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Unbalanced 5;16 Translocation in a Boy With Papillary Thyroid Carcinoma

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This is the first reported case of an unbalanced chromosome rearrangement resulting in trisomy 5q35.5→qter and monosomy 16p 13.3→pter, in a boy with mental and growth retardation, minor anomalies, and a history of bilateral papillary thyroid carcinoma. This was the result of a familial balanced translocation. The clinical and cytogenetic manifestations of the case are presented and the possible role of the chromosomal rearrangement in the etiology of the thyroid carcinoma is discussed. © 1994 Wiley-Liss, Inc.

KEY WORDS: human chromosome 5, human chromosome 16, mental retardation

INTRODUCTION

We report on a boy with trisomy 5q35.3→qter and monosomy 16p13.3→pter, who had mental and growth retardation, minor anomalies, and papillary thyroid carcinoma.

CLINICAL REPORT

An 8-year-old white male (Fig. 1, IV-5) was evaluated for developmental delay and facial anomalies. He was born at 36 weeks gestation by spontaneous vaginal delivery following an uneventful pregnancy to a 27-year-old G3P1 mother; the father was 31 years old and both parents were healthy. There were no teratogen exposures or illnesses during pregnancy. The neonatal period was uneventful. A bilateral inguinal herniorraphy was performed at age 3 months. He had a frenulectomy at age 4 years and a bilateral orchidopexy at age 7 years.

He presented at age 6 months with a right-sided neck mass and stridor. A thyroid computed tomography (CT) scan showed a mass in the right lobe of the thyroid gland causing minimal displacement of the gland. A right thyroid lobectomy and isthmectomy were performed. A diagnosis of follicular adenoma was made when pathological examination showed a cellular adenoma composed of small, closely packed follicles. The cells were cuboidal in shape and the nuclei were round and regular. Three months postoperatively his T4 was 9 μg/dl, thyroid-stimulating hormone (TSH) was 15 μU/ml, and T3 resin uptake was 28%. Six years later, in 1990, he developed a left-sided neck mass. Thyroid function tests were normal. A CT scan of the neck showed a well circumscribed 1 × 1.5 cm mass in the left lobe of the thyroid gland. A complete thyroidectomy was performed and histology showed an encapsulated low grade papillary carcinoma with no spread to local lymph nodes. Review of the pathology slides from the first tumor was consistent with papillary thyroid carcinoma; it was well differentiated, the follicles varied in size and shape, some forming papillary structures. The nuclei had a ground glass appearance and were often overlapping. Mitoses were not prominent. He was placed on thyroid hormone replacement.

A complete blood count showed hemoglobin 12.3 g/dl, hematocrit 37.7%, mean corpuscular hemoglobin 22 pg (NR 27–31), mean corpuscular volume 67.6 fl (NR 80–100), mean corpuscular hemoglobin concentration 32.6 g/dl (NR 32–36).

His development is delayed. He sat alone at age 9 months, crawled at age 2 years, and walked at age 3 years. At age 8 years he speaks some words and simple phrases, but his speech is difficult to understand (this predates his thyroid surgery). His hearing is normal and he can follow simple commands. He can perform simple activities of daily living—eating, dressing, and undressing with minimal supervision. He has been receiving special education since age 9 months.

On physical examination at age 8 years his weight was 41.8 kg (<3rd centile), height was 116 cm (<5th centile), OFC was 50.5 cm (<3rd centile) (Fig. 2). The skull was dolichocephalic in shape, the fontanelles were closed, and the sutures were normal. The face was narrow with a prominent forehead. The palpebral fissures were downslanting, the inner canthal distance was 3.5 cm (97th centile), interpupillary distance was 5.5 cm (75th centile), and the outer canthal distance was 8.5 cm (75th centile). There was a left-sided epicanthal fold. The nasal bridge was prominent and the nose appeared

