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Partial Trisomy of Short arm of Chromosome 6: A Case Due to Paternal Balanced Translocation*

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To our knowledge, there have been only six previous reports of partial duplication of the short arm of chromosome 6, involving nine patients where the clinical and cytogenetic descriptions are available.[1-6]

In this paper we report a further case of partial 6p trisomy and review the clinical and cytogenetic features of the patients with the partial 6p trisomy syndrome.

Case Report

The patient M. O. (III, 1 in Figure 1), a 2-month-old white female, was referred to St. Louis Children's Hospital for the evaluation of failure to thrive. She was a 2500 g product of a 35 week gestation, born to a 25 year-old healthy primigravida. The pregnancy was uneventful and there was no exposure to known mutagenic agents. Alcohol intake was denied. The delivery was uncomplicated, vaginal vertex. On the third day of life she developed jaundice which responded well to phototherapy. The rest of the neonatal period was uncomplicated. However, she fed poorly and gained weight slowly. She was not able to follow objects and head control was poor at the age of two months. The family history was negative for birth defects, mental retardation, and fetal wastage. Consanguinity was denied. The father was 27 years old and healthy.

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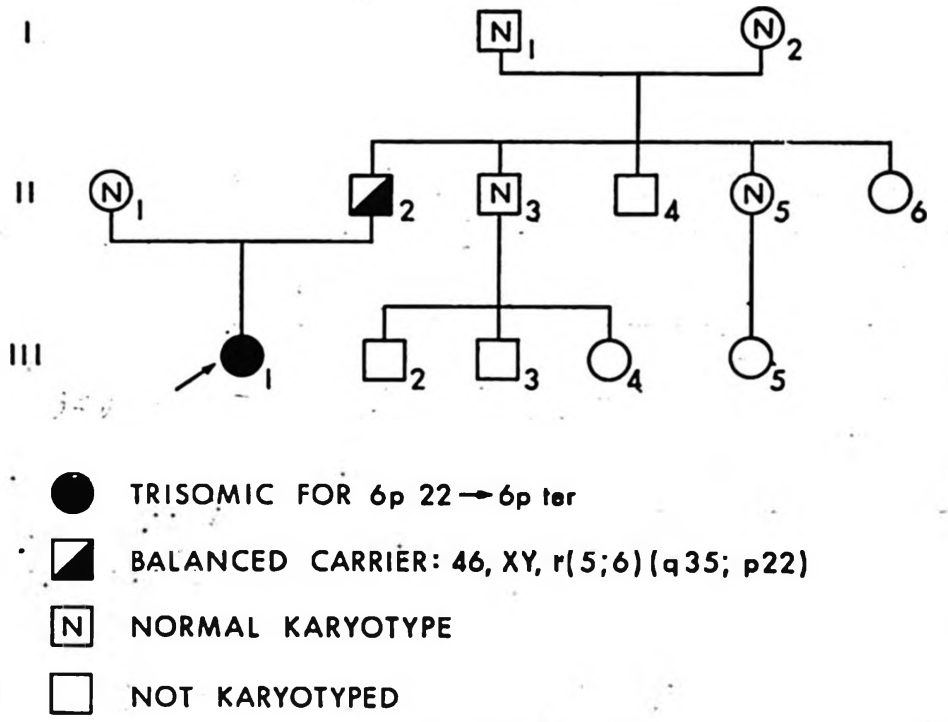

Figure 1
Pedigree

Physical examination revealed an underdeveloped infant with dysmorphic features (Figure 2). Her weight (2940 g), and length (51.5 cm) were less than 5th percentile and head circumference (36.5 cm) was on the 10th percentile for age. The asymmetric head was more prominent on the right, the forehead was high and the occiput was flat. The anterior fontanel was 7x7 cm open and there were cutaneous hemangiomata on the mid-forehead and posterior neck. The innercanthal distance was 2.8 cm (greater than 97th percentile) and palpebral fissures were normal. Both ears were low set, simple and large (75th-97th percentile). She had a prominent nasal bridge with upturned nares, and long, hypoplastic philtrum. The lips were thin and the chin was pointed. The cardiovascular examination revealed a 2/6 systolic murmur over the base and axilla with radiation to the back. The pelvis was small and there was a sacral skin dimple. The Moro was asymmetric and the thumbs were clenched. The dermatoglyphics were unremarkable.

