DELINEATION OF SYNDROMES DUE TO PARTIAL 6q IMBALANCES

Trisomy 6q21→qter and Monosomy 6q221→qter in Two Unrelated Patients

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Two unrelated patients carrying imbalances involving the long arm of chromosome 6 are described. In the first trisomy 6q21→qter had segregated from a maternal translocation t(6;16)(q15;q24). The clinical data of the proposita are compared with those of three other published cases. A partial 6q trisomy syndrome is postulated characterized by: growth deficiency of prenatal onset, psychomotor retardation, craniofacial abnormalities (microcephalia, hypertelorism, downward slanting palpebral fissures, flattened nasal bridge, long philtrum, hypoplastic perioral features, large jaw resulting in a round appearance of the face, receding chin, malformed ears) and dysmorphic extremities (contractures of limbs due to short flexor tendons, hypoplastic fingers, toes and nails). In the second case, monosomy 6q221→qter resulted from a de novo *rearrangement and was responsible for mental retardation and facial dysmorphism (reduced biparietal diameter, hypotelorism, absent eyebrows, prominent nose, ptosis, receding chin, dysmorphic ears). Studies of HLA and PGM_3 segregation showed normal inheritance patterns and ruled out the location of these genes in bands 6q221→qter.*

INTRODUCTION

Chromosome imbalances involving chromosome 6 in man are uncommon. Breuning et al. (1977*b*) have postulated the existence of a clinically recognizable trisomy 6p syndrome. Linkage studies in the patient's family, in which a translocation t(6;20)(p21;p13) was segregating, indicated that the HLA gene cluster is very close to break point 6p21 (Breuning et al. 1977*a*).

Robertson et al. (1975) have reported a girl with acrocephalosyndactyly who had a trisomy for part of the long arm of chromosome 6 (6q21→qter). Two additional cases of familial partial trisomy 6q, due to segregation of ins(5;6)(q33;q15q27) have been described by Chen et al. (1976) in individuals carrying a comparable spectrum of malformations. The suggestion has been derived that partial trisomy 6q may result in a characteristic dysmorphic syndrome. An interstitial deletion 6q13→q15 has been identified by McNeal et al. (1977) in a retarded, unusual appearing child with multiple malformations including the VATER association defects. Loss of chromosome material from the distal part of the long arm of chromosome 6, resulting from a tandem 6/15 translocation, has been observed in a severely mentally and physically retarded patient with peculiar appearance (Mikkelsen and Dyggve 1973). Possibly,

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monosomy for a distal 6q segment occurred also in cases of ring chromosome 6 (Moore et al. 1973, Van den Berghe et al. 1974, Fried et al. 1975, Salamanca et al. 1975, Sede et al. 1977). However, in the absence of detailed cytogenetic characterization, karyotype-phenotype correlations can hardly be established.

The purpose of this communication is to report two unrelated patients with unbalanced structural aberrations of the long arm of chromosome 6. In the first case, partial trisomy 6q derived from segregation of a maternal translocation t(6;16)(q16;q24). The clinical features of the patient, when compared with previously identified individuals, appear to be adequate to delineate trisomy 6q as a distinct clinical syndrome.

In the second case monosomy 6q221→qter results from a *de novo* rearrangement and it is associated with an unusual constellation of dysmorphisms. HLA typing and PGM_3 segregation studies in the patient's family ruled out the location of these genes in bands 6q221→qter.

CASE REPORTS

CASE 1

The proposita, the only child of healthy unrelated parents, was born after a full-term uncomplicated pregnancy to a 25-year-old mother and to a 39-year-old father. The birth weight was 3.0 kg.

Soon after birth, she was admitted to the Division of Pediatrics and the Department of Human Genetics, University of Genova, because of neonatal asphyxia, followed by diffuse intravascular coagulation. Death occurred after 19 hours, due to subarachnoidal haemorrhage.

