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Partial Trisomy 11 in a Child Resulting from a Complex Maternal Rearrangement of Chromosomes 11, 12 and 13*

Otto Sanchez, Jorge J. Yunis, and Javier I. Escobar

Medical Genetics Division, Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis

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Summary. A complex structural rearrangement of chromosomes 11, 12 and 13 was found in a normal female who gave birth to an affected child with partial trisomy for the short arm of chromosome 11 and a balanced translocation 12/13. The detailed analysis of the G-banded chromosomes from early metaphases permitted the delineation of new chromosomal bands which in turn proved essential to the identification of this unusual phenomenon.

Zusammenfassung. Bei einer normalen Frau, die ein Kind mit partieller Trisomie des kurzen Armes des Chromosoms 11 und eine balancierte Translokation 12/13 hatte, wurde ein kompliziertes strukturelles Rearrangement der Chromosomen 11, 12 und 13 gefunden. Eine detaillierte Analyse der Chromosomen nach Darstellung der G-Banden aus frühen Metaphasen erlaubte die Abgrenzung neuer Chromosomenbanden, die sich ihrerseits als notwendig für die Analyse dieses seltenen Phänomens erwiesen.

Introduction

The recent development of the chromosome banding techniques by means of which each one the human chromosomes is amenable to detailed analysis, has broadened the field of cytogenetics. In this way, new syndromes, the result of duplication or deficiency of specific chromosomal segments, are being uncovered. In this report, a case that was not possible to solve with the use of the standard chromosome technique has been revisited in an attempt to characterize the events that led to an unusual karyotype in a phenotypically normal mother and in her affected child. The application of the G-banding techniques to early metaphases made possible to identify a complex phenomenon of chromosomal rearrangement involving chromosomes 11, 12 and 13 in the mother, and a partial trisomy for the short arm of the chromosome 11 accompanied by a balanced translocation 12/13 in the child. A comparison was made between the proband's phenotype and a similar patient recently reported in the literature.

Case Report

S. G. was a 3-year-old girl, the full term product of an uncomplicated pregnancy and delivery. She was admitted for the first time at the University of Minnesota Hospitals at the age of 2 months for evaluation of congenital defects. At that time she was noted to be small,

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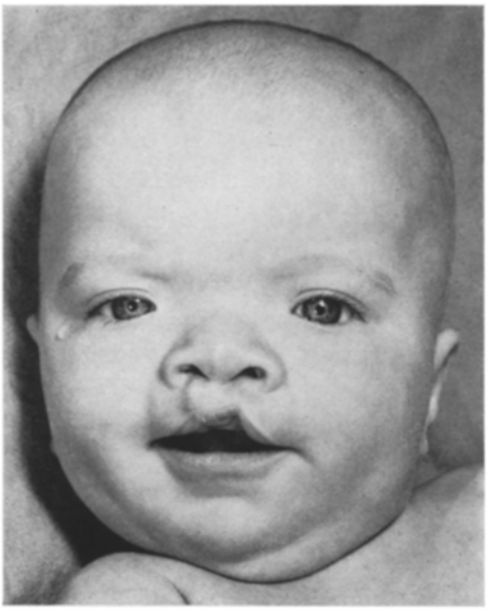

Fig. 1. Front view of the proband's face at the age of 9 months

active and irritable. OFC and body height were at the 50th percentile level and weight was below the 16th percentile. Other findings included a large anterior fontanel, hypertelorism, broad base nose, bilateral cleft lip and palate, bossing of the forehead, flat occiput, small hemangiomata at the base of the occiput and vertex, low set ears, antimongoloid slant of the eyes, nystagmus, right intermittent exotropia, slightly excentric and oval shaped pupils, broad first toes and slightly enlarged clitoris. The neurological examination revealed a weak suck and cry, increased spasticity of the legs and unsustained ankle clonus bilaterally. During her hospital course an intestinal malrotation was surgically corrected. Due to feeding problems related to her cleft lip and palate, a feeding gastrotomy had to be placed for adequate nutritional intake. The patient was noted to have a urinary tract infection which was successfully treated. Two voiding cystourethrograms showed a left ureteral reflux and IVP was considered normal. A pneumonencephalogram revealed a probable cyst of the septum pellucidum and mild ventricular dilation. X-rays of skull and chest, as well as bone survey were all normal. Laboratory tests including protein electrophoresis, electrolytes, calcium, phosphorous, alkaline phosphatase, BUN, creatinine, 17 ketosteroids and pregnanetriol were within normal limits. A mild anemia was noted.

