Detection of a de novo duplication of 1q32-qter by fluorescence in situ hybridisation in a boy with multiple malformations: further delineation of the trisomy 1q syndrome

Hans-Christoph Duba, Martin Erdel, Judith Löffler, Lothar Bereuther, Helmut Fischer, Barbara Utermann, Gerd Utermann

Abstract
We report a dysmorphic boy with a de novo partial trisomy 1q. The boy has microcephaly, bilateral cleft lip and palate, low set and dysmorphic ears, brain anomalies, pulmonary stenosis, duodenal obstruction, dysplastic kidneys, and bifid thumbs. The trisomic segment 1q32-qter is duplicated with an inverted insertion at 1p36.3. The aberration was initially detected at amniocentesis and confirmed and defined by GTG banding, chromosome microdissection, and FISH on postnatal blood samples. The parents had normal karyotypes. De novo partial duplications of chromosome 1q have rarely been reported. Comparison of our patient with other published trisomy 1q cases showed similarities which allowed the further delineation of the trisomy 1q syndrome.

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Keywords: partial trisomy 1q32-qter; FISH; reverse painting.

Trisomy 1q is a rare condition. In three recent reports clinical similarities and differences between patients with duplications of the long arm of chromosome 1 have been discussed and the cases published so far reviewed. The reported cases of partial trisomy 1q include trisomies of all segments of the q arm of chromosome 1 (1q21-qter), but most consist of trisomy 1q32-qter1–8 and 1q42-qter. Frequently, however, they are accompanied by other chromosome aberrations which have made the definition of a phenotype difficult.1–24 De novo duplications without another chromosome aberration appear to be rare since only three cases with pure trisomy 1q of the (1)(q32-qter) segment have been published.25–27 Here we describe a patient who has a duplication of the 1q32-qter segment, which is inserted at the terminal end of the short arm of the same chromosome in an inverted orientation. Our patient confirms the previously described features of trisomy 1q and allows further delineation of the associated syndrome. Diagnosis of the trisomic segment based on pure cytogenetic methods would have been difficult without the use of a chromosome paint, microdissection with reverse painting, a telomere 1q probe, and a terminal 1p probe. Therefore this case illustrates the significant diagnostic value of FISH in cases where the parental chromosomes are normal or not available.

Materials and methods

CASE REPORT
The proband is the second child of a 30 year old mother and a 29 year old father. In the 30th week of gestation amniocentesis was performed because of hydramnios, a vitium cordis, and suspected renal agenesis and gastrointestinal obstruction on ultrasound. The boy was born at 37 weeks of gestation by caesarean section (weight 2600 g, length 45 cm, head circumference 36.5 cm, Apgar 4–8–8). The following dysmorphic features were observed on physical and clinical examination after birth (fig 1): hydrocephalus, an asymmetrical skull, wide sutures and large fontanelles, a prominent forehead, and dilatation of the lateral ventricles and the frontal and temporal subarachnoid space. There were also low set, posteriorly rotated, anteverted ears, abnormal helix and antihelix, hypoplastic lobes, tragus, and antitragus, and sensory hearing loss, as well as blepharophimosis, congenital ptosis, sparse eyelashes, downward slanting palpebral fissions, bilateral hypoplasia of the papilla of the optic nerve, and alternating divergent strabismus. He had a broad, beaked, pointed nose with a flat nasal bridge, bilateral cleft lip and palate, oesophageal stenosis, tracheal stenosis, tracheomalacia, pulmonary stenosis, atrial septum aneurysm, tricuspid insufficiency, duodenal obstruction and malrotation, widely spaced nipples, 13 pairs of ribs, multicystic dysplastic left kidney, dysplastic right kidney, a mal-descended testis, hypospadias and phimosis, bilateral preaxial polydactyly (bifid thumbs as a result of duplication of the terminal phalanx), and long and overlapping toes (IV over V).