Physical examination (Fig. 1) showed generalized oedema. She had peculiar facies with downward slanting palpebral fissures, hypertelorism, deep set eyes, large and flattened nasal bridge, with small and rounded tip and anteverted nares. The philtrum was long, the mouth and perioral features hypoplastic, with introverted upper lip, high arched palate and pointed, small and receding chin. The jaw was large: the prominence of the mandibular angles resulted in a rounded appearance of the anteroposterior facial profile, which was further pronounced by the presence of chubby cheeks. The ears were dysmorphic with folded and depressed proximal helix, thick and hypertrophic anthelix surrounding a long concha, hypoplastic tragus and slightly prominent lobe. The neck was short and webbed.

Flexion contractures due to short flexon tendons were present at the upper and lower limbs. The hands were flexed at the wrists and contractures occurred in all fingers, involving the two distal phalanges. The digits were small and tapering, with hypoplastic nails. Examination of the feet revealed bilateral clubbing. Toes were grossly modeled: nails were present only on halluces, toes III-V showed hypoplastic proximal phalanges and large and bulbous distal phalanges. Due to varus deformity of distal phalanges, toes V overrode IV and IV III, respectively.

At necroscopy, no gross visceral malformations were observed.

Cytogenetic Investigations

Chromosome analyses were made from peripheral blood cultures. The conventional karyotype showed in the patient a modal number of 46, with the presence of a marker submetacentric chromosome, which was replacing a no. 16 chromosome. Cytogenetic investigations in the parents showed a normal karyotype in the father, while the mother was carrier of a translocation between the long arm of a C-group chromosome and the long arm of a no. 16 chromosome. G-banding studies showed that the translocation occurred between chromosomes 6 and 16, with break points at the interband 6q15/21, and 16q24. Thus, the maternal formula was 46,XX, t(6;16)(q15;q24) (Fig. 2).

Banding analysis in the proposita showed that she had partial trisomy 6q21→qter, resulting from segregation of the der(16) maternal chromosome. The chromosome formula was 46,XX,-16,+der(16),t(6;16)(q15;q24)mat (Fig. 2).

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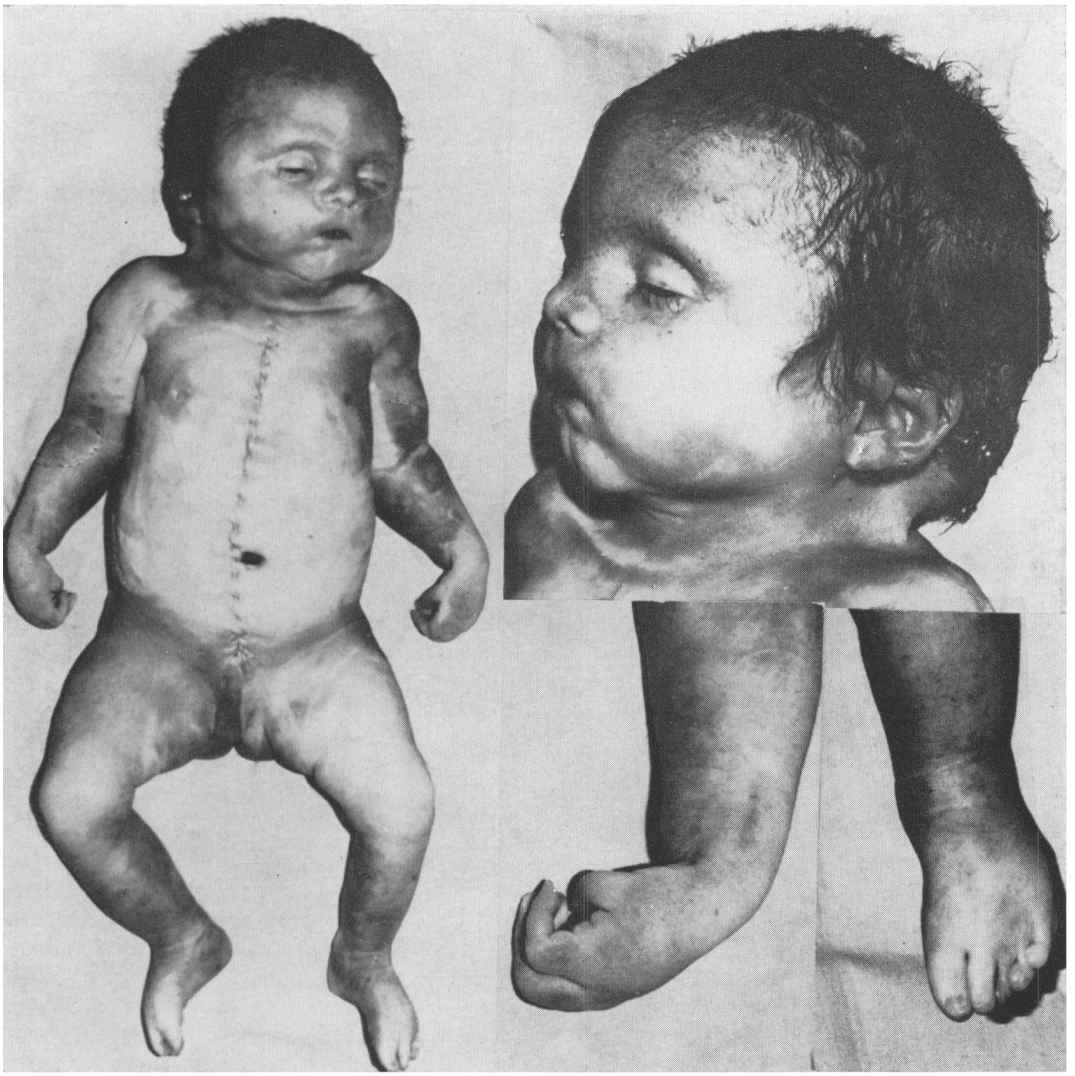