Normal laboratory findings included complete blood count, urinalysis, electrolytes, sweat Na and Cl. glucose, BUN TORCH titers, and blood amino acids. The roentgenograms of the chest and skeletal system were normal. However, her skull was slightly asymmetrical. Computerized tomography of the brain and the ECG were also normal. The cardiac catheterization and angiography were compatible with the coarctation

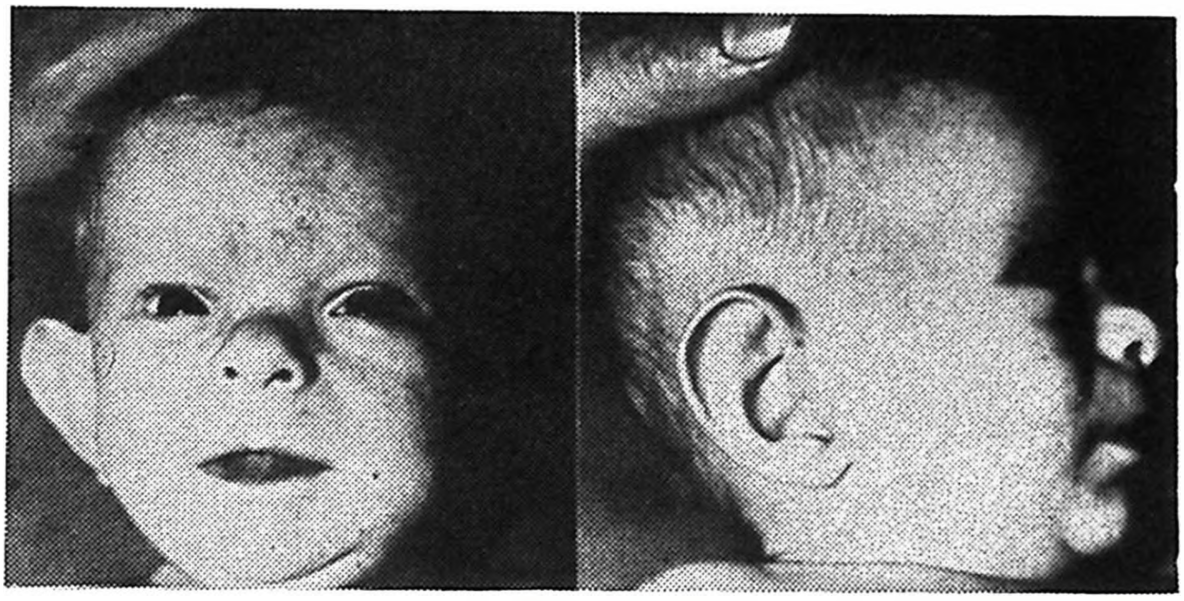

Figure 2
Proband at age 2 months