Fig 2 shows the boy at the age of 18 months. Surgery for the duodenal atresia, cleft lip, phimosis, and hypospadias was done within the first seven months. A tracheostomy was performed after two months. Whereas at birth the somatic data were in the normal range his development was delayed at the age of 18 months (weight 6380 g = <3rd centile, length 69 cm = <3rd centile, head circumference 42.5cm = <3rd centile). At the last follow up at
the age of 46 months examination showed a microcephalic boy with extreme developmental delay with all measurements far below the 3rd centile (weight 8440 g = <3rd centile, length 78 cm = <3rd centile, head circumference 46.5 cm = <3rd centile). From birth the boy has suffered from functional vomiting, recurrent aspirations, and recurrent infections of the respiratory, digestive, and urogenital tracts. Because of an uncorrected cleft palate and oesophageal stenosis the boy suffers from dysphagia and needs tube feeding. His vision and hearing are impaired and an examination at the department of development and movement disorders showed extreme psychomotor and mental retardation.

**CYTOGENETICS**

The first cytogenetic examination was performed on cultured amniocytes obtained by amniocentesis in the 30th week of gestation. The cells were harvested by the flask method and GTG and QFQ banded according to Benn and Pearle. After birth chromosomes of the proband and his parents were prepared from peripheral lymphocyte cultures using a modification of the synchronisation method of Yunis. High resolution banding was performed by treatment with trypsin followed by staining with Giemsa to obtain a GTG band pattern (fig 3). No cell line is available.

**FISH ANALYSIS AND MICRODISSECTION**

Metaphase spreads were prepared from PHA stimulated lymphocytes using the standard 3:1 (v/v) methanol:acetic acid fixation. Slide treatment and hybridisation was performed according to the protocol of Lichter and Cremer with minor modifications. A paint specific for chromosome 1 (AGS, Germany), a telomere 1q probe (D1S555, Oncor, USA), and a terminal chromosome 1 midisatellite probe (D1Z2, Oncor, USA) were applied to the metaphase spreads according to the manufacturer's specifications. Five p arm fragments of the aberrant chromosome 1 were microdissected, amplified by DOP-PCR, and hybridised to normal control metaphases according to the protocol described by Müller-Navia et al.

**Results**

Analysis of chromosomes from amniocytes showed additional unknown material on the short arm of one chromosome 1. The karyotype was 46,XY,add(1)(p36.3) (fig 3). Hybridisation with a chromosome 1 specific paint also hybridised to the additional segment on chromosome 1 (fig 4). Hybridisation with the telomere 1q probe showed a signal on the q arm of the normal chromosome 1 and a signal on both ends of the aberrant chromosome 1 (fig 5). Hybridisation with the terminal chromosome 1 midisatellite probe showed a signal on the p arm of the normal and of the aberrant chromosome 1 (fig 6). Reverse painting with the amplified p arm fragment of the aberrant chromosome 1 showed a hybridisation signal on the p arm and on the end of the q arm of chromosome 1 (fig 7). In combination with analysis of GTG banded high resolution prometaphase chromosomes, the trisomic area was defined as 1q32-qter. This region is duplicated and inverted at 1p36.3. The final karyotype therefore is 46,XY,inv ins dup(1)(p36.3qter-q32). The parental karyotypes were normal.

**Discussion**

For most chromosomal derivatives, GTG banded high resolution chromosomes produce a banding pattern sufficient for chromosome
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In our case it was difficult to make a definitive assignment of the trisomic area to chromosome 1. Only the combined use of (1) a whole chromosome paint, (2) a telomere probe, (3) a midisatellite probe, and (4) microdissection with reverse painting was sufficient for unequivocal identification of the extra chromosomal material and for diagnosing the aberration as inv ins dup(1)(p36.3qter-q32). The case presented here underlines the importance of combining different FISH methods for the identification of unknown chromosome segments, especially if the parents' chromosomes are normal or not available. By chromosome painting with a whole chromosome paint, the origin of the additional material could be determined and, subsequently, the exact assignment of the unknown chromosomal material to a defined chromosomal region was done by reverse painting with

Figure 3  G banded partial karyotype of proband showing normal (a, c) and duplicated (b, d) chromosome and ideogram of chromosome 1 with arrows indicating the breakpoints at p36.3 and q32 and the duplicated segment q32-qter.

Figure 4  Identification of 1p+ material as derived from chromosome 1 by FISH with a chromosome 1 paint.