Fig. 1. Case 1.

CASE 2

The propositus was the second child of healthy, nonconsanguineous parents. An older sister was physically and mentally normal. The family history was unremarkable.

The patient was born in April 1974, after a full-term uncomplicated pregnancy, to a 26-year-old mother and a 32-year-old father. He cried promptly; birth weight was 2.850 kg, lenght 51 cm and head circumference 35 cm. According to information obtained from parents, the neonatal period was considered normal; however, hypersomnia and apathy were apparent during the first seven months of life. At 8 months the patient was admitted to a regional Pediatric Hospital because of " cyanosis ". At that time thriving was considered satisfactory, but a severe psychomotor retardation was noticed. An EEG was normal.

He was able to sit unsupported from the age of 10 months.

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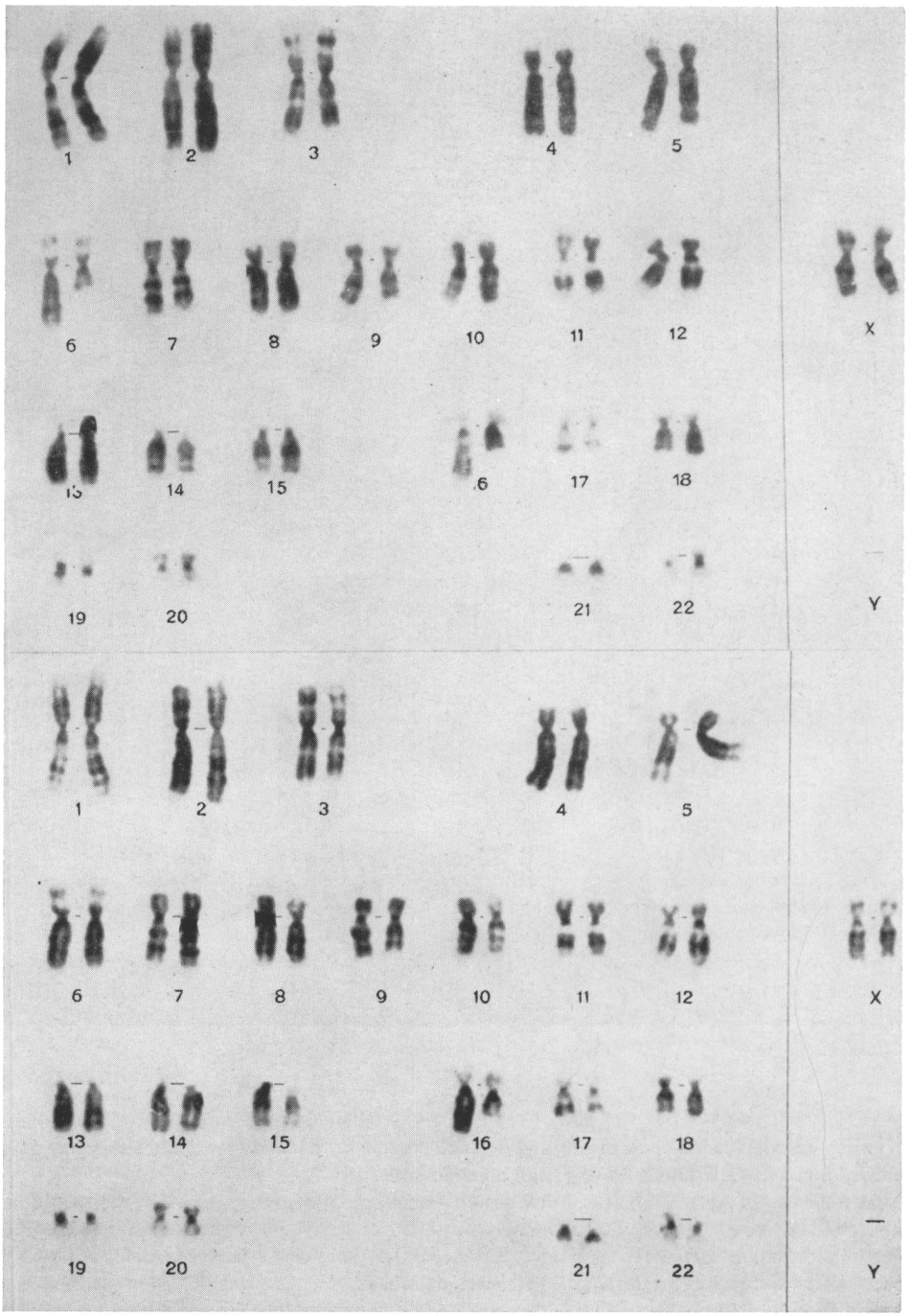

Fig. 2. Karyotype of the mother of case 1, showing 6/16 translocation (top) and karyotype of the proposita showing the der(16) maternal chromosome (bottom).

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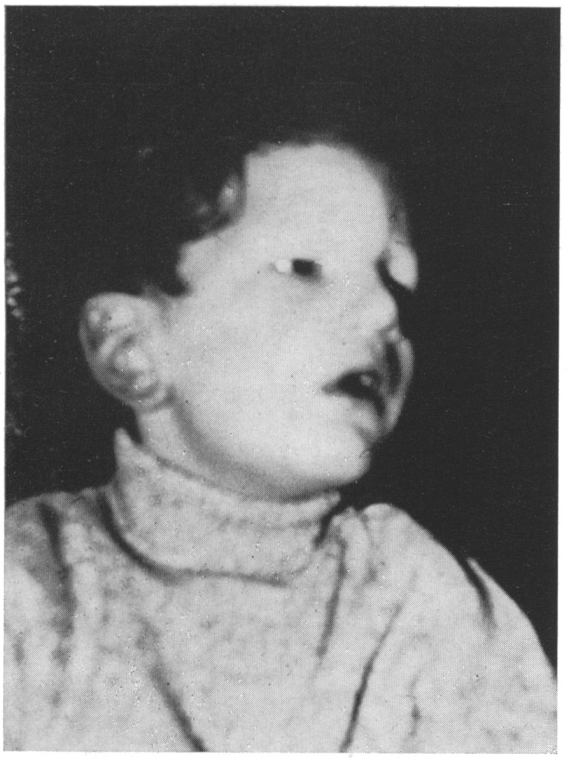

Fig. 3. Case 2.

