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Trisomy 16q13→qter in a infant from a t(11;16)(q25;q13) translocation-carrier father

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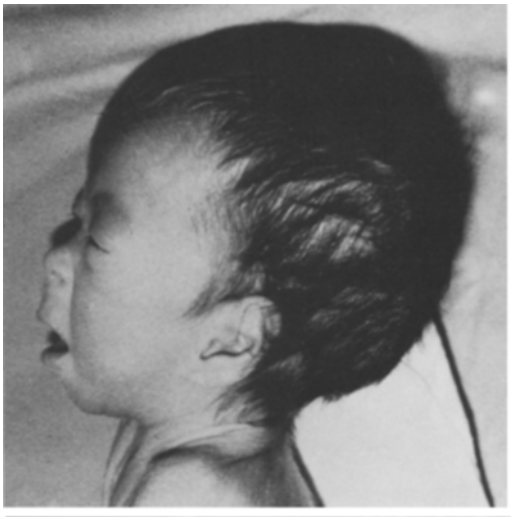
Summary. A female infant with 16q trisomy resulting from a paternally inherited balanced translocation is described and compared with five previously reported cases. All the babies were of low birth weight and expired within 1 year, with only one exception. Necropsy of the present case revealed atrial septal defect, single left lobe of the lung, anomalous lobulation of the liver, agenesis of the gall bladder, and anovestibular fistula.

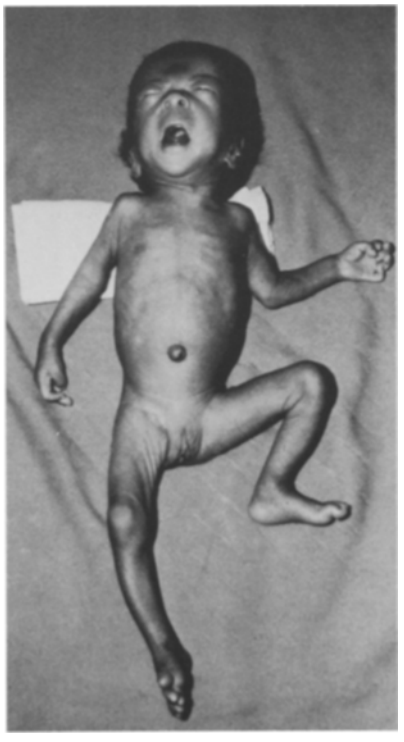
Introduction

Garau et al. (1980) found eight cases of trisomy 16q in the literature, including their own (Pergament et al. 1970; Eriksson et al. 1971; Francke et al. 1972; Alfi et al. 1973; Machin and Crolla 1974; Schmickel et al. 1975; Young et al. 1976). In addition to these reports, we found three others (Ridler et al. 1979; Balestrazzi et al. 1979; Hirai et al. 1980) and compared our case with five of the previous 11 reports in which the karyotypes were analyzed by banding methods and the phenotypes were described in detail.

Case report

This female infant was born at 35 weeks of gestation to a primigravida. Birth weight was 1500 g, length 40 cm, and head circumference 28 cm. Family history was negative. She was transferred to our nursery for intensive care at the age of 2 days because of low birth weight and imperforate anus. Emergency





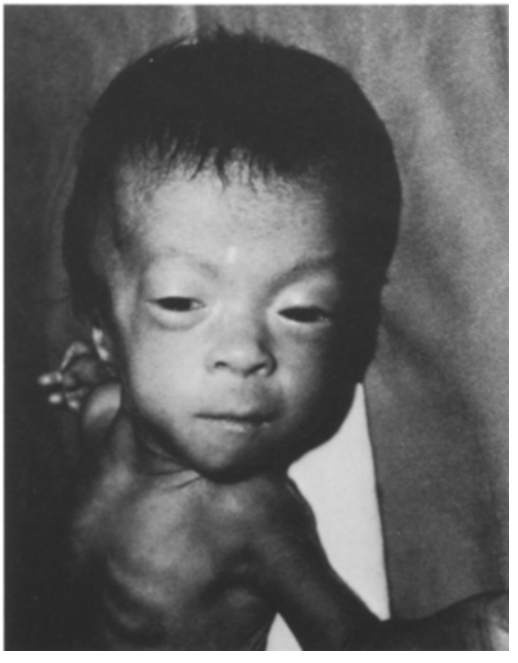


Fig. 1. Patient aged 4 months

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Table 1. Serum haptoglobin of the proband and parents compared to data from low birth babies with normal karyotype