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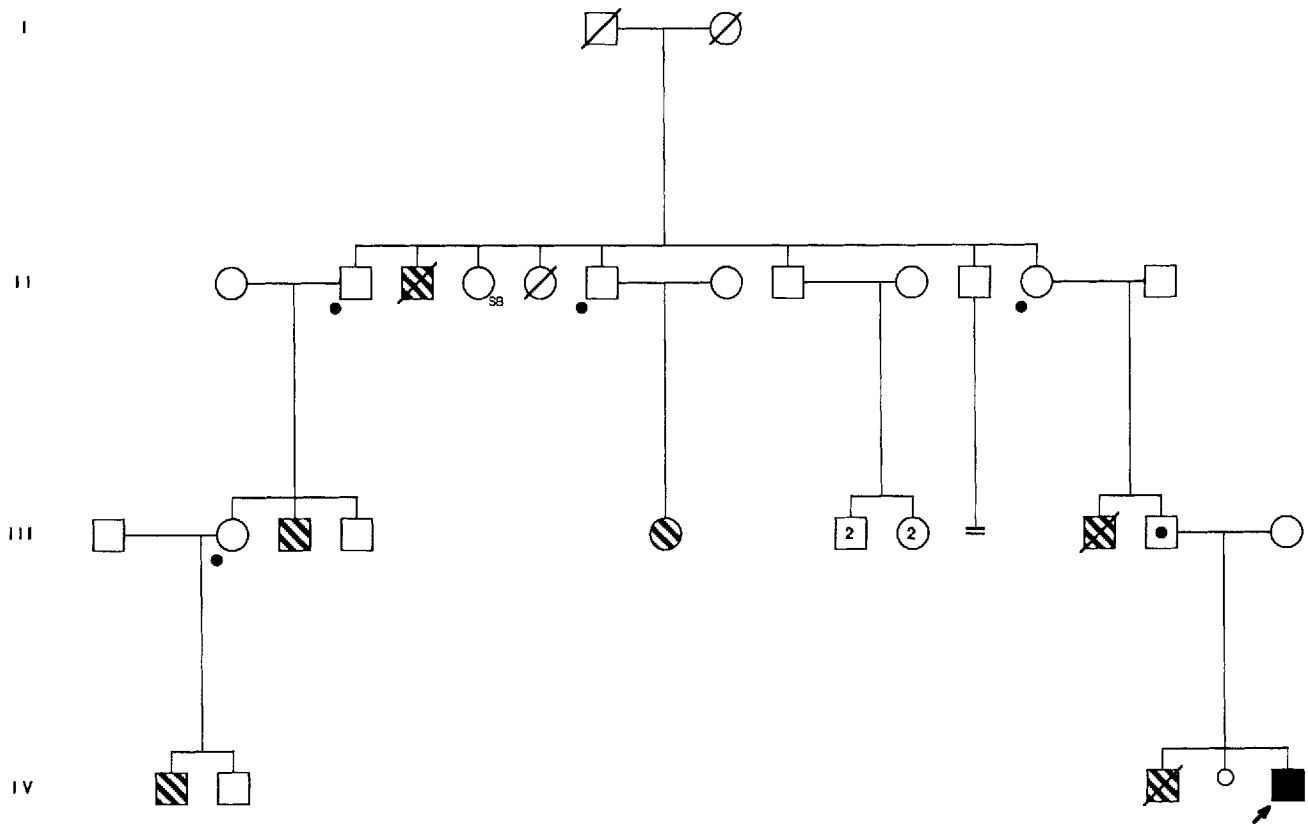

Fig. 1. Pedigree of family with 5;16 translocation. Individual II-3 was mentally handicapped and institutionalized. Individuals II-2, II-6, II-11, III-2 are presumed balanced translocation carriers as they have children who are mentally handicapped presumably secondary to an unbalanced chromosome rearrangement. □ Presumed translocation carrier, ⊡ balanced translocation carrier, ▨ presumed unbalanced translocation.