At 34 months he was referred for evaluation to the Department of Medical Genetics, University of Rome. At that time the following features were recorded: weight 13 kg (25th percentile); height 100 cm (95th percentile); head circumference 48 cm (< 50th percentile). The skull shape showed narrow biparietal diameter and prominent occiput. The anterior hairline was low, with dry and thick hairs. The supraorbital margins were well designed, but eyebrows were exceedingly scanty and thin. Hypotelorism (inner canthal distance 2.1 cm = 3rd-25th percentile), prominent eyes, bilateral ptosis and epicanthus and downward slanting palpebral fissures were apparent. The glabella was prominent, the nose long and narrow, with a rounded tip. The philtrum and perioral features were normal; the palate high-arched and mouth constantly opened and protruding, with a receding, small chin. Ears were large (total ear length 5.1 cm = > 50th percentile), and dysmorphic, with a well-designed helix, prominent anthelix surrounding a deep, long and narrow concha, and thick lobe. Pinna was large and showed bilaterally deep dimples on its medial face.

External genitalia were male, with bilateral cryptorchidism.

The hands were large (total hand length 7.1 cm = 75th percentile). Dermatoglyphic analysis showed 6 whorls and 4 loops on fingertips, normal main line distribution on palms and bilaterally displaced axial triradii.

The patient could babble with inarticulated sounds, fix on objects and smile. He could grasp for minor things, but he could not handle them with the degree of skill normal for his age. He could stand alone for a short while, and when supported by both hands he could make a few clumsy steps.

When reexamined by us at the age of 38 months, he was in the 90th percentile for weight (16.5 kg) and height (102 cm); head circumference was 49 cm (< 50th percentile). He could speak only a few simple words. He was able to walk unsupported from the age of 40 months.

