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Cytogenetic Evidence of Involvement of Chromosome Regions 15q12 and 12q15 in Conditions with Associated Overgrowth

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ABSTRACT

Syndromes with associated overgrowth are poorly understood. Besides their mode of inheritance, nothing is known regarding the basic genetic alterations that lead to their abnormal phenotypic manifestations. The chromosome localization of the genes involved remains unknown for this group of syndromes, with the only exception being the Wiedemann-Beckwith syndrome.

INTRODUCTION

An increased propensity for tumor development has been described in most of the overgrowth syndromes. This propensity has been well established in the Wiedemann-Beckwith syndrome (macrosomia, macroglossia, omphalocele, ear creases). Bannayan-Zonana syndrome (neonatal macrosomia with postnatal growth deceleration, macrocephaly, hamartomas). Ruvalcaba-Myhre-Smith syndrome (macrosomia, macrocephaly, polyposis of colon, pigmentary changes of penis), and Proteus syndrome (macrosomia, hemihypertrophy, macrodactyly, hamartomas), and also has been suggested by Maldonado *et al.* (1984) and Cole and Hughes (1990) for the Sotos syndrome (macrosomia, macrocephaly, poor coordination during infancy). This tendency points toward the possibility that different cellular growth factors might play an important role in this group of syndromes.

The localization of the genes that are responsible for the overgrowth syndromes is a very important clue toward understanding the basic mechanisms that lead to the clinical manifestations; consequently, this group of syndromes might throw some light on a few of the various mechanisms of tumorigenesis.

Chromosome aberrations have been a valuable tool for disease gene assignment. Among the syndromes leading to overgrowth, only the Wiedemann-Beckwith syndrome was assigned to a specific chromosomal region; rare karyotypic abnormalities, such as deletions, duplications, or translocations at 11p11-p15, were the initial hints leading to the final localization at 11p15.5.

Previously we have suggested the association of two chromosome regions (15q12 and 12q15) with overgrowth-associated syndromes (Wajntal and Koiffmann, 1991) and tumorigenesis (Wajntal *et al.*, 1991); however, clinical data and cytogenetic evidence remain unpublished. We present the cytogenetic data on structural chromosome aberrations detected in three proposita studied by use, two with overgrowth and malformations that are not typical of any of the already well-defined syndromes, and one with Sotos syndrome whose father is also affected and has the same chromosome abnormality. The clinical features of the patients who remained undiagnosed will also be described and discussed in view of their relevance to cytogenetic data.

MATERIAL AND METHODS

We studied 35 patients with overgrowth and multiple malformations: Sotos syndrome was diagnosed for 17 patients; Weaver syndrome for 2; Bannayan-Zonana syndrome, Klippel-Trenaunay-Weber syndrome, and Proteus syndrome, one case of each; 13 patients remained without a syndromic diagnosis because, as far as we know, their phenotypic characteristics did not match any of the criteria previously described. Patients with Wiedemann-Beckwith syndrome, endocrinologic abnormalities, or other well-es-

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tablished conditions such as Marfan syndrome, XYY, XXY, etc., were excluded from this study.

All patients were subjected to clinical, endocrinologic, radiologic, and cytogenetic studies. Parents and sibs were always examined and the family history was recorded. Cytogenetic studies were performed on lymphocyte cultures with GTG banding techniques. When considered necessary, other banding techniques were also used.

RESULTS AND DISCUSSION

Among the 35 patients studied, 2 were found to have gross abnormal chromosome constitution. Both patients had somatic characteristics different from any of the known overgrowth syndromes.