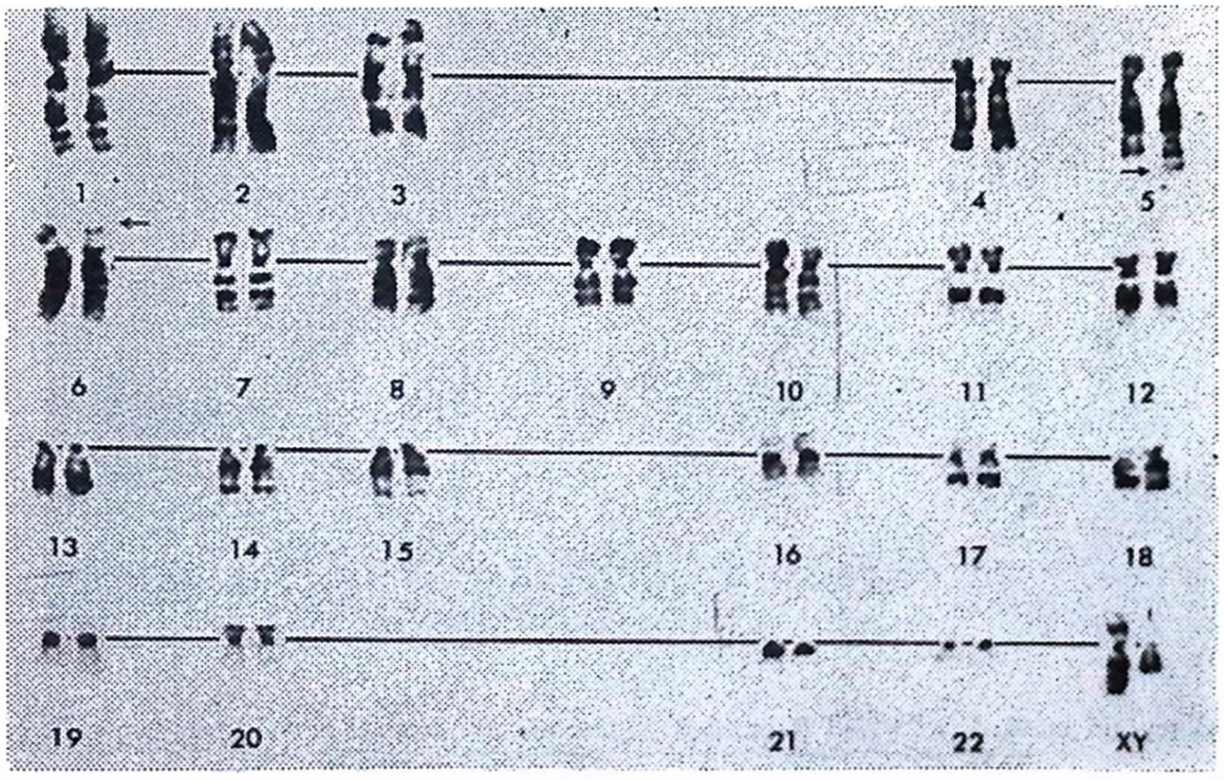

Figure 3
G-trypsin banded karyotype of the father: 46, XY, t (5;6) (q35;p22)

of the origin of left pulmonary artery, a large left atrium and minimal mitral regurgitation; cardiac function appeared normal.

The patient was seen again at age 4 months. Her weight, length, and head circumference were all below the 3rd percentile. She showed marked psychomotor delay. She began smiling at age 3 months. However, her head control was still poor and she was not able to roll over.