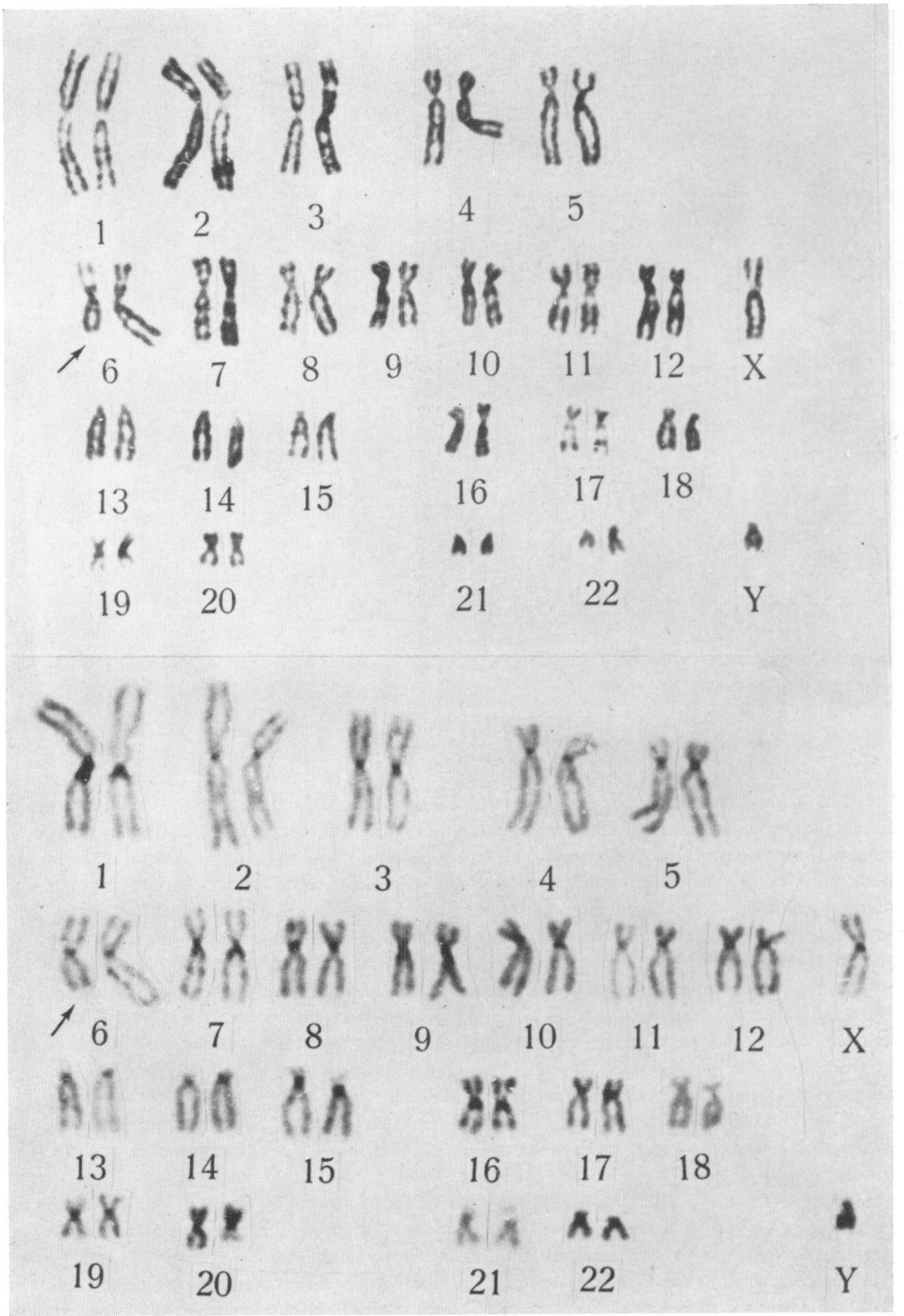

Fig. 4. GAG and GBC banded karyotypes from case 2.

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