Familial 'partial 9p' trisomy:
six cases and four carriers in three generations

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Summary. Six cases of translocation trisomy for the distal half of the short arm of a number 9 chromosome and four asymptomatic balanced translocation carriers are presented in a three-generation pedigree. The clinical features are remarkably similar to those recently recognized and increasingly reported in full short arm (9p) trisomy and should be considered a modification of the same syndrome. In addition to non-specific mental retardation and short stature, there is, in common, a characteristic facies, including down-turned corners of the mouth, a slightly bulbous nose, moderately large ears, suggestively wide-set eyes with an anti-mongoloid slant, dysplasia and hypoplasia of the nails, clinodactyly of the 5th fingers, and abnormal dermatoglyphs. It appears that the 'trisomy 9p syndrome' in its variant forms, including trisomies for more or less than just the short (p) arm, is one of the most common clinical autosomal anomalies in humans, exceeded only by trisomy 21 (Down's syndrome) and possibly trisomies of chromosomes 13 and 18.

In 1970, the first cases of trisomy for the short arm of a number 9 chromosome (9p trisomy) were published (Rethoré et al). Since then a total of 21 children in 14 families have been reported (Centerwall and Beatty-DeSana, 1975) indicating that this is indeed a cytogenetic entity of clearly diagnostic clinical features and significant frequency. The majority of these 21 cases involved chromosome translocations.

In 1973 an infant was reported to have trisomy for the complete number 9 chromosome (Feingold and Atkins). She had a somewhat similar facial appearance to the 9p trisomy cases but a more severe overall affliction, with death ensuing at 28 days of age. Excluding this case, trisomy for all of chromosome 9 in all cells (i.e. not including the bone marrow findings in some leukaemias and several cases of mosaicism) has been reported only in abortuses (Kajii et al, 1973).

In 1974, Lin, Holman, and Sewell described three sibs having a 9p/11p translocation trisomy for the distal two-thirds of a number 9 short arm. Most of the physical findings were similar to those observed in the cases of full 9p trisomy.

In 1975, Centerwall, Mayeski, and Cha reported a severely retarded infant who was trisomic for three-fourths of a chromosome 9 (the distal half of the long arm being deleted). Except for an increased intensity of some of the abnormal features, this child was a good fit for the trisomy 9p syndrome.

At this time we are reporting 6 cases of 'partial 9p' trisomy (9p/14q unbalanced translocation) and 4 balanced translocation carriers in a three-generation pedigree. The suspicion of 9p trisomy syndrome in the index cases, based on clinical features alone, was the basis for chromosome studies. It appears that the distal half of the short arm of the number 9 chromosome is responsible for the major clinically-specific features found in trisomies for all of the short arm and even for the whole of chromosome 9 (Table).

Case histories

In January 1970, 2 sibs, a 7-year-old girl and her 4-year-old brother, were brought to us by their normal parents for diagnostic evaluation and delayed growth and development and because of somewhat unusual facial appearance. Three maternal aunts were said to be

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After the children affected (She syndrome puffiness had growth and medical-centre chromatography, All she factors to periods. Parental to be pregnancies there spontaneous abortions, the parents, at mother and were so-called 4 living affected slant disproportionately ment too and Grosse, involved. chromosome single palmar creases and and Globular, prominent eyes Low Mildly or Slightly stature 58 The had mild retardation consistent a pseudo eye slant FOUND A PARTIAL 9p- chromosome 9p’ translocation of the cases both of trisomy for three-quarters (9q-) (2 case reports: Rott, Schwantz, and Grose, 1971; Centerwall et al, 1975) and for the whole of chromosome 9 (one case: Feingold and Atkins, 1973)—though these are too few cases upon which to make strong generalizations.

Similarly involved. The features included down-turned corners of the mouths, slightly bulbous noses, moderately large well-formed ears, and a minimal anti-Mongoloid slant to slightly wide-set eyes. The mentalities of the 4 living affected individuals fell within the 50 to 70 IQ or so-called mild retardation range, with speech development disproportionately affected. Head circumferences were somewhat small for their respective ages. Their personality-behaviour patterns (SQs) were considered to be consistent with their mentalities.

There had been no known possible contributing factors in any of the pregnancies, deliveries, or postnatal periods. Parental consanguinity was denied. The mother and father were 27 and 30 years old, respectively, at the time of the older child’s birth. From the 6 pregnancies there had been 3 early (2- to 3-month) spontaneous abortions, an older normal son, and these 2 abnormal children. Several years earlier these 2 children, the parents, and the 2 living affected aunts had conventional chromosome analyses at another medical centre. All analyses were interpreted as normal. The involved daughter also had normal blood levels of calcium and phosphorus, normal urine amino acid paper chromatography, and a normal serum PBI. At 54 years she had a 3-year bone age. A clinical diagnosis of pseudo-Turner’s syndrome was made, based on delayed growth and development, hypoplastic nippies, minimal puffiness of hands and feet, and slight webbing of the neck.

Cytogenetic follow-up

On 9 July 1974, at our monthly genetics grand-rounds medical-centre conference we presented a little boy whom we had recently diagnosed and reported as a case of the 9p trisomy (Centerwall et al). The mother of the 2 affected children we had seen 41 years earlier was in the audience. (She is a registered nurse by training and has sustained an interest in problems of the retarded.) After the conference she approached us to exclaim that the 9p trisomy boy presented at the conference looked remarkably like her own retarded children (Fig. 1). Could they have the same chromosome problem? We explained that at the time of the earlier studies the chromosome banding techniques necessary to make such a diagnosis were not yet available; also, the first cases of 9p trisomy had not yet been reported. We agreed that retesting was in order.