Patient 1 (Fig. 1)

ARA, a boy, was born on December 3, 1984, to healthy nonconsanguineous parents of 33 (father) and 30 (mother) years of age, after normal pregnancy and elective caesarian delivery. He was his mother's second delivery; his older sister is healthy. Birth weight was 3,780 g (>97 centile), birth length 50 cm, OFC 37 cm (97 centile). APGAR was 5 (1 min) and 7 (2 min). He started sitting by 1 year, walking by 2 years, and speaking when 3 years of age; at age 4½ he was referred to a genetic study because of overgrowth and psychomotor retardation. His physical examination showed: height 112 cm (>90%), weight 26 kg (>97%), OFC 54 cm (>98%), peculiar facies with high forehead and temporal receding hair, large posteriorized ears with antihelix hypoplasia, hypertelorism (inner canthal distance 3.5 cm; outer canthal distance 8 cm), bulbous nose, macrostomia, thin upper lip, micro- and retrognathia, short broad neck, large hands: middle fingers 5.5 cm (>75 centile), palms 8.5 cm (>97 centile) clinodactyly of the 5th fingers, Sydney-type palmar crease, and bilateral dislocation of triradius t to a t'' position. He had fair skin and blond hair differing from parents and sister.

Chromosome analysis of the patient disclosed the following constitution: 45,XY,t(15;15) (qter→p11::q12 or q13→qter) with a consequent deletion of 15q12 or q13 (Fig. 2). The father, mother, and sister are karyotypically normal.

Patient 2 (Fig. 3)

JAA, a girl, was born on November 26, 1988, from healthy nonconsanguineous parents. The father was 22 years and the mother 18 years old. The mother, a primigesta and primipara young woman, had a normal pregnancy except for one episode of bleeding during the fourth month of gestation. Delivery was by caesarian section because of the child's size. Birth weight was 6,200 g (>>97 centile), birth length was not recorded, and she had cyanosis and neonatal jaundice and was treated for 4 days with phototherapy. She was referred for genetic evaluation because of overgrowth, dysmorphism, and hypotonia when 10 months old. On this occasion her physical examination