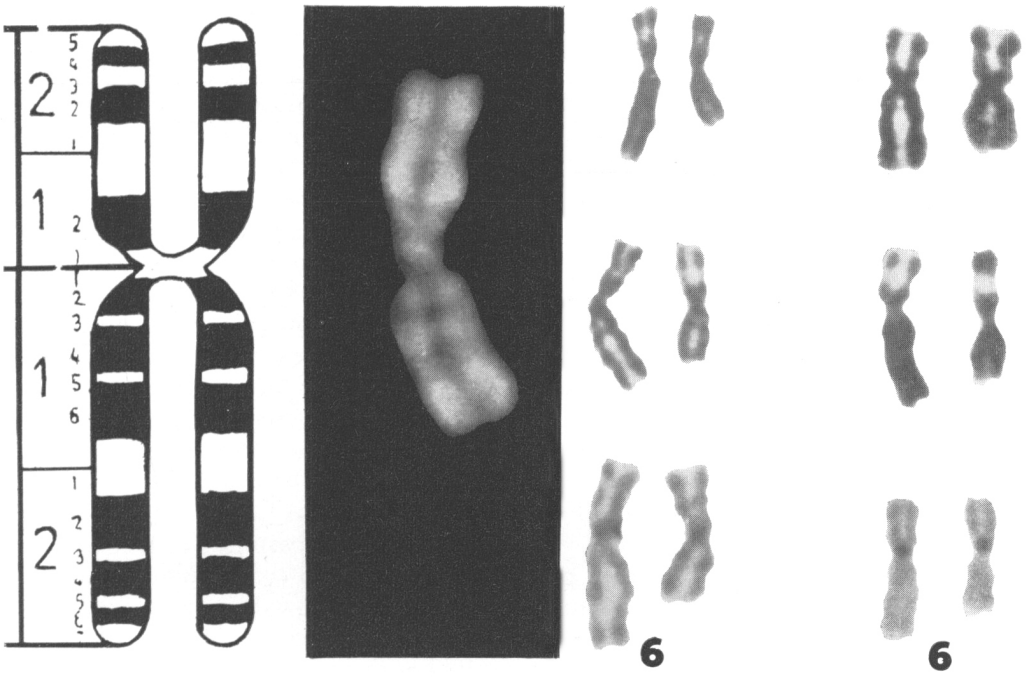

Fig. 5. Selected no. 6 chromosomes from case 2 (RBA, GAG and CBG bands).