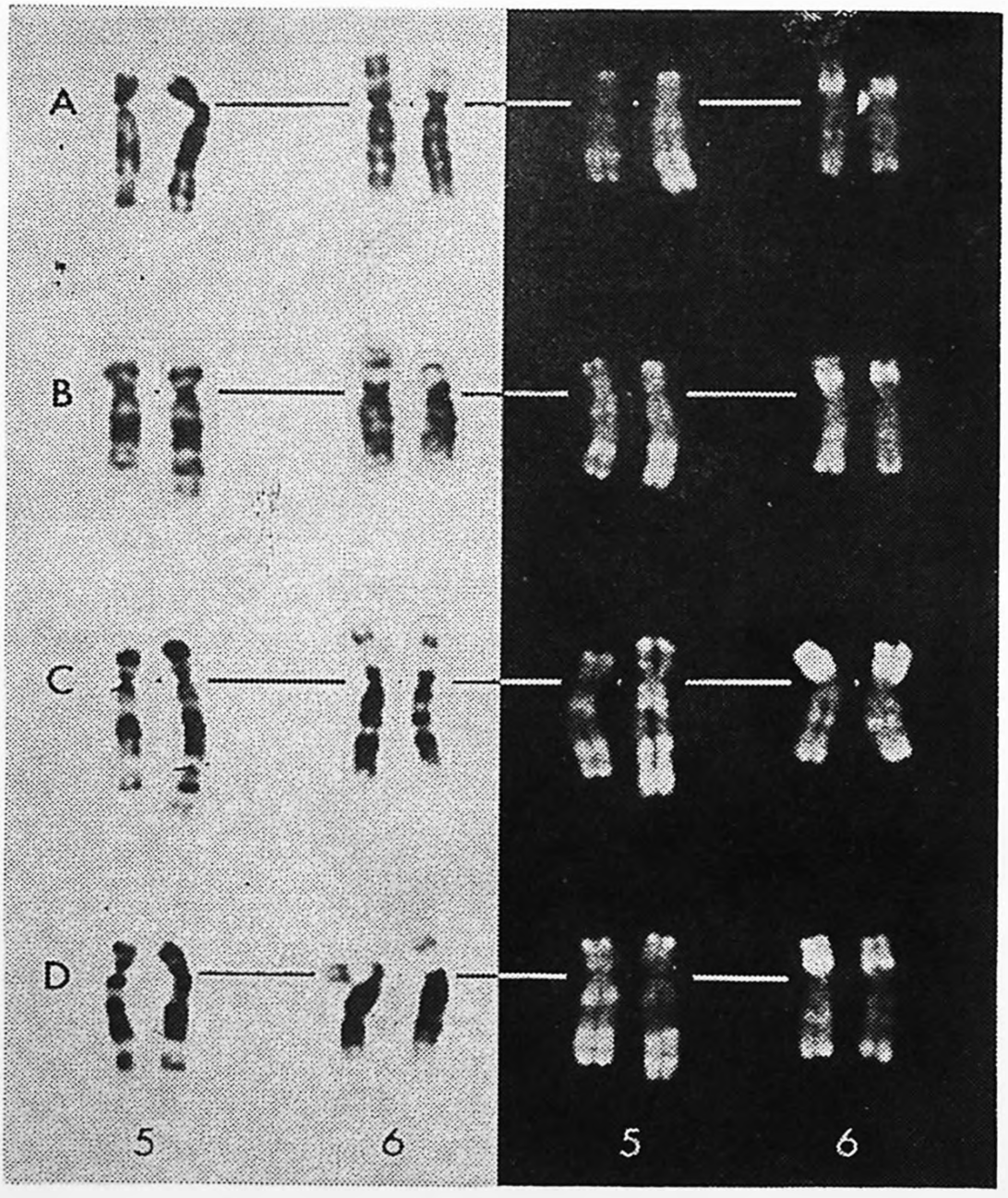

Figure 4

G-trypsin banded (left) and R-banded (right) chromosome 5 and 6 from two cells of the father (A-B) and two cells of the proband (C-D)

Cytogenetic Studies

Chromosome studies of the patient and available family members were performed from peripheral lymphocyte cultures. Slides were examined after G-banding using trypsin and R-banding, with heat denaturation using acridine orange. The patient's modal chromosome number was 46, with extra chromosome material on the long arm of chromosome 5: karyotype 46, XX, 5q+.

