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Chromosome studies

G- and C-banding were performed as described previously (Daniel and Lam-Po-Tang, 1976). N-banding was by the simple method (Bloom and Goodpasture, 1976) of 18 hours incubation in 50% aqueous AgNO3 at 50°C and counterstaining with Giemsa. A fusion translocation between the short arms of chromosomes 13 and 18 was found in the proposita, her sibs, mother, and nephew (III.7). The G positive band 18p11.2 was reinforced in the translocation chromosome by the satellites of chromosome 13 (Fig. 2). The satellites could be clearly seen in the C-banded translocation chromosome (Fig. 2), and the satellite stalks were also present on N-banding (Fig. 3). Therefore, the centromere of chromosome 13 was present though a centric constriction was never observed at that site. There was a net deletion of the G negative terminal band 18p11.3 and the 13p telomeric region.

Discussion

In contrast to the previous reports of dicentric translocations involving one submeta/metacentric chromosome, this translocation is familial. The phenotype of the carriers is normal notwithstanding the small deletion of a G negative region. This deletion must be small compared with those occurring in the other cases who, apart from one relatively normal girl (Warburton et al., 1973), range to the severely retarded (Nakagome et al., 1976). The fact that this translocation has been transmitted through three generations, and possibly a fourth considering the interval between the offspring of the maternal grandmother, indicates its stability. The suppression of one (usually the acrocentric) centromere in these dicentrics is likely to be the mechanism of this stability. At this stage of our understanding of centromeric suppression, it is important to document the karyotypes at meiotic metaphase II and of the products of miscarriages in these carriers as further cases are described.

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A. Daniel, I. D. Perel, A. J. Clarke and Toni Saville

1Cytogenetics Unit, Prince of Wales Hospital, Sydney, NSW; 2Queensland Medical Laboratory, Brisbane, Queensland; and 3Medical Centre, Morpeth, NSW, Australia

References


Requests for reprints to A. Daniel, Cytogenetics Unit, Prince of Wales Hospital, High and Avoca Streets, Randwick, NSW 2031, Australia.

The 9p—syndrome

SUMMARY A 13-year-old boy with 9p—(p22→pter) is reported. He had many features in common with previous 9p—cases, as well as several distinctive features including polydactyly and precocious puberty. Cytogenetic studies revealed a de novo deletion distal to band 9p22, which was the reported site of chromosome break in 9 of the 10 previous 9p—cases. Evaluation of the human GALT enzyme suggests that its locus is not on the deleted segment.

Ten patients have previously been described with deletion of a distal portion of the short arm of chromosome 9 (Orye et al., 1975; Alfi et al., 1976; Serville et al., 1976; Kuroki et al., 1977; Nielsen et al., 1977). The patients had several features in common which suggest a recognisable syndrome: mental retardation, trigonoccephaly or prominent forehead, flat occiput, flat nasal bridge, anteverted nostrils, long philtrum, micrognathia or retrognathia with wide goniol angle, abnormal auricles, short
neck, wide set nipples, long fingers usually due to long middle phalanges, and hyperconvex nails. We report a patient whose clinical findings included polydactyly and precocious puberty as well as many of the features of previous 9p—cases. Cytogenetic evaluation revealed a de novo deletion terminal to region 9p22.

Case report

The patient, born 12.12.63, was referred for genetic evaluation at age 13 years. At birth his mother and father were 25 and 31 years old, respectively. They were healthy and unrelated. Pregnancy and delivery were normal, birthweight was 2.95 kg, and reported length was 43 cm. His cry was weak and there was cyanosis requiring oxygen therapy for one week. Supernumerary ulnar digits were removed from both hands in the neonatal period. From infancy there was excess tearing in the left eye because of left nasolacrimal duct obstruction, and left orbital cellulitis developed at 8 years of age requiring admission to hospital and subsequent dacryocystorhinostomy. At 8 years and 10 months of age there was an endocrine evaluation for precocious puberty. Examination at that time showed a height of 147 cm (143 cm = 97th centile) and near adult development of testes, phallus, and pubic hair. In addition, there was a right cystic hydrocele of the spermatic canal. Bone age was 13 years and serum testosterone was in the adult range. Skull x-rays showed mild hypertelorism and a wide mandibular gonial angle. Haematological evaluation showed mild iron deficiency anaemia which responded to dietary treatment. Additional laboratory investigations, including serum electrolytes, creatinine, BUN, total protein, albumin, uric acid, alkaline phosphatase, total bilirubin, glucose, cholesterol, LDH, AST, thyroxine, T3, radioiodine uptake, CSF protein and glucose, brain scan, and electroencephalogram, were all normal.