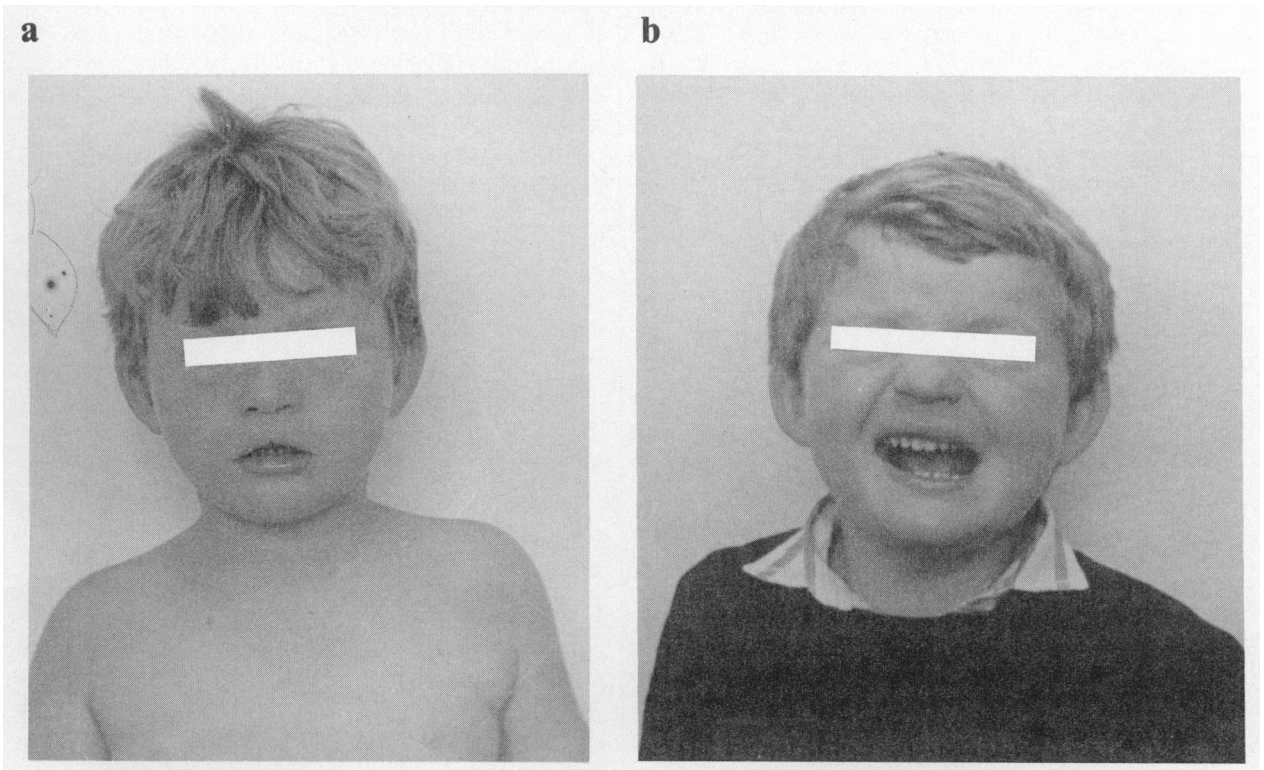

FIG. 1. Patient 1 at 4½ years of age (a) and when 5 years 1 month of age (b).

showed: height 80 cm (>>97 centile), weight 9,750 g (>75 centile), OFC 43 cm (<50 centile), asymmetric head and face with increased size on the right; prominent forehead and metopic suture, large posteriorized ears with preauricular pit on the left, bilateral palpebral ptosis, epicanthus, telecanthus, blepharophimosis, high congenital myopia and horizontal nystagmus, antimongoloid slanting of palpebral fissures, blue sclerae, flat nose, highly arched palate, short neck with a hypochromatic spot under the chin region on the left, umbilical hernia, small hands with clinodactyly of the fifth fingers and hyperflexibility of finger joints, cyanosis of fingertips and toes, halux of increased size, echinovarus deformity of the feet, global hypotonia, and psychomotor retardation: she started sustaining her head at 8 months and was not yet sitting at the time of examination. EEG and TAC findings were normal. Bone age at 6 months was 9 months. Her paternal aunt had a child that died after the first 24 hours of life with microcephaly and polydactyly of hands and feet on which further information is not available.

Cytogenetic analysis disclosed the chromosome constitution 46,XX/46,XX,12p+, the extra material present being consistent with dup 12 (q11→q15) (Fig. 4). The abnormal constitution was present in 21% of the cells analyzed. Parental karyotypes were not available.

Among the overgrowth patients with chromosome abnormalities described in the literature the same breakpoints as found in our patients 1 and 2 have been described in two patients with Sotos syndrome: Koyama *et al.* (1985) describe a girl with 47,XX,+inv dup (15) (pter→q12 or q13; q12 or q13 pter) and Tamaki *et al.* (1989) describe a girl with t(2,12) (q33.1;q15). In common with our patients are the chromosomal breakpoints in 15q12 and 12q15. In addition to those, there are two more reports on chromosome alterations in Sotos syndrome involving other chromosome regions: the case described by Nakada *et al.* (1982) with 46,XX inv 8(p21.3;q22.1) and the case described by Schrander-Stumpel *et al.* (1990) with 46,XY,t(3;6) (p21;p21).

Because both chromosome breakpoints 15q12 and 12q15 have been described previously among Sotos syndrome patients, we reexamined those chromosomal regions in all our Sotos syndrome patients. We found that one of our patients (patient 3) and his affected father have a del (15) (q12 or q13) (Fig. 5 and Fig. 6). The somatic features of this patient and his father have been described previously (Moretti-Ferreira *et al.*, 1991).