The child was admitted twice for repair of the cleft lip and palate which was carried out without complications. Fig. 1 shows a frontal view of the patient's face after cleft lip repair at age 9 months. At age 3 years most of the features described above have persisted, the bossing of the forehead was more prominent, specially on the left and there was a severe psychomotor retardation in the presence of normal tonicity. The child was unable to seat or speak, uttering just a few sounds.

Dermatoglyphics showed absent axial palmar triradii on both hands accompanied by a radial arch in the hypothenar areas. The right hand showed an orange peel appearance, a horizontal palmar crease and absence of the third interdigital triradius. The dermatoglyphics on the parents were unremarkable.

The proband was the only living product of five pregnancies. The first one ended in a spontaneous abortion at 3½ months, the second pregnancy produced a child that died 12 hrs after birth for which autopsy showed atresia of the left ventricle and proximal aorta, the third

pregnancy produced a stillborn reported as having multiple congenital anomalies, the proband was the product of the fourth pregnancy and the fifth ended in a therapeutic abortion performed at 20 weeks, the fetus being described as slightly macerated. Neither cytogenetic nor clinical reports were available in any of the abnormal products. Two maternal uncles of the proband were mentally retarded, otherwise the family history is unremarkable. Unfortunate social and familial factors did not allow us to study relatives in this family.

Chromosome Techniques

Lymphocyte cultures of the proband and her parents were performed according to Hungerford's procedure (Hungerford, 1965), following minor modifications: Colcemid 0.02 mcg was added 1 hr before harvesting, KCl 0.075 M was used as the hypotonic solution for 5 min at 37°C, acetic acid-methanol ⅓ was used as the fixative and the slides were prepared by the air-dried technique. G bands were obtained by simply staining 1 week old slides with Wright's stain freshly diluted 1 to 4 with phosphate buffer 0.13 M pH 6.7, for 1½ to 2 min (Sanchez *et al.*, 1973; Yunis and Sanchez, 1973).

Results and Discussion

The child's standard karyotype showed 46 chromosomes that included a metacentric C (6—12) chromosome and a slightly enlarged D (13—15) chromosome. The mother showed a similar karyotype except for the additional presence of a small sub-metacentric chromosome substituting a second C chromosome which resembled a chromosome of the E (16—18) group. The father's karyotype was normal. The study of the chromosomal G banding pattern in the mother showed the presence of three abnormal chromosomes that were identified as number 11, 12 and 13 (Fig. 2). The child's karyotype showed two similar abnormal chromosomes 12 and 13 and two normal chromosomes 11 (Fig. 3). Although the identity of the involved chromosomes was clear, it was not possible to determine the exact nature of the rearrangements present due to the insufficient resolution of banded chromosomes in mid-metaphase. This problem was solved through the detailed analysis of the G banding patterns of chromosomes from early metaphases which showed more detailed banding characteristics. This approach enabled us to visualize new chromosome sub-bands which in turn made possible the identification of the rearrangements present in the abnormal chromosomes of mother and proband (Fig. 4). In chromosome 11, band 11q14 was subdivided into sub-bands 11q14. 1; 11q 14.2; and 11q14.3. In chromosome 12, band 12q21 was subdivided into sub-bands 12q21.1; 12q21.2; and 12q21.3; in the same chromosome 12 band 12q24 was subdivided into sub-bands 12q24.1; 12q24.2; 12q24.3; 12q24.4 and 12q24.5. In chromosome 13, band13q21 was subdivided in three subbands, 13q21.1; 13q21.2 and 13q21.3. Thanks to this increased resolution in the banding pattern of chromosomes we were able to make an interpretation of the events that led to the abnormal karyotype in the mother, which based on the terminology developed at the Paris Conference (Paris Conference, 1971), would be the following: Breaks are believed to have occurred at the level of bands p15, p12, q14.1 and q23 in a chromosome 11; at bands p11 and q24.1 in a chromosome 12; and at the level of band q34 in a chromosome 13. It is also believed that part of the short arm of chromosome 11 (11p14 to 11p12) was inserted into the short arm of chromosome 12 in the middle of band 12p11 and that a portion of the long arm of chromosome 11,