	Age (months)	Birth weight (g)	Hp level (mg/dl)	Hp type
Proband	4	1500	16.3	2
Father			55.0	2
Mother			60.0	2
Control				
D.T.	4	1614	10.9	2
M.S.	4	1800	19.4	2
K.H.	7		59.4	2-1
K.K.			68.4	2
T.T.	15	1685	50.2	2

colostomy, however, was not necessary at that time as she had defecation through an anovestibular fistula. Standard formula and parenteral therapy were started; soon after abdominal distention and diarrhea developed. Acute enterocolitis was diagnosed with physical and X-ray examination. After the disease was cured, she failed to gain on an adequate formula. Weight at 2 months was 1436 g, at 4 months 2270 g, and at 6 months 2882 g with length 52 cm and head circumference 37 cm. At 4 months (Fig. 1), a grade 3/6 systolic murmur was heard at the upper left sternal border with heart enlargement. A large ductus arteriosus and a relatively small left ventricle with an atrial septal defect were diagnosed with echocardiograph. At that time, generalized cyanosis appeared, and chest X-ray showed a markedly enlarged heart with increased pulmonary vascularity. The patient was then placed on digitalis therapy. She died at 6 months of age.

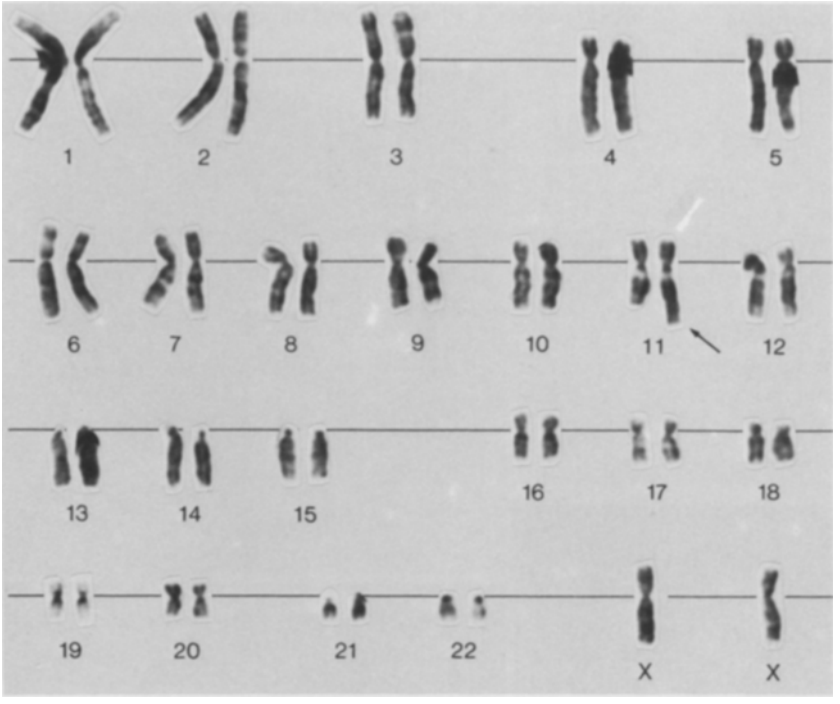

Fig. 2. A karyotype of the patient demonstrating the abnormal No. 11 chromosome

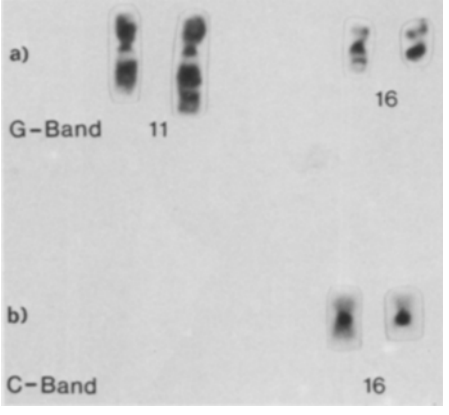

Fig. 3a and b. Partial karyotype in G-bands (a) and No. 16 chromosome in C-band (b) of the patient's father