On re-evaluation the children (III.5 and III.6 of Fig. 2a) indeed did show many of the features seen in the 9p trisomy syndrome. Giemsa-trypsin (G-banding) of the chromosomes revealed an extra band at the distal end of the long arm of one of the number 14 chromosomes (Paris Conference, 1971). The rest of the chromosomes appeared unaffected (Fig. 3a).

The parents and normal older brother were similarly studied. It was discovered that the father (II.4) had normal chromosomes but the mother (II.5) and brother (III.4) each had the same involvement of a number 14 chromosome but also had a deletion of the distal half of the short arm of a chromosome number 9 (Fig. 3b). This was interpreted as a balanced translocation t(9;14) (p22;q32). Other relatives on the maternal side, the majority of whom lived in Kansas, were then similarly studied by heparinized blood samples. The two living retarded aunts (II.1 and II.3) had the same unbalanced translocation ‘partial 9p’ trisomy. The 3rd aunt (II.7) who had died at 9 months of age is presumed to have the same syndrome on the basis of delayed development (not crawling by 9 months) and similarities of facial features. One of the two maternal uncles (II.8) and the maternal grandmother (I.2) had the balanced translocation carrier state. At the time of this discovery the involved uncle’s wife (II.9) was 8 months’ pregnant. A month later studies on the cord blood showed the ‘partial 9p’ trisomy. The facial features were characteristic and, in fact, the diagnosis was suspected in advance of the chromosome analysis results (III.7 of Fig. 2b). In the meantime the 8 full sibs (5 younger and 3 older) of the
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maternal grandmother (I.2), all living and seemingly normal, were shown by G-banding to have normal appearing chromosomes.

Discussion

A family with 6 members retarded mentally and physically has been ascertained because unusual facial features so closely resembled those seen in reported cases of trisomy for the short arm of chromosome 9 (trisomy 9p syndrome). Most clinically characteristic and diagnostic are the down-turned mouth, somewhat bulbous nose, and prominent philtrum (Fig. 1 and 2a). By special G (Giemsa-trypsin) banding these 6 persons are shown to be trisomic for the distal half of the short arm of chromosome 9.

Fig. 4 shows the probable origin and transmission of the chromosome translocation in this family. It is estimated that the risks for 'offspring' of this type of balanced-translocation carrier is 25% for early pregnancy spontaneous abortions (the 9p-deletions), 25% for the 'partial 9p' trisomy syndrome, 25% for
Fig. 3. (a) G (Giemsa-trypsin) banding of chromosomes of affected child, Case III.6 of Fig. 2 showing an extra band on the distal end of the long arm of a number 14, i.e. 46,XY,14q+. Without analysis of the parents' chromosomes it is impossible to know what this extra material is. (b) G (Giemsa-trypsin) banding of chromosomes of mother, Case II.5 of Fig. 2, showing that the extra band on the end of the number 14 has been translocated from the distal half of the short arm of one of the number 9 chromosomes, i.e. t(9;14)(p22;q32).

Fig. 4. Drawing of G (Giemsa-trypsin) banded chromosomes depicting the probable origin via a reciprocal balanced translocation during meiosis in gamete formation—and the probable four equally-occurring 'offspring' from such balanced translocation carriers. As indicated, the exchange of the distal third of a No. 9 chromosome short arm for the distal tip of a No. 14 long arm means that each of the cases of 'partial 9p' trisomy in this family has a concomitant terminal long arm deletion of a No. 14 chromosome—which probably is of little or no clinical significance.

balanced translocations the same as the parent, and 25% for normal chromosomes. Thus half (on the average) of the normal-appearing children of a carrier parent will be carriers like the parent. Therefore, the likelihood that all 8 sibs of the maternal grandmother carrier (I.2 of Fig. 1b) would have normal chromosomes by pure chance (if indeed one of their parents was a carrier) is (1/2)^8 = 1/256—thus the assumption that the maternal great grandparents were not involved—that the chromosome aberration had its origin in the maternal grandmother as a result of a reciprocal translocation during meiotic formation of a gamete before conception.

Genetic counselling of this family had included the calculated risk figures for offspring of carriers, and the prenatal diagnostic possibilities. Amniotic fluid taken at about the 16th week of pregnancy can be cultured and analysed for fetal chromosome complement—in time for ethical, safe interruption of that pregnancy if it is determined that the fetus is
affected. Unfortunately, this knowledge came only a few months too late to be of help in the pregnancy which produced the youngest of the affected persons in the pedigree (III.7 of Fig. 1).

With regards to cases of trisomy for varying proportions of the number 9 chromosome, it appears that the degree of deficit, in general, varies directly with the amount of excess chromosome material, i.e. hands, ears, neurological (e.g. mild retardation in 'partial 9p', very severe in trisomy 9q-, and neonatal death in trisomy 9). The clinical features of each are sufficiently characteristic and similar enough to lead one to suspect a specific syndrome. All also have in common a trisomy for the distal half of a chromosome 9 short arm. It seems, therefore, that a cytogenetically proper label for all such cases would be the 'distal 9p trisomy syndrome'. We suggest, in these circumstances, that it would not be inappropriate alternatively to call this the 'Rethoré syndrome' in honour of the pioneering and major scientific contributor (Rethoré et al, 1970, 1973).

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