A family with three independent autosomal translocations associated with 7q32→7qter syndrome*

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SUMMARY Two persons within the same family were discovered to be trisomic for the segment 7qter. However, several features differed from those described in other patients with this syndrome, for example, normal birth weight and neck size, cleft palate, and beaked nose. In addition to the phenotypic variation, there were three independently segregating autosomal translocations in the pedigree: t(1;7)(q43;q32), t(1;6)(p22·3;q14·1), and t(3;10)(q26·1;p11·21). This is a finding that, to our knowledge, has not been previously reported.

People with a partial duplication of 7q may fall within one of three groups. The largest group involves dup 7q32→7qter and the clinical picture includes low birth weight, developmental and growth delay, hypertelorism, small nose, and very short neck.

In the second group, the duplicated segment is 7q31→7qter. The findings closely resemble those of the first group but with the added presence of cleft palate and micrognathia. An insertional duplication 7q22→7q31 or 7q22→7q32 has been reported in three other patients, but none of these had micrognathia or clefting. In all three groups the 7q duplications have generally been inherited from carriers with a single balanced translocation.

The present report describes a family with three independently segregating balanced translocations in which both the proband and his 29 year old uncle had dup 7q32→7qter. Unlike previously reported subjects with a similar duplication, our patients were of normal birth weight and had normal necks. In addition, the proband had a cleft palate and his uncle had prominent nasal beaking.

Of particular significance, however, was the occurrence of three independently segregating rearrangements in this pedigree. This is a finding

that, to the best of our knowledge, has not been reported previously.

Case reports

The proband (V.4, fig 1) was born at term to a 20 year old primigravida and her 22 year old husband. The pregnancy was complicated by maternal pre-eclampsia in the two months before delivery.

Birth weight was 3·9 kg, length 53 cm, and head circumference 33·7 cm. Clefting of the soft palate, prominent occiput, simian crease in the right hand, clinodactyly of the fifth fingers, hammer toe deformities, and a heart murmur were noted. Because of his dysmorphic features, the infant was referred to us at the age of 18 days (fig 2).

Additional findings were hypertelorism, sloping forehead, a capillary haemangioma over the glabella, low set, posteriorly rotated ears with protuberant lobes, micrognathia, and widely separated first and second toes. Cardiac examination was normal. Dermatoglyphs showed distally placed axial palmar triradii. In the right hand, digits 1 to 5 contained an arch, ulnar loop, radial loop, and two whorls. In the left hand were an arch, radial loop, arch, and two whorls.

At 9 months of age, weight and length were at the 50th centile and the head circumference at the 75th. The infant's developmental milestones were at a 6

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month level, indicating a developmental quotient of 67.

Trypsin-Giemsa banded chromosomes showed a complement of 46,XY,1q+. The additional material on 1q was subsequently identified as 7q32→7qter. This was inherited from the proband's father (IV.10), who carried two balanced translocations, one of these being t(1;7)(q43;q32) and the other t(3;10)(q26·1;p11·21).

One other subject in the pedigree was found to have partial trisomy 7q, the proband's paternal uncle (IV.7), a profoundly retarded 29 year old man. At birth, he weighed 3·29 kg and was 51 cm

long. On examination in January 1983, his height was 158 cm and he weighed 42 kg. He had a normal head circumference (56 cm). The forehead was high. The eyes were almond shaped with downward slanted palpebral fissures. The ears were long and posteriorly rotated. The nose was long and narrow with a prominent tip. The palate was high arched and the chin pointed, giving a triangular appearance to the face (fig 3).

There were bilateral pes planus and calcaneovalgus. A simian crease was present in the left hand. The right hand contained two whorls and three ulnar loops, and the left hand two ulnar loops and three whorls.

Two other subjects in this kindred (IV.2 and V.1) had cleft palates. From the inheritance pattern, neither would be expected to share the chromosomal abnormalities found in the proband and his uncle, although V.1 was said to be mentally retarded but without other dysmorphic features.

CYTOGENETIC STUDIES

In addition to initial studies on trypsin-Giemsa banded chromosomes, high resolution banding was performed on peripheral blood lymphocytes of all members of the pedigree identified as having a chromosome abnormality (fig 4).

The proband (V.4) was found to have a complement of 46,XY,-1,+der(1),t(1;7)(q43;q32)pat, and was therefore trisomic for 7q32→7qter. His father (IV.9) showed the presence of two balanced reciprocal translocations: 46,XY,t(1;7)(q43;q32), t(3;10)(q26·1;p11·21)mat. The proband's paternal grandmother (III.5) had both translocations plus a third one involving chromosomes 1 and 6: t(1;6)(p22·3;q14·1).

The proband's paternal uncle (IV.7) inherited the

FIG 1 Family pedigree showing the inheritance pattern of three independent translocations.

FIG 2 The proband at 3 weeks of age. Note the low set ears with protuberant lobules, micrognathia, and glabellar haemangioma.

FIG 3 Paternal uncle of the proband (subject IV.7, fig 1). Physical features included downward slanted palpebral fissures, almond shaped eyes, long nose with prominent tip, and pointed chin.