Physical examination revealed the following: Marked failure to thrive; generalized cyanosis from the fourth month; dricocephalus, broad nasal bridge, long philtrum, thin upper lip, micrognathia, high arched palate, cleft palate, tongue-tie, and low set ears with deformed auriculas; shield chest, low set nipples, increased inter-nipple distance, and umbilical hernia; flexed fingers and clinodactyly of the fifth fingers; and an anovestibular fistula.

Biochemical and bacteriological tests were negative. ECG showed right ventricular hypertrophy. X-ray examination of the hands showed marked shortening of the middle phalanx of the fifth finger. Intravenous urography was normal.

Necropsy examination revealed an atrial septal defect, large ductus arteriosus, right ventricular hypertrophy, a relatively hypoplastic left ventricle, a single left lobe of the lung, and malrotation of the intestine. The liver had anomalous lobulation with agenesis of the gall bladder.

Table 2. Cytogenetic and clinical features of patients with 16q trisomy

	Schmickel (1975)	Ridler (1977)	Balestrazzi (1979)	Garau (1980)	Hirai (1980)	The study
Sex	M	F	M	M	F	F
Maternal age	25	31	28	27	32	20
Paternal age	?	24	29	30	34	24
Gestational age	40 weeks	?	40 weeks	40 weeks	41 weeks	35 weeks
Birth weight	1860 g	1600 g	2600 g	2470 g	2160 g	1500 g
length	44 cm	43.5 cm		40 cm	47 cm	40 cm
head circ.	30.5 cm	29 cm				28 cm
Age at first examin.	At birth	At birth	3½ years	7 days	10 days	2 days
Survival	7 weeks	12 days	Living	22 days	11 months	6 months
Karyotype Proband	47,XY,+der(16) t(15;16)(p11; p11)	46,XX,−15,+ der(15),t(15 ;16)(p11;q11)	46,XY,−22,+ der(22),t(16; 22)(q21;p12)	46,XY,−18,+der (18),t(16;18) (q21;p11.2)	46,XX,dir,dup (16q)(pter→ q24::q13→qter)	46,XX,−11,+der (11),t(11;16) (q25;q13)
Carrier	Mother	Mother	Mother	Father	Not examin.	Father
Trisomic portion	16p11→qter	16q11→qter	16q21→qter	16q21→qter	16q13→q24	16q13→qter
Monosomic portion				18p11→pter		11q25→qter
Clinical findings						
Failure to thrive	+	+	−	+	+	+
Scrub subcutaneous fat	+	+	−	+		+
Hypotonia	+		Hyper	+	+	+
Abnormal shape of skull	High forehead	Large	High forehead	High forehead		Prominent occipit
Peri-orbital edema	−		+			+
Small palpebral fissures	+	−	+	+	−	+
Depressed nasal bridge	+	Beak like	+	+	+	+
Long philtrum	+	+	+			+
Thin upper lip			+		+	+
Cleft palate						+
Micrognathia	+	+	+		+	+
Low set dysplastic ears	+	+	+	+	+	+
Depressed and short sternum						+
Umbilical hernia	+		+			+
Clinodactyly of 5th finger	+	+	−		+	+
Flexion of fingers and limbs	+	+	+	+	+	+
Simian crease		+			−	+
Small penis	+		+	+		
Undescended testis	+		+	+		
Anorectal anomaly		+		+		+
Congenital heart diseases	VSD	ASD	−	+?	VSD	ASD, PDA
Intestinal malrotation	+		−		−	+

In searching for a genetic marker, type and quantitative analysis of serum haptoglobin were examined in the patient and her parents. As the patient's haptoglobin level was a little lower than that of her parents, data on the haptoglobin analyses from five low birth weight babies having normal karyotypes were compared (Table 1). Because two of the five who were age-matched to the proband showed the same haptoglobin level as the proband, we evaluated our patient's level as being in the normal range.