Patient 1 with t(15;15) and deleted regions 15q12 (or 13)—the Prader-Willi/Angelman region—presents phenotypic features that resemble both syndromes: light skin,

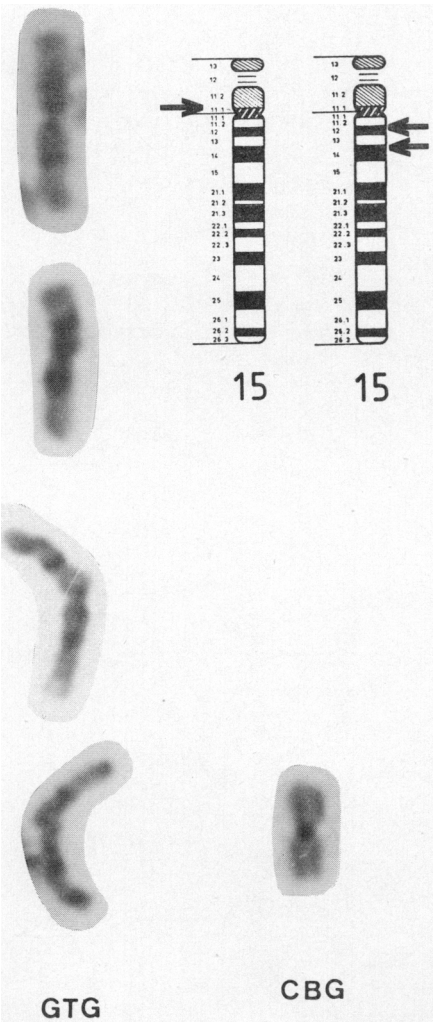

FIG. 2. Partial karyotypes of patient 1 showing the transocation between chromosomes 15; the chromosome with del 15(q12 or q13) is oriented upward. GTG banding technique (4 cells) and CBG (1 cell). Arrows indicate the breakpoints on the schematic representation.

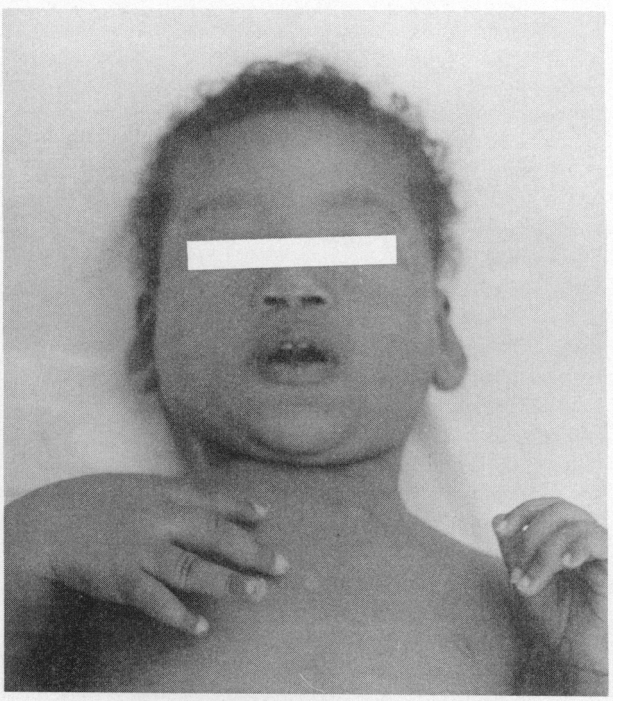

FIG. 3. Patient 2 at 10 months old.