Examination at 13 years of age showed a height of 160 cm (80th centile), weight 47 kg (70th centile), head circumference 58 cm (97th centile), and blood pressure 110/70. The craniofacial findings included hypertelorism with left exotropia, antimongoloid slant of the eyes, small and thick auricles with adherent lobes, narrow arched high palate, anteverted nares and long philtrum, prominent lower lip, and a long, down-pointing mandible which appeared to be the result of the wide gonial angle (Fig. 1). Teeth were malpositioned and a lower right incisor was missing. Ocular funduscopia was normal. The neck was short and broad with mild webbing and the nipples were widely spaced. There was no cardiac murmur. There was adult development of the external genitalia, with a cystic mass superior to the right testis and a second urethral meatus (first degree hypospadias). Dermatoglyphic examination of the digits showed 3 whorls, 4 low arches, and 3 ulnar loops. The mother had a combination of 7 ulnar loops, 2 radial loops, and 1 arch, and the father had 5 arches, 4 ulnar loops, and 1 radial loop. The patient’s palmar axial triadii were proximally positioned. Midphalanges were long and several digits had excess flexion creases. Fingernails were hyperconvex. There were no joint contractures though there was limited anterior flexion of the spine. Muscle tone was normal and there was no ataxia. There was mild hyperreflexia with unsustained ankle clonus and extensor plantar responses bilaterally.

The boy did not begin to walk unaided until age 5, at which time he used less than 10 single words. He was enrolled in classes for the trainable mentally retarded and the Stanford-Binet (L-M) IQ at age 11 years and 7 months was 33.

The father was born in Puerto Rico and the mother in Mexico. There are five healthy sibs and the mother had one spontaneous abortion. One male paternal first cousin was mentally retarded and one male maternal first cousin had Down’s syndrome. Physical examination of both parents was normal.

Cytogenetics

Trypsin-Giemsa chromosome analysis of peripheral blood lymphocytes (Fig. 2) and skin fibroblast culture showed an apparent terminal deletion of
bands p23 and p24 of the short arm of a chromosome 9 in all 27 cells examined. As shown in Fig. 3, reverse banding suggested that the deletion was terminal, though an intercalary deletion of bands p21 and p22 could not be ruled out. C-banding showed normal heterochromatin staining in both no. 9 chromosomes. The karyotype was therefore designated 46,XY,del(9) (pter→p22:). Both parents had normal trypsin-Giemsa karyotypes and C-banding again showed no heterochromatin variation of their no. 9 chromosomes. The two sibs examined had normal routine karyotypes.

Red cell galactose-1-P uridyl transferase (GALT, EC 2.7.7.12) activity was assayed using the consumption method of Beutler and Baluda (1966). Electrophoresis of this enzyme was done by the method of Sparkes et al. (1977). The red cell GALT activities were normal (range 18·5 to 28·5 IU/g Hb): proband, 24·6; mother, 25·7; father, 28·4. Electrophoresis showed all to be homozygous for the normal allele (N/N).

Discussion

Findings from the current patient and previously reported 9p− cases are summarised in the Table. In addition to those listed, the following features occurred once among the 9p− patients: hypotelorism and bifid tongue (Serville et al., 1976); mild microcephaly, low forehead, narrow thorax, seizures, and infantile autism or schizophrenia (Nielsen et al., 1977); malpositioned and missing teeth, and hydrocele of spermatic canal (current case); diaphragmatic hernia (Alfi et al., 1973); and diastasis recti, short fingers and arms, small hands, abnormal TVP, and hypotonia (Orye et al., 1975). As can be seen, the current patient had several features in common with previous 9p− cases, including prominent forehead, hypertelorism, anteverted nares and long philtrum.
prominent lower lip, high arched palate, abnormal auricles, wide mandibular gondal angle, short and broad neck, wide set nipples, large middle phalanges with hyperconvex nails, and moderate mental retardation. Our patient differed from previous 9p—cases in the absence of trigonocephaly, flat nasal bridge, and a large number of digital whorls. Though our patient had a wide mandibular gondal angle, prognathism was not a feature of previous 9p—cases.