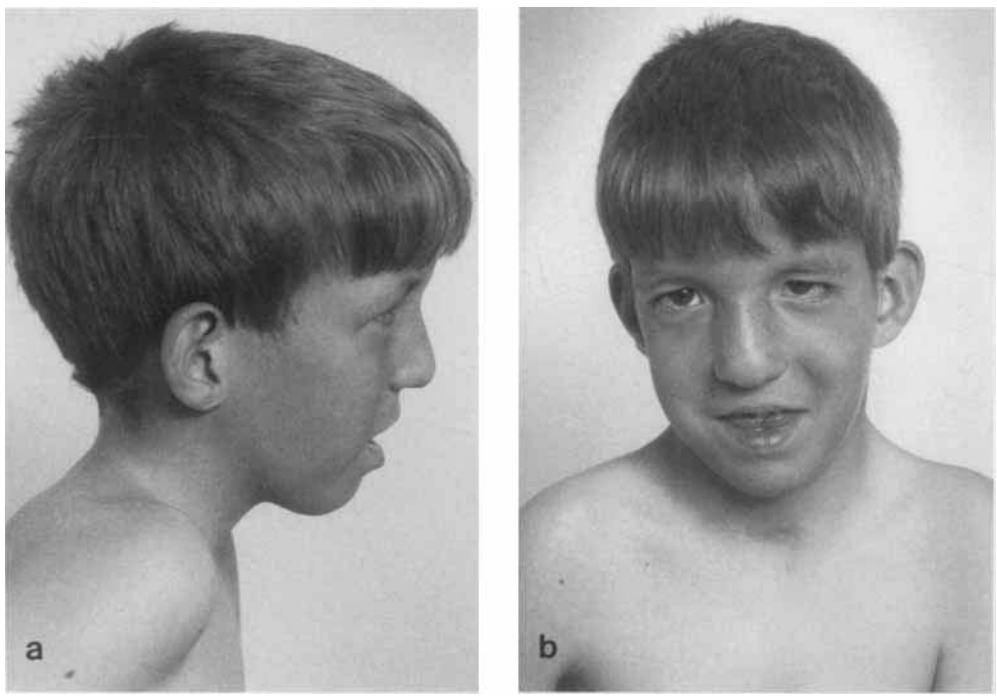

Fig. 2. **a,b:** Photograph of the propositus's head and neck showing dolichocephaly, downslanting palpebral fissures, prominent nose, protruding ears, and thyroidectomy scar.

large. The philtrum was smooth and the upper lip was thin. The mouth tended to remain open, the palate was intact, and the teeth were crowded. The chin was normal. The ears were simple, low set, and protruding. There was slight neck webbing.

He had a pectus excavatum, hypoplastic nipples, and a thoracic scoliosis concave to the left. The lung fields were clear. Cardiovascular examination was normal. There was no organomegaly and no lymphadenopathy. The scrotum was small, both testes were palpable, and the penis was normal. He had thin limbs. Bilateral fifth finger camptodactyly was present at birth. Hand, palm, and finger lengths were normal. The feet were narrow and the foot length was 15 cm (<3rd centile) bilaterally. There was bilateral pes planus and the toenails were hypoplastic. Central nervous system examination was normal.

Family History

He is the only child of healthy unrelated parents. Their first child, IV-3 (Fig. 3) had multiple congenital anomalies and died at age 18 months and the second pregnancy ended in miscarriage at approximately 3 months gestation.

The medical records of the first child, IV-3, were reviewed. He was born in 1980, the 6 pound 7 ounce product of a full-term normal pregnancy to a 24-year-old primigravida. He had failure to thrive with weight and length below the third centile. The skull was brachycephalic and the OFC was 34.8 cm (25th centile). Scalp hemangiomas were present. The face was square in shape. There was telecanthus and blue sclerae. The nasal bridge was broad and the nose was short. He had an incomplete cleft of the left upper lip and a high arched palate. The ears were posteriorly rotated, the superior helices appeared "crushed down" bilaterally, and a right preauricular skin tag was present. The nipples and umbilicus were hypoplastic. He had bilateral inguinal herniae and bilateral congenitally dislocated hips. The penis was short with chordee and hypospadias. The testes were undescended bilaterally and he had a horseshoe kidney. Soft tissue syndactyly of toes 2 and 3 was present on both feet. Cardiac catheterization showed anomalous origin of the left coronary artery from the pulmonary artery and a dilated poorly contracting left ventricle. He continued to have failure to thrive and developmental delay and he died at age 18 months. Autopsy showed acute focal bronchopneumonia and chronic hypoxemic heart disease; the congenital heart defects were confirmed and in addition, severe endocardial fibroelastosis of the left ventricle was found. No