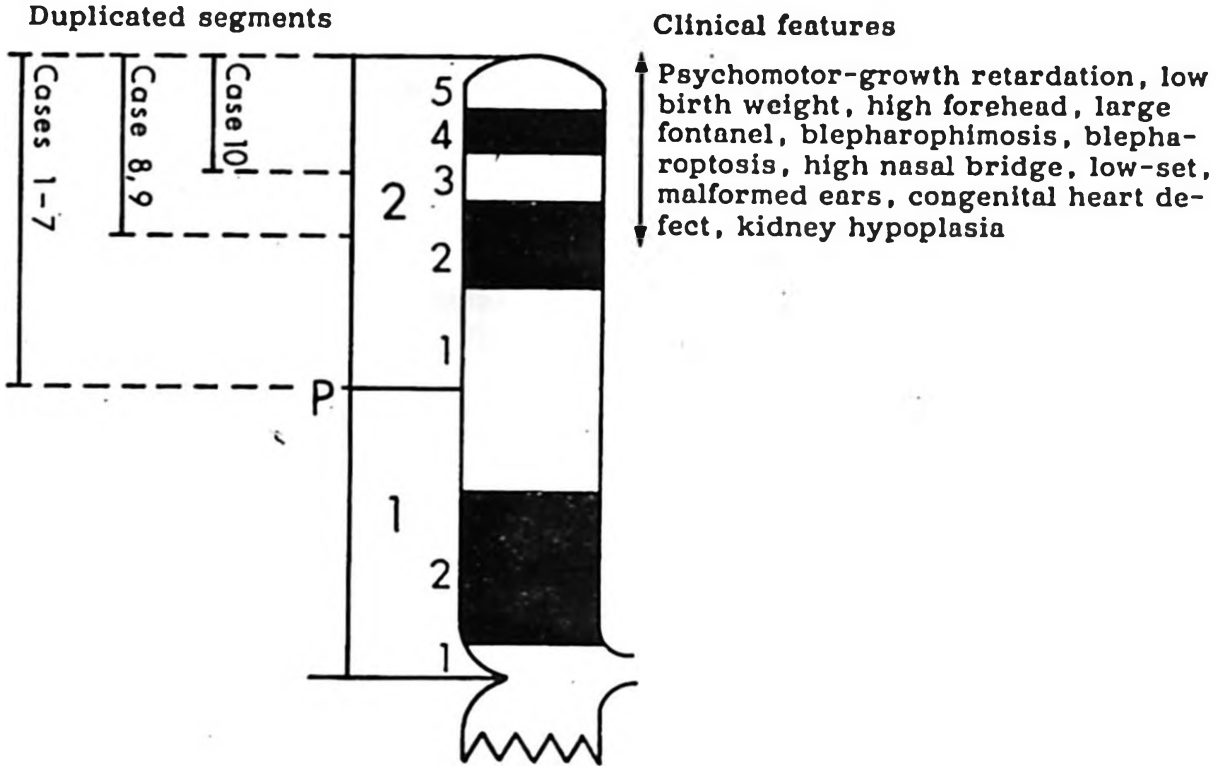

Figure 5

Duplicated chromosomal segments and clinical findings in ten patients with the partial trisomy of 6p. (Case numbers correspond to those shown in Table I)

The karyotype of the father which revealed 46 chromosomes and a reciprocal translocation between the long arm of chromosome 5 and the short arm of chromosome 6 was characterized as 46, XY, t (5;6) (5pter→5q35: :6p22→6pter; 6qter→6p22: :5q35→5qter) (Figure 3). The patient had inherited the derivative 5 chromosome from the father and one normal chromosome 6 from each parent, and she therefore had a partial trisomy of the distal short arm segment of chromosome 6 (6p22→ 6pter) (Figure 4). We assumed that she must also be heterozygous for a small deletion of 5q (5q35→5qter). The patient's karyotype can be formulated as: 46, XY, der (5), t (5;6) (q35;p22) pat. according to the Paris nomenclature. The karyotypes of the mother, paternal aunt and uncle, and paternal grandparents were normal (Figure 1).

Discussion

The clinical and cytogenetic findings of ten patients identified, as having a partial trisomy of the short arm of chromosome 6 by banding techniques and for whom detailed clinical information is available are summarized in Table I. A study of the table indicates that the main clinical features common to all ten patients are low birth weight, psychomotor retardation, facial dysmorphism including high forehead, large fontanel, high nasal bridge, low set, malformed ears, and skin abnormalities