FIG 4 Composite of the partial karyotypes transmitted through three generations. The proband (V.5) is represented at lower left; his paternal uncle (IV.7), who also has partial trisomy 7q, is in the centre; and the proband's paternal grandmother (III.5), with three balanced rearrangements, is at the top. Breakpoints are represented by horizontal lines with the symbol for each translocated segment appearing next to the chromosome involved.

three translocations, one of which, $t(1;7)(q43;q32)$, was present in unbalanced form resulting in partial trisomy 7q ($7q32 \rightarrow 7qter$).

The proband's paternal aunt (IV.8) and her daughter (V.4) carry the $t(1;6), t(3;10)$ and the $t(1;6)$, respectively. No other person in the pedigree was found to have a chromosomal rearrangement.

Discussion

This report concerns two members of a family with partial trisomy 7q having several unusual features: phenotypic differences from previously described patients, intrafamilial variation, and the presence in a single pedigree of three independently segregating translocations.

Until now, 18 subjects with partial duplication of 7q have been reported. Based on clinical and cytogenetic findings, these patients can be divided into three groups.¹

Group 1, involving $\text{dup } 7q32 \rightarrow 7qter$, and inherited in every case from the carrier of a balanced translocation, consists of patients with low birth weight, growth delay, mental retardation, hypertelorism, downward slanting palpebral fissures, high forehead, low set, elongated ears, small nose, and very short neck.² None of the six previously reported patients in group 1 had micrognathia or cleft palate. The cleft palate found in our proband, therefore, might have been coincidental since two other members of the pedigree also had cleft palates but were not descended from a translocation carrier. However, the normal birth weights and neck sizes in our proband and his uncle, both of whom have $\text{dup } 7q32 \rightarrow 7qter$, and the uncle's greatly elongated nose with prominent tip, are exceptions to the clinical syndrome ascribed to group 1.

It is possible that the intrafamilial variation between proband and uncle was due to the effects of unrecognised deletions or duplications within the uncle's chromosomes 1, 3, 6, 7, and 10. The uncle's features, however, do not fit any of the known duplication or deletion syndromes involving these chromosomes. A second possibility would be phenotypic variation due to age. The oldest previously noted patient with partial trisomy 7q, and the only one beyond the age of 2, was a 12 year old girl.³ Phenotypic changes with advancing age in other chromosomal disorders, such as trisomy 18 and trisomy 18 mosaicism, are not uncommon.⁴

In group 2, the duplication is also inherited but involves $7q31 \rightarrow 7qter$. The clinical picture closely resembles that of group 1, with the addition of cleft palate and micrognathia.¹

The three subjects comprising group 3 had an inherited insertional duplication $7q22 \rightarrow 7q31$ or

$7q22 \rightarrow 7q32$. The small number of cases makes it difficult to define a specific syndrome. All three patients had strabismus and growth and developmental retardation, and two had low set ears, hypertelorism, small palpebral fissures, and fuzzy hair.¹ None, however, had micrognathia or clefting. One of the families with $\text{dup } 7q22 \rightarrow 7q31$, that of Berger *et al.*,⁵ had a complex rearrangement involving chromosomes 5, 7, and 17.

Independently segregating autosomal balanced translocations are uncommon. We were able to find only five reports of such translocations, four of which were inherited. All of these involved only two translocations.^{6,7}

In the present case, the proband's paternal grandmother had three independently segregating translocations: $t(1;7)(q43;q32)$, $t(1;6)(p22.3;q14.1)$, and $t(3;10)(q26.1;p11.21)$. Whether these arose *de novo* could not be determined, since her mother had a normal karyotype and her father had died several years before the family came to our attention. During World War I, this man (subject II.4, fig 1) was exposed to 'nerve gas' (phosgene) and possibly to nitrogen mustard (mechlorethamine). The latter is teratogenic in rodents and produces azoospermia, amenorrhoea, bone marrow depression, and secondary tumours in humans, but we are not aware of any reports that exposure to mechlorethamine results in cytogenetic abnormalities.

Of particular interest to us was the paternal grandmother's translocated chromosome 1. Each of her three children inherited the abnormal chromosome 1 but with a different configuration in all three (fig 4). One son (IV.7), the proband's uncle, inherited his mother's translocated chromosome 1 intact. This man's sister's (IV.8) chromosome 1 was joined at p22.3 by material from her mother's 6q ($q14.1 \rightarrow qter$), but it contained no 7q on the long arm. In the proband's father (IV.9), on the other hand, the only additional material on his maternally derived chromosome 1 (at 1q43) was from 7q ($q32 \rightarrow qter$).

We found no evidence in these last two subjects that the respective 6q or 7q segments missing from their maternally derived chromosome 1 had been translocated to other chromosomes.

It should be noted, in view of the proband's paternal grandmother's three independently segregating translocations, that she experienced only a single spontaneous abortion and had only one child (out of three) with a chromosomal imbalance. Based on adjacent 1 meiotic segregation during gametogenesis, of the 64 possible gametic combinations in a person with three independent translocations, 24 would be unbalanced. Six of these gametes would

carry a single unbalanced chromosome, 12 would have two unbalanced chromosomes, and six would contain three such chromosomes. When two balanced translocations are present, 16 gametic combinations are possible, of which six would be unbalanced, two resulting in a single imbalance and four containing two unbalanced chromosomes.

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