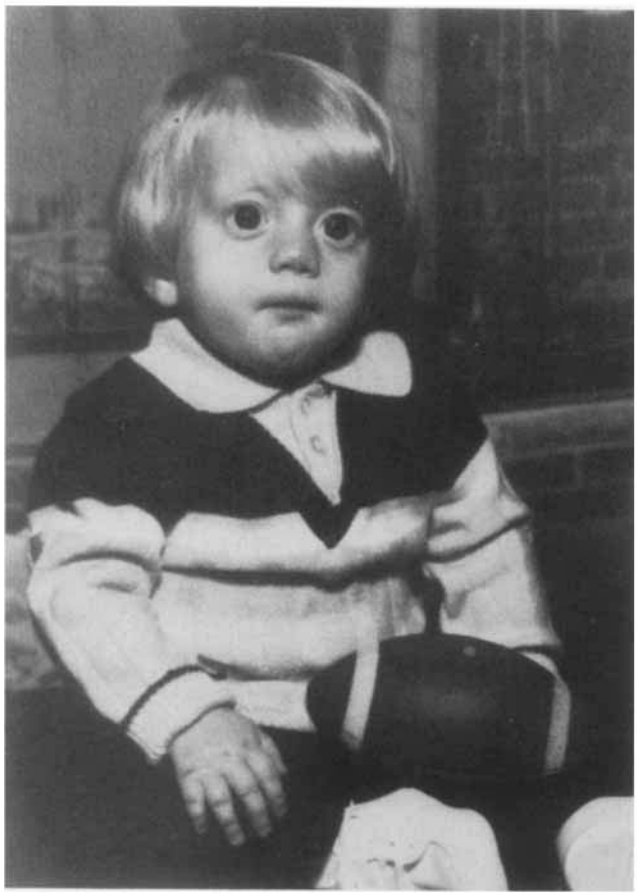

Fig. 3. Photograph of the deceased brother (IV-3) showing wide-set eyes, short nose, and cleft lip repair.

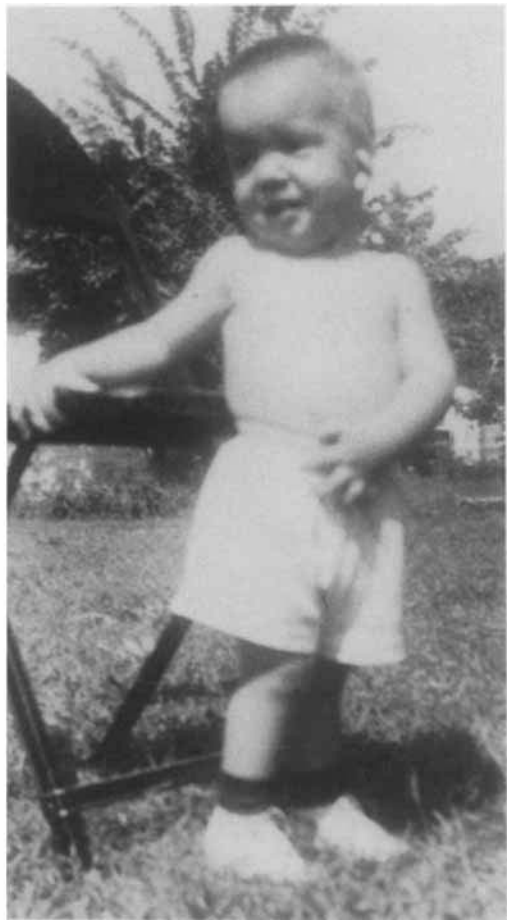

Fig. 4. Photograph of the propositus's paternal uncle (III-10), his facial features are similar to the propositus.

other additional findings were noted. A karyotype was reportedly normal.

