Tetrasomy 9p: confirmation by enzyme analysis

SUMMARY A 4-day-old Caucasian male presented with midline defects of the skull and face and extensive skeletal malformations. Chromosome analysis of peripheral blood lymphocytes showed tetrasomy 9p (47,XY,+i(9p)) with no evidence of mosaicism. Confirmation of the cytogenetic interpretation was obtained from the assay of the enzyme galactose-1-P uridyl transferase, the locus for which is on 9p, which showed twice the normal activity.

Tetrasomy 9p was first described by Ghymers et al.1 Four more cases have been described since.2-5 These patients all differ in their phenotypic presentation and although all of them have the extra apparent isochromosome 9p, the amount of chromosome material between the short arms of the isochromosome is variable. In three instances mosaicism was present in the tissue or tissues sampled,1,3,4 and in two cases in which chromosome analysis was done on peripheral blood lymphocytes only no mosaicism was found.2,5

Case report

The patient was the product of a non-consanguineous mating; the mother was 19 and the father was 24 years old at the time of the patient's birth. The pregnancy was full term and uncomplicated. Labour and delivery were normal and the Apgar scores were 4 at 1 minute and 3 at 5 minutes. Birthweight was 2600 g and multiple congenital anomalies were noted at birth.

Findings at 4 days of age (fig 1, 2) included widely patent metopic and sagittal sutures extending to the posterior fontanelle, flattening of the posterior of the skull, soft consistency of the skull, head circumference of 33·5 cm (25th to 50th centile), hypertelorism (inner canthal distance of 3 cm), bilateral cleft lip and palate, micrognathia, anteriorly rotated but normally placed ears with reduced cartilage on palpation, preauricular skin tag on the left, short neck, no cardiac murmur or organo-
megaly, bilateral cryptorchidism, sacral dimple, shortened limbs with an arm span of 40 cm compared to total body length of 45.5 cm with upper to lower segment ratio of 2, contractures of the interphalangeal joints with each finger having only two phalanges and a single crease, hypoplastic to absent nails, limited abduction of the hip joints with hyper-extensible knee joints and bilateral varus deformity, increased mobility of the elbow and wrist joints suggesting joint dislocation, hypoplastic scapulae with kyphosis of the spine, and short pelvis. Muscle tone was decreased and the cry was weak. Dermatoglyphs showed bilateral simian lines with hypoplastic dermal ridges.

Radiological studies showed a small anterior cranial fossa, hypoplastic facial structures compared with the remainder of the skull, midline cleft face, hypertelorism, dislocation of the hip, knee, and elbow joints, bilateral varus deformity, and absent or poor ossification of the sternum, carpal bones, and phalanges of the hands.

The infant was later placed in a foster home where he developed apnoeic spells and died at 2 months of age. Because of circumstances, necropsy and further studies could not be performed.

The father of the patient had had numerous x-ray exposures during the past few years after injury to his face requiring extensive reconstructive surgery which was further complicated by seizures. The mother had had an induced abortion of her first and only other pregnancy which was by another man. The mother is of German extraction and the father’s natural parents are said to be of American Indian-French origin. The remainder of the family history is otherwise unremarkable.

**Cytogenetic studies**

Peripheral blood lymphocytes of the patient were analysed by Giemsa banding and all 60 cells counted showed an XY pattern with an extra chromosome similar in size and appearance to a number 16 chromosome, but with a banding pattern consistent with an isochromosome of the short arm of chromosome 9 (fig 3). This aberrant chromosome appeared to have only one positive C banding area, which suggests that there is probably no extra chromosome
material present in the centromeric region. Both parents have normal chromosomes.

**ENZYME STUDIES**

Assay for the enzyme galactose-l-P uridyl transferase (EC 2.7.7.12) was performed using the UDPG consumption assay of Beutler and Baluda. Normal red blood cell enzyme activity with this method is 18·5 to 28·5 units. The patient's red cell activity was measured twice on the same sample and gave 47·7 units (average of 46·7 and 48·7) which is about twice the mean of the control values. An NN electrophoretic pattern for the enzyme was found in the patient's red blood cells by the method of Sparkes et al. Both parents had normal red blood cell enzyme activity and an NN electrophoretic pattern.

**Discussion**

The phenotypic expression and the cytogenetic findings in the previously described tetrasomy 9p cases are variable. Besides the facial dysmorphic features and mental retardation, the most common congenital anomalies are high arched palate, or cleft palate or cleft lip or both, congenital heart disease, urogenital defect, strabismus, hydrocephalus, and microcephaly (table). The case reported by Wisniewski et al appeared to be the most severely affected and similar to ours. In addition, our patient had extensive skeletal anomalies which have not been described before.

In three cases, in which one or more tissues were karyotyped, mosaicism was present, while in three other cases, including ours, analysis was performed on peripheral blood lymphocytes only and did not show mosaicism. The morphology of the extra isochromosome in these cases also differs. Two cases were actually tetrasomic for the 9p region as well as the proximal part of 9q, band q21–22, whereas the four other cases, including ours, showed involvement of the secondary constriction to a variable degree. It is, therefore, probably not surprising that all the cases have variable phenotypic features.