Also, the unlar hexadactyly and precocious puberty present in the current patient appear not to have been present in previous 9p—cases. Though polydactyly was reported in one patient with short arm deletion of a C group chromosome (Elliott et al., 1970), that patient did not have a banded karyotype, and the deleted chromosome did not have the appearance of a no. 9 in that there was no evident centromeric constriction. Precocious puberty was not mentioned in 3 previous patients who were old enough to have this feature (2 female patients, ages 10 and 20 years, Alfi et al., 1976; and one 61-year-old male, Nielsen et al., 1977). However, several 9p—patients had anomalous external genitalia: female patients had hypoplasia of labia majora and prominent labia minora (Alfi et al., 1976). The current patient had a right cystic hydrocele, and one male patient had hypospadias (Alfi et al., 1974). The latter patient also had ocular hypertelorism with marked left exotropia (evident from published photographs) and appeared very similar to the current patient.

Prieur and colleagues identified 4 additional 9p monosomy patients, 2 with simple 9p deletions and 2 with 9p— in combination with partial trisomy of another chromosome (Rethoré, 1977). However, details of clinical features were not sufficient for these cases to be included in the current review of 9p—patients.

Evaluation of human galactose-1-P uridy transferase was carried out on the current patient because recent studies have mapped a locus for this enzyme to chromosome 9 (Mohandas et al., 1977). The normal activity for this enzyme in the proband and his parents suggests that its locus is not on the deleted segment 9p22—pter.

The site of the chromosome break appears to be at band 9p22 in all the reported 9p—cases except one, where the deletion was reported to be terminal to band 9p21 (Serville et al., 1976). In two cases the deletions resulted from balanced parental translocations: t(9;16)(p22;q24)mat (Alfi et al., 1973), and t(9;15)(p22;q26)mat (Orye et al., 1975). In the remaining cases the 9p deletion occurred de novo as in the current patient. Interestingly, C-banding showed heterochromatin variation of the deleted chromosome 9 in both of the previous translocation cases. In one, the heterochromatin block was completely missing (Alfi et al., 1973), and in the second case it was mildly reduced in size (Orye et al., 1975). The relationship of the heterochromatin variation to the translocation is those cases remains speculative. Neither the current patient nor his parents had any heterochromatin variation in chromosome 9. Therefore, the findings reported here do not support an aetiological relationship between pericentric heterochromatin variation and break in the short arm of chromosome 9. It is anticipated that further reports of 9p—patients will help to clarify their clinical picture and possibly give clues to the aetiology of the short arm deletion.
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STEVE J. FUNDERBURK,1 ROBERT S. SPARKES,2 AND IVANA KLISAK2

1Department of Psychiatry, Mental Retardation Research Program, and 2Departments of Psychiatry, Pediatrics, and Medicine, UCLA School of Medicine, Los Angeles, California, USA

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Requests for reprints to Dr S. J. Funderburk, Neuropsychiatric Institute, 760 Westwood Plaza, Los Angeles, California 90024, USA.

Variation in chromosome 19

SUMMARY Variations in centromeric staining of chromosome 19 appear to be an uncommon polymorphism inherited in a Mendelian manner and easily seen in G-banded cells. It should not be misinterpreted as a structural cytogenetic abnormality.

Although Craig-Holmes et al. (1973) were the first to draw attention to additional centromeric banding in the F group of chromosomes, it was Crossen (1975) who specifically implicated chromosome 19. However, there has been very little documentation of this variant. McKenzie and Lubs (1975) and Nakagome et al. (1977) paid scant attention to it and other reviews of chromosome polymorphism (Buckton et al., 1976; Muller and Klinger, 1976) fail to mention it entirely.

We report variations in centromeric banding of chromosome 19 detected in the fetus during amniocentesis and also present in the mother.

Results and discussion

Amniocentesis was performed routinely because the mother would have been 35 years of age by the time the baby was born. Twenty-two cells representing a primary culture with 7 colonies and a secondary culture with an additional 7 colonies were banded by the trypsin-Giemsa technique. In all cells, one

Fig. One pair of chromosomes 19 from fetus (above) and mother (below) stained by the trypsin-Giemsa method. The variant is placed to the left in each pair. It is larger and submetacentric, with an increased amount of subcentromeric heterochromatin, and readily seen by G-banding.
The 9p-syndrome.

S J Funderburk, R S Sparkes and I Klisak

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