The family history on the maternal side was noncontributory. The father had one sib, III-10, who died in 1953 between age 2 and 3 years (Fig. 4). His facial appearance bears a striking resemblance to that of the propositus. The limited medical records available indicate that he had developmental delay, bilateral congenital hip dislocation, and bilateral undescended testes. His hemoglobin was 8.5 g/dl with hypochromic, microcytic red cells. In 1953 he developed an abdominal mass. Pathological examination revealed multiple segments of fibrous connective tissue with diffuse infiltrating neuroblastoma; some of the malignant cells were arranged in rosettes. There were a number of multinucleated giant cells and multiple areas of necrosis and hemorrhage.

Cytogenetics

A karyotype (Fig. 5) at the 750–850 band stage showed an apparently reciprocal unbalanced translocation between chromosomes 5 and 16, 46,XY,−16,+der(16)t(5;16)(q35.3;p13.3). He is trisomic for the small segment 5q35.3→qter and apparently monosomic for 16p13.3→pter. The father carries a balanced translocation: 46,XY, t(5;16)(q35.3;p13.3).

DISCUSSION

This is the first reported case of this chromosomal imbalance, trisomy for the distal segment of chromosome 5q and monosomy for the distal segment of 16p. The main clinical manifestations are mental retardation, growth retardation, and minor facial anomalies.

