td>Increased OFC; weight and length normal</td>
<td></td>
</tr>
<tr>
<td>Postnatal growth</td>
<td>Severe growth retardation</td>
<td>Persistent cavitum pelliculium</td>
<td>Psychomotor retardation</td>
<td></td>
</tr>
<tr>
<td>Development</td>
<td>Psychomotor retardation</td>
<td>Absent speech; delayed cognitive function</td>
<td>Absent speech; severe psychomotor delay</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Immune deficiency</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

were not identical. The dysmorphic features in the infant reported by Merens et al\(^{1}\) (whose photographs were published), including micrognathia, narrow palpebral fissures, prominent nose, and rounded face, appear similar to the adult reported here.

The 3 year old patient reported by Say and Carpenter\(^{2}\) had right sided hemihypertrophy of the face and forehead, multiple cavernous haemangiomata, and macrocephaly, suggestive of Proteus syndrome. These findings have led to the suggestion that the locus for the Proteus syndrome gene or genes may be within the (1)(q11q25) region or that the duplication may result in a phenocopy of the Proteus syndrome. No features suggestive of Proteus syndrome were present in the other reported cases. Cohen,\(^{3}\) in his review of Proteus syndrome, reiterated the hypothesis of Haple\(^{7}\) that this disorder is the result of a somatic mutation which is lethal in the non-mosaic state. The Proteus phenotype could be the result of a dosage effect or altered expression of a gene within the duplicated region. The absence of the Proteus phenotype in all the other reported cases may suggest that the critical gene or region may be within chromosome (1)(q23q25), which was duplicated in the case of Say and Carpenter\(^{2}\) only, or the result of mosaicism for the duplication within different tissues. Alternatively, the duplication in the patient reported by Say and Carpenter\(^{2}\) may be a coincidental finding.

The child reported by Germain-Lee et al\(^{3}\) was found to have an obstructive cardiomyopathy, Wolff-Parkinson-White syndrome, and selective immune deficiency with an impaired response to polysaccharide antigens, although none of the other cases are reported to have had these features. It is possible that these immunological and cardiac findings are coincidental or inherited as separate traits (no paternal family).

There are a variety of possible mechanisms by which chromosomal duplication may occur in either pre- or postzygotic cells. Reciprocal translocations between homologous chromosomes involving noticeably different break-points and unequal sister chromatid exchanges (SCEs) may be the most likely mechanisms. Less likely would be three break insertional translocations. These mechanisms would be expected to result in two cell lines, one with a duplicated chromosome and one with the corresponding deleted chromosome. For most localities of the genome, this would be expected to result in strong selective pressure against the deleted cell line.

It may be reasonable to suggest that a distinction between post- and prezygotic events could be made by the presence or absence, respectively, of a karyotypically normal cell line. However, a rescue mechanism involving loss of the abnormal chromosome followed by non-disjunction of the normal homologue or chimerism may also account for the normal cell line in our patient. Molecular investigations to confirm the likely origin of the duplication have not been performed in this case. Blouin et al\(^{4}\) reported a tandem duplication of chromosome 21 where 10% of the cells had a normal karyotype and where molecular studies indicated a prezygotic origin for the duplication, although the origin of the normal cell line could not be elucidated.

In the three cases of duplicated chromosome 1 cited here, only one of them\(^{1}\) was not associated with a normal cell line. In two cases the majority of cells had the duplicated karyotype, while in the case of Say and Carpenter\(^{2}\) there was a sizeable minority of cells with the duplicated karyotype in both lymphocytes (39%) and fibroblasts (42%). Even in the case of Blouin et al\(^{4}\) with a duplicated chromosome 21, the normal cell line represented only 10% of the lymphocytes. A postzygotic event, such as translocation or unequal SCE, might be expected to be initially associated with a higher proportion of normal cells which might increase through selection. The explanation of the high frequency of normal cells in our patient and the others discussed above may be chimerism, a rescue or reversion event in later embryogenesis, or the partitioning of the normal cells mainly to unexamined extrafetal tissue (which accounts for the majority of early embryonic cells). Patients with
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small numbers of abnormal cells with this duplication may have been missed, resulting in ascertainment bias. The mosaicism may also be the basis for the variability of the phenotype in the reported cases.

No cell line is available from the patient. As it was not clinically indicated, we have not examined other tissues for the chromosome duplication.

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