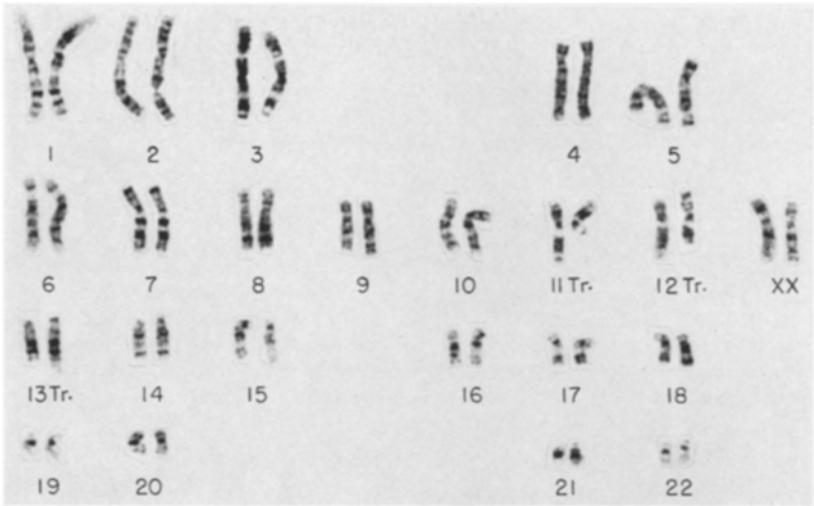

Fig. 2. G-banding karyotype of the patient's mother. Note that the abnormal chromosomes 11, 12 and 13 can be identified although their detailed structural rearrangement cannot be established

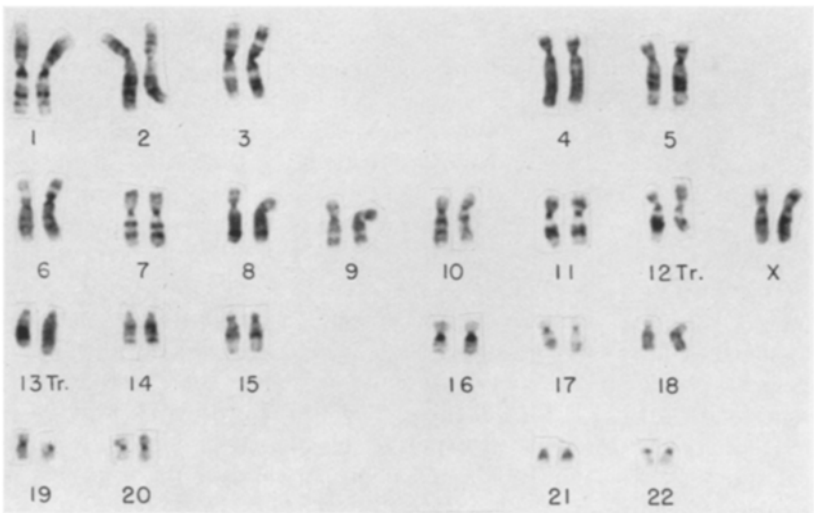

Fig. 3. G-banding karyotype of the proband. The abnormal chromosomes 12 and 13 are similar to those found in the mother

including bands 11q14.1 to 11q23, was inserted into the short arm of the same chromosome between bands 11p15 and 11p11. In addition, it was interpreted that the most distal portion of the long arm of chromosome 11 (11q24 to 11qter) fused to the proximal segment of the same chromosome arm at the level of band 11q13 and that there have been a receiprocal translocation between the distal segments of the long arms of chromosomes 12 and 13 likely involving bands 12q24. 1 to