Figure 5  (A) Identification of duplicated material on chromosome 1 by FISH with telomere 1q probe showing normal chromosome 1 with one FITC signal at qter (single white arrow) and duplicated chromosome 1 with two FITC signals (two white arrows) at qter and duplicated 1q segment at p arm. (B) Grey scaled DAPI image of the same metaphase showing qter of normal chromosome 1 (single black arrow) and terminal ends of duplicated chromosome 1 (two black arrows).

Figure 6  Hybridisation with terminal chromosome 1 midisatellite probe (D1Z2, Oncor, USA), showing a signal on both chromosomes 1.
Table 1 Clinical findings in patients with pure trisomy 1q32-qter

<table>
<thead>
<tr>
<th></th>
<th>Our case</th>
<th>Clark et al</th>
<th>Steffenson et al</th>
<th>Flatz and Fonatsch</th>
<th>Cases with trisomy 1q32-qter</th>
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<tbody>
<tr>
<td>Low birth weight</td>
<td>–</td>
<td>+</td>
<td>+</td>
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<td>Wide sutures and fontanelles</td>
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<td>Prominent, wide forehead</td>
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<tr>
<td>Downward slanting palpebral fissures</td>
<td>+</td>
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<td>Small palpebral fissures</td>
<td>+</td>
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<td>Broad, flat nasal bridge</td>
<td>+</td>
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<td>+</td>
<td>–</td>
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<tr>
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<td>+</td>
<td>–</td>
<td>+</td>
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</table>

+ = presence of a symptom, − = absence of a symptom or not mentioned in the clinical description.

Figure 7 Reverse painting on a normal control metaphase with microdissected and amplified fragments of the p arm of the aberrant chromosome 1, showing a signal on the whole p arm and the 1q32-qter region (white arrows).

microdissected fragments. Probes from telomeric and terminal regions proved the integrity of the terminal arms of the chromosome investigated.

Most previously reported cases with trisomy 1q show trisomy 1(q32-qter) or trisomy 1(q142-qter), frequently with additional chromosomal aberrations.1–20 Abnormalities which are regularly found in trisomy 1q cases include low birth weight, wide sutures and fontanelles, prominent, wide forehead, downward slanting and small palpebral fissures, broad, flat nasal bridge, pointed and beaked nose, low set, posteriorly rotated, and malformed ears, cardiopathies, urogenital abnormalities, abnormal fingers and toes, and delayed development. Cases of trisomy 1q spanning 1q32-qter without involvement of another chromosome have been described by Steffenson et al20 and Flatz and Fonatsch.20 They show a tandem duplication of 1q32-qter. The patient of Clark et al27 and our case also have a pure duplication of the 1q32-qter region, though with a different position within the chromosome. Table 1 lists the relevant clinical characteristics of trisomy 1q32-qter cases and their presence/absence in the four cases with pure trisomy 1q32-qter and cases with trisomy 1q42-qter. These features are also found in patients with trisomy 1q42-qter,1–2,17–24 which can be expected to share features with trisomy 1q32-qter. However, not all patients with trisomy 1q42-qter have these signs and no cases with pure trisomy 1q42-qter have been published. Therefore it is unclear whether and which clinical features are caused by the trisomy 1q42-qter in these patients. Clinical features which are shared by at least three of the patients with pure trisomy 1q32-qter are low birth weight, wide sutures and fontanelles, prominent, wide forehead, small palpebral fissures, broad, flat nasal bridge, low set, posteriorly rotated, and malformed ears, cardiopathies, urogenital abnormalities, and abnormal fingers or toes or both. Since the three previously described cases together with the case presented here share a single duplication of 1q32-qter, the phenotype cannot be attributed to another chromosome aberration, for example to a monosomic segment of another chromosome. Although the extent of the clinical descriptions is different in the reported cases, which makes comparison difficult, we conclude that the characteristics shared by at least three of these four patients represent abnormalities which define a specific trisomy 1q32-qter syndrome. A gene which is associated with the 1q32 segment is the gene for Van Der Woude syndrome (VWS) (OMIM 119300). Patients with VWS show cleft lip and palate. This suggests that the VWS gene may contribute to the phenotype found in our patient.

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