Trisomy 1q24→1q41 in two sibs with an insertion in an inverted chromosome 4

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SUMMARY We report two patients whose karyotype revealed an additional segment 1q inserted into an inverted chromosome 4. The patients were partially trisomic for the region 1q24→1q41, karyotype 46,XY or XX, inv ins(4;1)inv(4)(q28;q24q41)(p15·3q28), while in the mother the chromosomal aberration was balanced. The inserted segment was inverted.

In six patients from three other families with insertions, the segment 1q25→1q32 was inserted into the short arm of chromosome 1. In another patient, the segment 1q25→1q42 of the mother was inverted and inserted into the long arm of chromosome 6. These findings suggest an increased susceptibility for a segment of the long arm of chromosome 1 to be inserted and inverted in rearrangements.

The ability to recognise small chromosomal abnormalities has resulted in improved delineation of clinical syndromes. Trisomy for the interstitial segment 1q25→1q32 has been reported in seven cases resulting from a familial intrachromosomal insertion.¹⁻⁴ We report here two patients whose karyotype revealed an additional segment 1q inserted in an inverted chromosome 4. The clinical picture of the patients with trisomy 1q25→1q32 is fairly consistent, allowing delineation of a syndrome which includes a characteristic facies with a markedly receding chin, flexion of the proximal interphalangeal joint of the fingers, and congenital heart defects.

Case reports

The proband, who was the fifth child of a 32 year old mother and a 35 year old father, weighed 1300 g and had a head circumference of 29 cm at birth (at 32 weeks' gestation). He had a broad, flat nasal bridge, narrow palpebral fissures, and microphthalmia. The ears were small, low set, and posteriorly rotated with thin, downward folded superior helices. The mouth was small and the palate was arched. The patient had seizures and frequent periods of apnoea and cyanosis. Meningitis was detected. The patient died at 36 hours. Culture of his nasotracheal mucous and CSF grew *Listeria monocytogenes*. Chromosome studies were performed on lymphocytes.

The pathology report showed a 4 mm wide defect in the ventricular septum and a persistent ductus arteriosus. The meninges were purulent.

The family originated from Vietnam. The mother had a brother and a sister, each of whom had two phenotypically normal children. The sister had another child who died young. He had congenital heart disease and was mentally retarded. There are no reports in the father's family of persons with birth defects, miscarriages, stillbirths, or mental retardation.

The mother had had four other pregnancies. The oldest child of the family, a boy, was phenotypically normal. He died at the age of 10 years of bronchopneumonia. The second and third children of the family, a girl and a boy, were phenotypically

FIG 1 The proband's sister at 8 months of age.

FIG 2 The chromosomes of the mother (a), the proband (b), and his younger sister (c) (RHG banding and high resolution, bottom row).

normal. Clinical examination of the younger sister of the proband at the age of 8 months revealed a macrocephalic and hypotonic girl (fig 1). Weight (7100 g) and length (72 cm) were below the 3rd centile. Head circumference (47.5 cm) was between the 50th and 75th centile. The neurocranium was disproportionately large, mainly owing to a dolichocephalic configuration of the skull, and the lower segment of the face was small owing to severe retraction of the mandible. The nasal bridge was broad and the mouth was small and narrow. The eyes were deep set and the ears were low set and posteriorly rotated with folding of the upper helical segment. The neck was short and broad. The fingers were held in flexion and the distal phalanges were short. The finger nails were hypoplastic. A grade 3 systolic murmur was audible over the heart. She was mentally retarded. She sat without support at about 15 months and does not stand or speak. Chest x-ray revealed a generally enlarged heart and cardiac catheterisation demonstrated a complex heart defect including ASD, VSD, pulmonary stenosis, and a persistent ductus arteriosus.

CYTOGENETIC EXAMINATIONS

Chromosome investigations of the proband, his parents, and sibs were performed on peripheral blood using R, Q, and C banding. The mother had a structural aberration of chromosomes 1 and 4 in all cells analysed. The patients had an asymmetrical chromosome 4 containing an extra segment composed of a light and dark band inserted into the short arm (fig 2). When the mother was studied, this segment proved to be region q24→q41 of chromosome 1 which was inserted into the inverted chromosome 4 between p15.3 and q28 and which was deleted from the long arm of chromosome 1. The patients carried the inserted segment in chromosome 4 but not the deletion in 1q (fig 2). They were therefore partially trisomic for region 1q24→1q41: 46,XY or XX, inv ins(4;1)inv(4)(q28;q24q41)(p15.3q28) while the mother was balanced for the chromosomal aberration. The inserted segment was inverted. Additional family members were not available for study.

Discussion

Our patients represent the eighth and ninth cases of partial trisomy for the median segment of chromosome 1. The seven previous patients had trisomy 1q25→1q32¹⁻⁴ but our patients were trisomic for 1q24→1q41.

Taysi and Sekhon⁵ and Forabosco and Dallapiccola⁶ have tentatively divided the partial 1q

trisomies into three distinct groups. The first group is characterised by duplication of two thirds of the long arm of chromosome 1, regions 2, 3, and 4. The second group comprises trisomy of region 3 and 4 (duplication of the distal third of the long arm of chromosome 1). The third group comprises duplication of the interstitial segment, regions 2 and 3. The patients in this group show variability ranging from a mildly abnormal phenotype and normal growth to gross phenotypical anomalies. Our two patients were trisomic for only 1q24 of region 2 but also for 1q41 of region 4. As was pointed out by Lungarotti *et al.*,⁷ because of the overlap of features in the three groups it is impossible to delineate the clinical profile of these chromosomal syndromes. Nevertheless, our patients had the most common features of 1q trisomies: mental retardation, receding chin, low set ears, cranial anomalies, and congenital heart defects.

In six patients from three families with intra-chromosomal insertions,¹⁻³ the segment 1q25→1q32 was inserted into the short arm of chromosome 1. A patient of Hustinx *et al.*⁸ was trisomic for 1q25→1qter. The segment 1q25→1q42 of the mother was inverted and inserted in the long arm of chromosome 6. In our patients the segment 1q24→1q41 was inserted into the short arm of chromosome 4. The inserted segment was inverted. Such an aberration could only have occurred during meiosis. These findings suggest an increased susceptibility for a

segment of the long arm of chromosome 1 to be inserted and inverted in rearrangements.

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