The continued expansion of the human gene map now affords opportunities to confirm cytogenetic interpretations. The locus for the human enzyme galactose-l-P uridyl transferase has been mapped to 9p by somatic cell hybridisation studies. Assay for the enzyme galactose-l-P uridyl transferase in our case showed twice the normal activity in the red blood cells. This value is consistent with the presence of four genes for this enzyme based upon a gene dose effect resulting from the tetrasomy 9p.

We thank Dr C Barrett for referring this patient. We also gratefully acknowledge the assistance of A Teng and I Klisak for the cytogenetic analysis and M C Sparkes and M Crist for the enzyme studies.

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**TABLE**  

Common features* and cytogenetic findings of tetrasomy 9p

<table>
<thead>
<tr>
<th></th>
<th>Ghymers et al^1</th>
<th>Ritten et al^2</th>
<th>Orzy et al^3</th>
<th>Abe et al^4</th>
<th>Winsiewski et al^5</th>
<th>Present case</th>
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<tbody>
<tr>
<td>Microcephaly</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>2/6</td>
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<tr>
<td>Hydrocephalus</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>2/6</td>
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<tr>
<td>Wide open sutures and fontanelles</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
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<td>3/6</td>
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<td>Hypertelorism</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>5/6</td>
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<tr>
<td>Epicanthic folds</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
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<td>3/6</td>
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<tr>
<td>Strabismus</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>3/6</td>
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<tr>
<td>Bulbous/beaked nose</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>4/6</td>
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<tr>
<td>Low set ears</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>4/6</td>
</tr>
<tr>
<td>Protruding/abnormal ears</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>5/6</td>
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<tr>
<td>High arched palate/cleft palate/lip</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Micronomia</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
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<td>Short neck</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Congenital heart disease</td>
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<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>4/6</td>
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<tr>
<td>Urogenital defect</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>4/6</td>
</tr>
<tr>
<td>Karyotype (as designated by authors) Lymphocytes</td>
<td>47,XY,i(9) (9p,h+,9p)</td>
<td>46,XX/47, XX,i(9p)</td>
<td>47,XX,+i(9)</td>
<td>47,XY,+i(9)</td>
<td>47,XY,+i(9)</td>
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<tr>
<td>Skin</td>
<td>46,XY</td>
<td>–</td>
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</table>

*Features reported in at least two cases.
Case report

The proband was the third child born to healthy, unrelated parents when the mother was 39 and the father 38 years of age. His sibs were aged 9 and 7-5 years at this time and there had been one spontaneous first trimester abortion. He was born at term after a normal delivery, birthweight 2.33 kg. There were respiratory and feeding difficulties with failure to thrive as an infant. Feeding problems have remained to the present time. All milestones were delayed and he is now severely retarded. Fits began at 17 months of age and he has been on continuous anticonvulsant medication since that time.

When seen here at 18 years of age, his height was 114.5 cm, weight 22 kg (on the 50th centile for a 5 to 7 year-old), head circumference 49 cm (on the 50th centile for a 2-year-old) (fig 1). He had a slightly asymmetrical skull with the left side more prominent, a low hair line on the forehead and two abnormal vortices of hair posteriorly, low set on each side of the neck. He had a short neck, sloping shoulders, and a slightly asymmetrical chest. The face was asymmetrical with a dimple on the left side of the chin, a flat nasal bridge, deep set small eyes, small slit-like normally orientated palpebral fissures, and flat supraorbital ridges. The nose was large and bulbous, and there was a small thin carp-like mouth with retrusgnathia. His hands showed tapering fingers, thumbs anteriorly placed and low set, a simian crease variant on the left, and all fingers and the thumb were hyperextensible. Both feet showed pes cavus and talipes equinovarus and all the toes were hyperextensible. The abdomen was protuberant. Both testes were descended and small and there was no sign of puberty. There was a sacral dimple.

Investigations included routine serum haematological and biochemical parameters and urinary studies, which were normal. Ophthalmic examination under anaesthesia showed hypermetropia and astigmatism, and a suspicion of early keratoconus, with irregular cornea. An electroencephalogram was normal.

Cytogenetic analysis

Chromosome analysis of standard peripheral blood cultures gave a modal number of 47 chromosomes in each of 62 cells, the extra chromosome being morphologically indistinguishable from a normal G group chromosome. G banding showed this extra fragment to be a deleted D group chromosome. All other chromosomes in the complement were normal in length and structure. Dermatoglyphic analysis showed absence of d triradius bilaterally.

A severely retarded 18-year-old boy with tertiary partial trisomy 14

Summary

An 18-year-old, severely mentally and physically retarded boy was found to have an unbalanced chromosome complement 47,XY, +14q-. He had the characteristic facial dysmorphism, abnormal hands, and other features described previously in cases of partial trisomy 14, but appears to be the oldest case reported. His mother is a reciprocal translocation carrier, and lack of other carriers in the family is noteworthy.

Subjects with partial trisomy 14 have similar phenotypic abnormalities associated with markedly delayed motor and mental development. In the majority, a balanced translocation was present in the mothers. This report outlines another case of partial trisomy 14, in an 18-year-old boy, where the mother was a balanced translocation carrier.

References


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