TABLE I

CLINICAL AND CYTOGENETIC FINDINGS IN NINE PATIENTS WITH PARTIAL DUPLICATION OF THE SHORT ARM OF CHROMOSOME 6

		Therkelsen et al. (1971)			Chiyo et al. (1975)	Bruening (1977)	Bernheim (1979)	Cote et al. (1978)	Present patient	Turleau et al. (1978)
	1	2	3	4	5	6	7	8	9	10
Clinical features										
Sex	M	M	F	M	F	F	F	M	F	M
Maternal age (y)	24	26			30	24	27	25	25	25
Paternal age (y)	29	31			30	26	26	30	27	24
Survival time	Alive (2-4/12y)	Dead ($8^1/_2$m)	Dead (11m)	Dead (5m)	Alive (1-6/12y)	Dead (2-8/12y)	Dead (6m)	Dead (13m)	Alive (4m)	Alive (8m)
Low birth weight	+	+	+	+	+	+	+	+	+	+
Growth/mental retardation	+	+	+	+	+	+	+	+	+	+
Craniofacial:										
High, prominent forehead	+	+	+	+	+	+	+		+	
Flat occiput	+					+			+	
Large fontanel	+	+	+	+		+			+	
Wide sagittal suture	+	+	+			+				
Close-set eyes	+	+	+	+		±	+			
Blepharoptosis	+	+	+		+	+		+		+
Blepharophimosis	+	+	+			+	+			+
High nasal bridge	+	+				±	+		+	+
Low set-malformed ears	+	+	+	+	+	+	+	+	+	+
Skin hemangioma/sacral dimple		+/			/+	+/+		/+	+/+	
Heart defect/murmur	+	+	+			+			+	+
Small kidney	+	+	+			+			+	+
Cytogenetic features										
Trisomic segment		6p21→6pter			6p21→6pter	6p21→6pter	6p21→6pter	6p22→ 6pter	6p22→6pter	6p23→6pter
Monosomic segment		20p12-13→20pter			15p12-13→15pter	20p13→20pter	2p25→2pter	22q13→22qter	5q35→5qter	18q21→18qter

such as hemangioma and a sacral dimple. The majority of the patients also had blepharophimosis, blepharoptosis and hypoplastic kidneys. Half of the patients have had definite congenital heart defects demonstrated with cardiac catheterization or autopsy; most of these have been septal defects, semilunar valvular deformities, unexplained biventricular hypertrophy, and endocardial fibroelastosis. None of the previous reports have noted peripheral pulmonary artery stenosis which occurred in this patient. She has most of the other clinical features except the eyelid abnormalities. Unfortunately. an intravenous pyelogram was not done to demonstrate whether she had hypoplastic kidneys. However, repeated urinalysis failed to show proteinuria.

Comparison of the clinical features and the duplicated short arm segments of chromosome 6 in ten patients suggested a tentative karyotype phenotype correlation (Figure 5). The duplicated segment involved almost half of the short arm of chromosome 6 in seven out of ten patients (6p21→6pter) and in two patients, including the one presented here, the duplicated segment was smaller (6p22→6pter). The patient reported by Turleau et al.[5] had the smallest duplicated segment (6p23→6pter). Therefore the trisomic segment common to all ten patients with similar clinical features included bands 6p25, 24, and 23. Since the negative or early replicating (R) bands were thought to identify the regions of essential genes,[7] it may be concluded that the duplication of bands p23 and/or p25 is responsible for the clinical features of 6p trisomy syndrome. It is also worthwhile to note that the majority of the patients died in early childhood indicating the severity of this recently recognized partial trisomy syndrome. Cause of death in most cases appeared to be related to infection, particularly involving the respiratory system.

Summary

A partial trisomy for the distal segment of the short arm of chromosome 6 (6p22→6pter) was found in an infant with psychomotor retardation, multiple congenital anomalies and dysmorphic features. The phenotypically normal father had a balanced translocation between the long arm of chromosome 5 and the short arm of chromosome 6.

Distinct similarities of the clinical features observed in 10 patients with the partial trisomy of the short arm of chromosome 6 allowed the delineation of the syndrome of 6p trisomy. The correlation of the clinical features of the patients reported here with their cytogenetic findings suggest that the main clinical features of this newly recognized chromosomal syndrome are due to the excess of a specific short arm segment of chromosome 6 that includes bands p23 and/or p25.

Acknowledgements

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