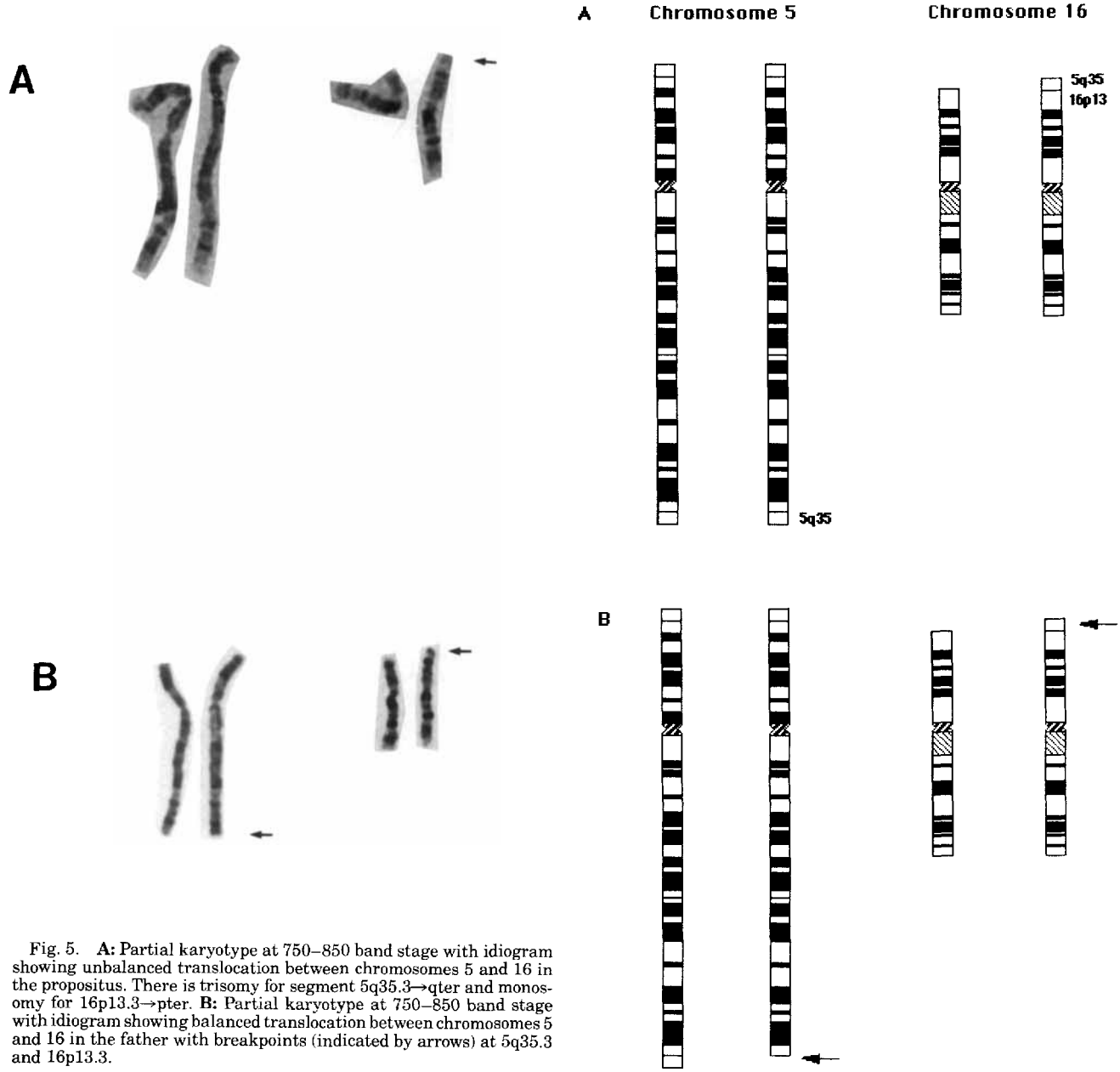

Fig. 5. **A:** Partial karyotype at 750–850 band stage with idiogram showing unbalanced translocation between chromosomes 5 and 16 in the propositus. There is trisomy for segment 5q35.3→qter and monosomy for 16p13.3→pter. **B:** Partial karyotype at 750–850 band stage with idiogram showing balanced translocation between chromosomes 5 and 16 in the father with breakpoints (indicated by arrows) at 5q35.3 and 16p13.3.

TABLE I. Clinical Manifestations of Distal Trisomy 5q

Duplicated segment	5q35.3 →qter	5q35 →qter	5q34 →qter	5q33 →qter	5q31 →qter
Number of cases	Present case	2[a]	4[b]	9[c]	9[d]
Growth retardation	+	2	4	7	5
Microcephaly	+	2	1	7	8
Mental retardation	+	2	4	6	4
Hypertelorism	−			7	4
Epicanthus	+			1	3
Antimongoloid slant	+	2		4	3
Strabismus	−		4	2	4
Prominent nasal bridge	+	1	4	8	2
Small mouth	−	1		4	
Micrognathia	+	2		5	4
Low-set ears	+	1	2	7	6
Dysplastic ears	−	2	1	1	1
Congenital heart disease	−	2		8	6
Inguinal hernia	+	1	2	1	

[a] Kumar et al. [1987]; Sonoda et al. [1989].
[b] Curry et al. [1979].
[c] Bartsch-Sandhoff and Liersch [1977]; Beemer et al. [1984]; Martin et al. [1988]; Passarge et al. [1982]; Watanabe et al. [1977]; Zabel et al. [1978].
[d] Elias-Jones et al. [1988]; Ferguson-Smith et al. [1973]; Jones et al. [1979]; Lazjuk et al. [1985]; Osztovics and Kiss [1975]; Rodewald et al. [1980]; Schroeder et al. [1986].

Review of the literature reveals 24 previously reported cases of trisomy of distal 5q (Table I). The trisomic segment in these cases is larger than in our case but he does share certain clinical manifestations with these other cases—growth retardation, microcephaly, mental retardation, inguinal herniae, and facial features such as downslanting palpebral fissures, prominent nose, and low-set ears. The monosomic segment is unique in each of these cases which may account for the clinical differences between them.

Wilkie et al. [1990] reported 8 children with monosomy 16p13.3→pter in their analysis of the alpha thalassemia/mental retardation syndromes; 4 had unbalanced translocations and 4 had del(16)(p13.3) alone. The clinical features in these 8 children were alpha thalassemia, mental retardation, and facial anomalies which varied among the group. Hypertelorism was however, a frequent finding (5 of 8 cases). Exclusion of the 4 cases with aneuploidy of a second chromosome leaves a more homogeneous group with hypertelorism, downslanting palpebral fissures, prominent nose, crowded teeth, and small chin. Other features in these patients included pectus excavatum, inguinal hernia, speech delay, and poor articulation. These features are also present in our case. The alpha globin genes map to 16p13.3 [Breuning et al., 1987]. The propositus and his paternal uncle (III-10, who appeared to have the same unbalanced chromosome rearrangement) both had hypochromic, microcytic anemia. While iron deficiency is a common cause of this, disruption of the alpha globin gene at 16p13.3 leading to alpha thalassemia trait could also account for it.