Laboratory Investigations

Chemical and hematologic data, including blood-cell count and differential, blood glucose, BUN, serum calcium and electrolytes, alkaline phosphatase, CPK, T_3, T_4, rT_3, IgA, IgG and IgM and serum aminogram, were normal.

Fundus oculi and electrocardiogram were unremarkable.

Complete X-ray skeletal survey demonstrated large parietal bones, " J " shaped sella, coxa valga and dysmorphic metacarpal bones. Bone age was corresponding to chronological age.

Cytogenetic Investigations

Chromosome investigations were performed on short-term peripheral blood cultures. The chromosome number was 46. Standard Giemsa showed the constant absence of a C-group chromosome, which was replaced by a metacentric chromosome, the size of a D-group chromosome. GAG, CBG and RBA banding studies identified the abnormal chromosome as a deleted number 6, with break point at band 6q221. The chromosome formula was 46,XY,del(6)(q221) and the patient was monosomic for band 6q221 to band 6q27.

Cytogenetic analyses of parents and sister showed normal chromosome constitutions.

Genetic Marker Studies

Various genetic markers so far assigned to human chromosome 6 were investigated in available family members. Uninformative results were obtained on the localization of the loci for Glyoxalase, Properdin factor B (Bf) and C_2.

A normal segregation pattern was noted in the HLA and PGM_3 study. The propositus had inherited the haplotype HLA A1, B8 from the father and A1, B7 from the mother. The PGM_3 2.2 genotype was segregating

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Table. *Findings in four cases of partial trisomy 6q*

Authors:	Robertson et al. (1975)	Chen et al. (1976)		Present report (Case 2)
Familial chromosome aberration:	t(6;10)(q21;q24)	ins(5;6)(q33;q15;q27)		t(6;16)(q15;q24)
Trisomy:	6q21→qter	6q15→q27		6q21→qter
Monosomy:	10qter			16qter
Sex	F	M	M	F
Birth weight (kg)	2.43	3.0	2.7	3.0
Normal gestational age	+	+	+	+
Growth retardation	+	+	+	
Psychomotor retardation	+	+	+	
Head:				
Microcephaly	+	+	+	+
Acrocephaly	+	—	—	—
Eyes:				
Hypertelorism	+	+	+	+
Downward slanting palpebral fissures	—	+	+	+
Deep set	—	—	—	+
Nose				
Flattened bridge	+	+	+	+
Round tip	+	+	+	+
Anteverted nares	+	+	+	+
Philtrum: long	—	+	+	+
Mouth:				
Hypoplastic perioral features	—	+		+
High-arched palate		+	+	+
Jaw: large (round facial appearance)	+	+		+
Chin: receding	+	+	+	+
Ears: malformed		+	+	+
Neck: short	+			+
Limbs:				
Hypoplastic fingers/toes	+	+		+
Abnormal flexion creases		+	+	
Flexion contractures	+		+	+
Overriding toes	+			+

from PGM_3 1.2 heterozygote parents. The results rule out the localisation of these systems from region 6q 221→qter.

A normal segregation was also observed for the following blood groups: ABO, Rh, MNSs, Fy, Kk, Lu and P.

DISCUSSION

The advances in cytogenetic techniques have allowed the identification of partial trisomies and partial deletion for every chromosome. Sufficient data have been collected to establish precise karyotype-phenotype correlations in most of these chromosome imbalances (Yunis 1977). However, due to the exceptional occurrence of unbalanced structural aberrations involving chromosome 6, scanty information is available concerning the clinical features associated with partial 6p and 6q aneuplodies. Only recently, Breuning et al. (1977*b*) and De Grouchy (1977) have tentatively isolated a syndrome associated with partial trisomy 6p.