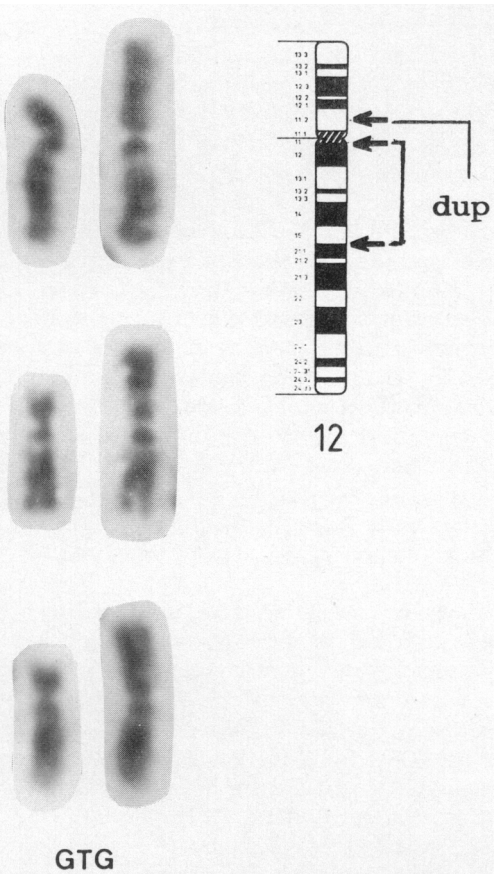

FIG. 4. Partial karyotypes from patient 2 showing duplication 12(q11–q15). Normal homolog on the left. Arrows indicate the breakpoints on the schematic representation. GTG banding technique (three cells).

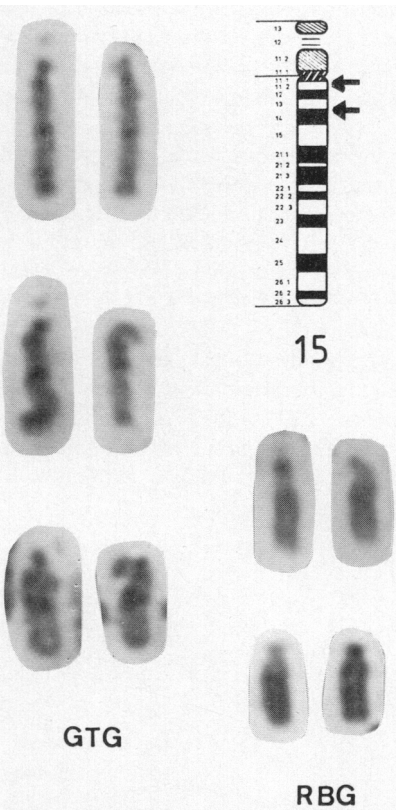

FIG. 5. Partial karyotypes of patient 3 demonstrating del 15 (q12 or q13); three cells with GTG banding technique and two cells with RBG banding technique, normal homolog on the left. Arrows indicate the breakpoints on diagram.

hair, and eyes are observed in Prader-Willi patients who have visible cytogenetic deletions of 15q11–13 (Butler, 1990); a tendency to obesity, though the fat distribution is not typical of the Prader-Willi syndrome; macrostomia; and a smiling face are observed in patients with Angelman syndrome.

Patient 2 presents a chromosome aberration in a mosaic form, a postzygotic event, and the product of the disrupted gene on chromosome 12, possibly a disturbed growth factor, present even in part of the cells, could be responsible for the global overgrowth observed in this patient.

The results of our chromosome studies in patients with overgrowth syndromes point toward the hypothesis that in the chromosomal regions 12q15 and 15q12 there are loci related to cellular growth factors; germinal and/or somatic mutations in those loci, and probably others not yet detected, may lead to overgrowth syndromes and predisposition to tumorigenesis.

Cytogenetic studies of patients with rare syndromes are important for the future understanding and identification of the molecular mechanisms involved in the developmental anomaly, as they identify the chromosomal regions in-

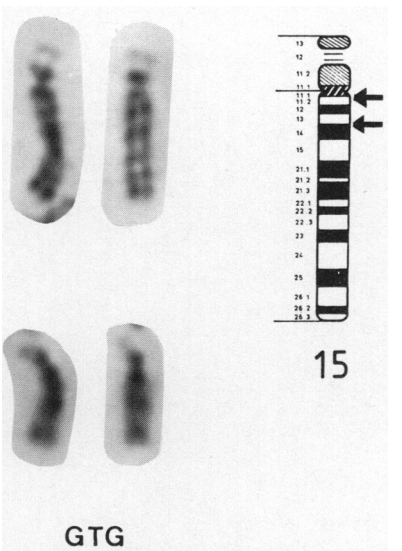

FIG. 6. Partial karyotypes of patient 3's father, demonstrating the same deletion present in his son; two cells with GTG banding technique.

volved, pointing out new routes for further investigations. This knowledge will certainly improve the diagnostic and prognostic procedures and enhance the genetic counseling offered the patients and their families.

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