The propositus' deceased brother, IV-3 (Fig. 3), presumably also had an unbalanced chromosomal complement. His physical appearance and other clinical features are sufficiently different to suggest that he inherited an alternative unbalanced arrangement. His karyotype was reported as normal 12 years ago. A chromosome abnormality could have been missed since the duplication/deletion in the propositus is subtle and requires high resolution chromosome banding for its detection. We postulate that individual III-10 (Fig. 4) had a similar chromosomal imbalance to the proband due to the striking similarity in facial features and the history of developmental delay, undescended testes, and congenital hip dislocation. Other family members on the paternal side with mental retardation may also have an unbalanced translocation; the pedigree is certainly suggestive of a chromosome translocation segregating in this family.

The occurrence of papillary thyroid carcinoma in the propositus at age 6 months and again at age 6 years is unusual. Papillary thyroid carcinoma is a rare tumor in children representing approximately 1.5% of all tumors before age 15 years; the peak incidence is between age 7 and 12 years. Samuel and Sharma [1991] reported a 26-year review of thyroid cancer, 59 cases occurred in persons less than age 18 years and no cases of papillary thyroid carcinoma were observed in children under age 10 years. It is an attractive hypothesis to implicate the propositus' chromosomal rearrangement in the etiology of his thyroid carcinoma. The father who is a balanced translocation carrier and other family members who are presumed carriers do not have a history of cancer. This suggests that the breakpoints themselves may not be involved in tumorigenesis. An alternative explanation is the presence of a tumor suppressor gene on 16p. Germline loss of 16p in the propositus followed by loss of the second allele in thyroid tissue may underlie his tumor development.

Cytogenetic analysis of 26 papillary thyroid carcinomas and 5 follicular carcinomas by Herrmann et al. [1991] showed clonal abnormality in 9 (3 follicular thyroid carcinoma and 6 papillary thyroid carcinoma), and included −Y (2 cases), +5 (2 cases; the sole clonal ab-

normality in one of these), or inv(10)(q11.2q21.2) (one case) in papillary thyroid carcinoma. Loss of the Y chromosome represents a nonspecific finding in tumor cells. The chromosome 10 rearrangement is significant as Grieco et al. [1988] reported an oncogene mapped to 10q11.2 which is frequently activated in papillary thyroid carcinoma [Donghi et al., 1989]. It is possible that distal 5q may also harbor a candidate chromosomal locus involved in the pathogenesis of papillary thyroid carcinoma and this would provide an alternative explanation for the unusual occurrence of this tumor. A case of papillary-follicular thyroid carcinoma in a young woman with an unbalanced chromosome translocation, dup 20p and del 12p, was reported recently [Clark et al., 1993]. The authors suggested that the terminal part of 12p contains genes involved in suppression of thyroid carcinogenesis.

Individual III-10 who appears to have the same clinical phenotype as the propositus also developed a malignancy—neuroblastoma. Genetic abnormalities implicated in the pathogenesis of neuroblastoma include chromosome 1p deletions (loss of a putative tumour suppressor gene) [Brodeur and Fong, 1989] and amplification of a specific oncogene N-myc [Seeger et al., 1985]. No references to implicate chromosome 5 or 16 in the cause of neuroblastoma were found in the literature. Unlike papillary thyroid carcinoma, neuroblastoma is a recognized pediatric tumor and its occurrence may have been coincidental; however, a potential tumor suppressor gene on 16p may be involved in the pathogenesis of several tumors.

In summary, this is the first reported case of an unbalanced chromosome translocation with trisomy 5q35.3-qter and monosomy 16p13.3-pter. This was an inherited familial translocation and other family members also appear to be affected. The main clinical features are mental retardation, growth retardation, and facial anomalies. These features appear to be a composite of those previously described in cases with trisomy distal 5q or monosomy 16p13.3. The occurrence of papillary thyroid carcinoma in this case is an unusual feature which merits further attention; the chromosomal rearrangement may have altered or activated genes involved in growth regulation leading to early papillary thyroid carcinoma.

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