Our case 1, as well as the case described by Robertson et al. (1975) and the two patients reported by Chen et al. (1976), have a duplication of a 6q segment which, on the basis of the clinical data listed in Table I, may be considered as the causal factor in their malformation syndrome. In the presence of nonhomogeneous duplicated segments and due to the occasional coexistence of monosomy for part of another autosome in different patients, the attempts to establish phenotypic correlations must be cautious. However, the occurrence of similar clinical manifestations suggests the possibility to delineate a partial 6q trisomy syndrome. The prenatal growth is adversely affected, both in terms of linear size and brain growth. Thus, growth deficiency and mental deficiency are common features. The craniofacial abnormalities include: microcephaly, hypertelorism, downward slanting palpebral fissures, flattened nasal bridge with small, rounded tip and anteverted nostrils, long philtrum, hypoplastic perioral features, high-arched palate, large jaw resulting in a round appearance of the face, receding chin, dysmorphic ears. Short flexor tendons are responsible for contractures at the distal upper and lower limbs; fingers, toes and nails are hypoplastic.

Thus, the peculiar constellation of dysmorphisms associated with this rare autosomal imbalance appears adequate to establish partial trisomy 6q as a clinically recognizable syndrome. Description of more cases is needed to refine this provisional 6q+ phenotype outline and to expand the list of features identified so far.

The clinical manifestations of partial monosomy 6q, as derived from our case 2, seem to be rather characteristic. However, no information concerning similar imbalances is available, and the existence of a distinct syndrome associated with the deletion of the distal part of the long arm of chromosome 6 may be postulated, but not fully demonstrated. In fact, the so far reported partial 6q deletions do involve less chromosome material than our case (Mikkelsen and Dyggve 1973) or different chromosome bands (McNeal et al. 1977), so that phenotypic comparisons seem not be justified.

The most striking features in our patient are severe mental retardation and facial dysmorphisms. Reduced biparietal diameter, hypotelorism, absent eyebrows, prominent eyes with ptosis, receding chin, dysmorphic ears, large extremities, appear to be the most outstanding signs. Interestingly, and rather unusual for an autosomal deletion, growth does not appear to be affected. On the whole, some signs, like skull shape, ocular telorism, eyes and nose prominence, large hands and feet could be considered as the countertype features of trisomy 6q syndrome. However, the significance of these speculations must be proved by accumulation of information on other patients.

Deletion mapping has led to regional assignment of a few gene loci (Ferguson-Smith et al. 1973, Marsh et al. 1974, Mayeda et al. 1975, De la Chapelle et al. 1976, George and Francke 1976). HLA typing in the family of a patient with an interstitial deletion 6q13→q15 (McNeal et al. 1977) ruled out the location in this region of the major histocompatibility gene cluster, which had been assigned to chromosome 6 (Lamm et al. 1974). Studies of HLA and PGM_3 segregation in our case 2 showed normal inheritance patterns and ruled out the location of these genes in bands 6q221→qter.

Gene marker studies in a large kindred in which a reciprocal translocation t(6;20)(p21;p13) was segregating, point to a localisation of HLA genes on the short arm of chromosome 6, close to the transition between band 6p21 and p22 (Breuning et al. 1977*a*). Interspecific cell hybrids between human fibroblasts containing a balanced reciprocal translocation t(1;6)(p3200;p2100) and Chinese hamster cells have confirmed the location of the major histocompatibility complex in region 6p2100→6pter (Francke and Pellegrino 1977). Thus, our results

do not contrast with the available evidence concerning the regional assignment of the HLA gene cluster.

It is known that PGM_3 is on the D side of HLA and their recombination frequency is 0.15 in the male (Lamm et al. 1972). Data derived from ovarian teratoma have shown linkage between PGM_3 and the centromere, at a map distance of about 17 centimorgans (Ott et al. 1976). Somatic cell hybrids have assigned the gene coding for PGM_3 to region 6p21→qter (Francke and Pellegrino 1977, McBreen et al. 1977). The results presented here restrict the PGM_3 gene map in region 6p21→q221.

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