Cytogenetic studies

Chromosome study was performed on a culture of the patient's peripheral blood and analyzed by Trypsin-Giemsa banding. The proband was found to have a karyotype of 46,XX,11q+ (Fig. 2). Her mother had a normal karyotype, but her father had the same abnormal chromosome 11 as the proband and, in addition, a chromosome 16 in which the distal end of the long arm was missing.

Table 3. Necropsy findings of patients with 16q trisomy

Organ	Present study	Hirai et al. (1980)	Ridler et al. (1977)	Schmickel et al. (1975)
Brain			Transverse lineal separation of occipital bone	3 cm cystic lesion in left frontal lobe, poor myelination
Heart	ASD, large ductus arteriosus, R-ventricular hypertrophy, L-ventricular hypoplasty	A little finger tip sized high VSD, marked R-ventricular hypertrophy	ASD, Pericarditis	VSD (4 mm)
Lung	Single left lobe	Abnormally narrow trachea	Primary infarct of base of left lung, atelectasis and macrophages	
Intestine	Malrotation			Duodenum malrotation and elongation
Liver and gall bladder	Anomalous lobulation Agenesis of gall bladder	Vesica fella occulta with short biliary duct	Congestion with biliary thrombi and fibrosis	
Spleen		No incisura of spleen		
Kidney		Marked fetal lobation in both	Patchy haemorrhages	
Genitalia	Anovestibular fistula	Elongated cervical canal and hypoplasia of uterine body	Anterior displacement of anus with common introitus with vagina	
Others		Short frenulum lingae		Thymus with depletion of lymphocytes loss of distinction of cortex and medulla

The breakpoint of this shortened chromosome 16 was verified by G- and C-banding (Fig. 3). These results indicated that the proband had a partial trisomy of the distal end of the long arm of chromosome 16 and possibly a small deletion of the distal end of the long arm of a chromosome 11, giving a karyotype of 46,XX,−11,+der(11),t(11;16)(q25;q13)pat. The normal chromosome complement was found in an amniotic culture on the second pregnancy of the mother after the proband died.

Discussion

At least 11 cases of partial trisomy of the long arm of chromosome 16 have been published. We selected five cases from these, which had detailed descriptions of both phenotype and karyotype, and compared these with the clinical features of our case (Table 2). Many features of these cases, such as postnatal growth deficiency, varied nose, eye and ear anomalies, hypotonia, and mental retardation are non-specific and common to many unbalanced chromosome abnormalities. Other features, however, such as low birth weight, marked failure to thrive, decreased subcutaneous fat, flexion abnormality of fingers and limbs, and a common facial appearance comprising a high forehead, small palpebral fissures, thin upper lip, and long philtrum appear to be fairly characteristic of most patients with 16q duplications. It is of interest that four of the six cases had a septal heart defect, and each of the three males had a small penis. The patients described by Gerau et al. (1980) and Ridler et al. (1977) each had an anorectal anomaly as did our patient. Three patients died perinatally, two within 1 year, and one survived 3.5 years.

Necropsy was performed in four of the patients. These findings are summarized in Table 3. Septal heart defect was observed in all cases. Intestinal malrotation was found in our patient and in the patient reported by Schmickel et al. (1975). Anoractal anomaly was confirmed in our patient, and in those of Ridler and Gerau.

Although patients with trisomy 16q have similar phenotypes, there are some clinical differences among them. These variations may be due to differing loss of genetic material, e.g., the patient described by Garau et al. was monosomic for the distal portion of 18q11→pter while our patient was monosomic for the distal portion of 11q25→qter. An additional variable phenotype could be attributed also to a different breakpoint on the long arms of chromosome 16 in each case.

We suggest that the duplication of the 16q region is critical for early infant death and for the clinically common phenotypes as mentioned above.

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