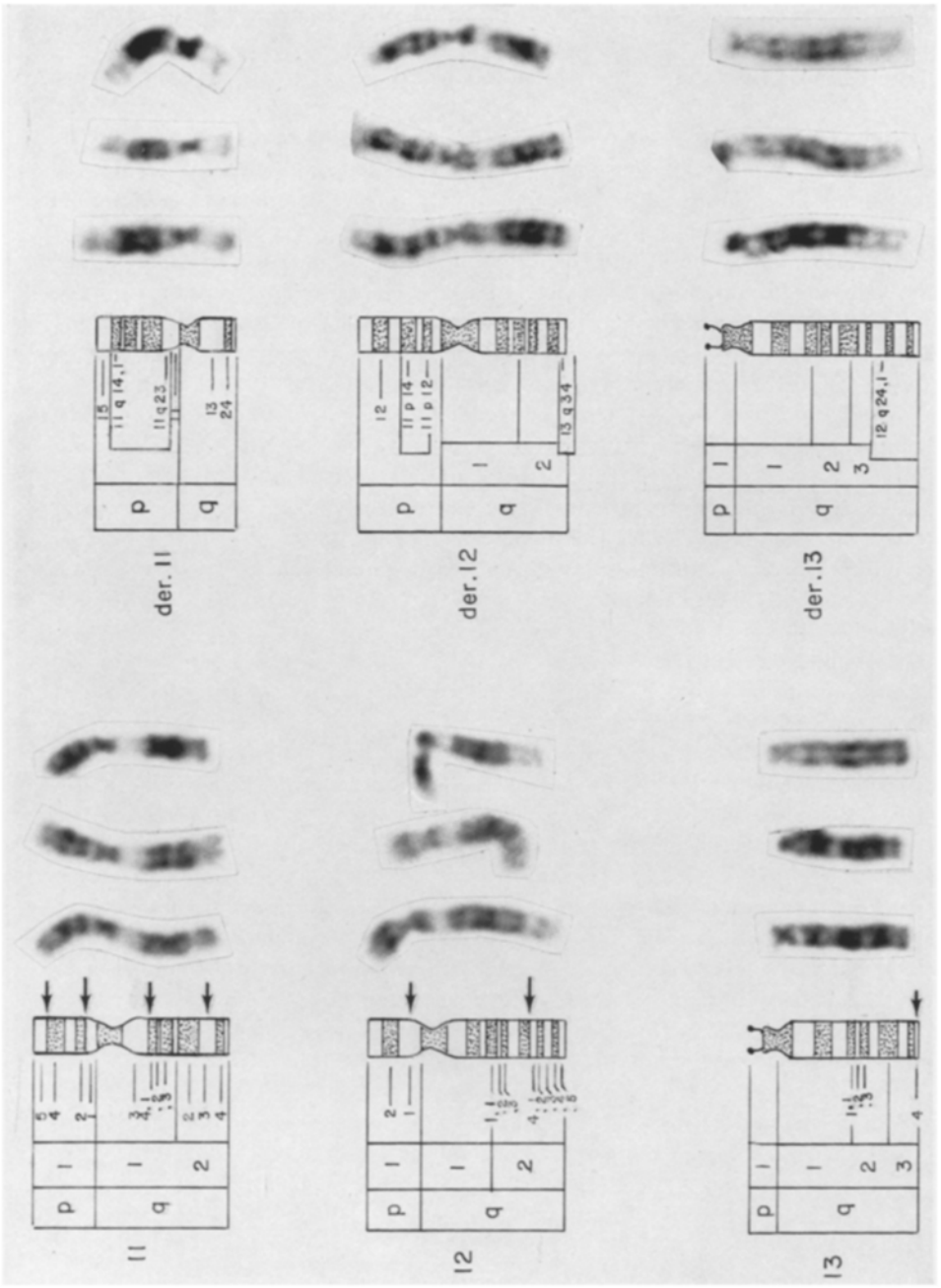

Fig. 4. Diagram and representative examples of normal (left) and derivative (right) chromosomes 11, 12 and 13 from early metaphases of the proband's mother. Arrows indicate the break points. See text for details

12qter and band 13q34. This interpretation of the mother's karyotype can be described in the terms developed at the Paris Conference (Paris Conference, 1971) as follows: 46,XX,t (11;12;13)(p12p15q14.1q23;p11q24.1;q34)(11pter → 11p15::

11q14.1 → 11q23::11p11 → 11q13::11q24 → 11qter;12pter → 12p11::11p14 → 11p12::12p11 → 12q23::13q34 → 13qter;13pter → 13q33::12q24.1 → 12qter).

The definition of this complex balanced translocation in the mother was essential for the clarification of the chromosomal abnormalities present in the proband. A comparison of the two karyotypes showed that both mother and child had the same abnormal chromosomes 12 and 13 but the child lacked the abnormal chromosome 11, indicating that the child inherited from the mother the abnormal chromosomes 12 and 13 as well as a normal chromosome 11. Since the child had two normal chromosome 11 and the abnormal chromosome 12 carries part of the short arm of chromosome 11 within its short arm (see diagram in Fig. 4), it is believed that the proband's abnormal phenotype was the result of a partial trisomy for the short arm of chromosome 11. The presence of a reciprocal translocation between the distal segments of the long arms of chromosomes 12 and 13 in mother and child, obviously derived no phenotypic consequences. Following the Paris system, the proband's karyotype could be described as: 46,XX,—12,—13,+der (12),+der(13),t(11;12;13)(p12p15q14.1q23;p11q24.1;q34)mat.

The characterization of chromosomal abnormalities of the C(6—12) group has received a great impetus since the introduction, a few years ago, of the banding techniques. Specific syndromes have been recently described for trisomy 8 (Caspersson *et al.*, 1972) and for partial trisomies of the short arm of chromosome 9 (Rethoré *et al.*, 1973) and the long arm of chromosome 10 (Yunis and Sanchez, 1974). In addition, identification of isolated cases of partial trisomies for the long arm of chromosomes 7, 11 and 12 and partial trisomy for the short arm of chromosome 12, have been made possible (Grace *et al.*, 1973; Francke, 1972; Hirschhorn *et al.*, 1973; Uchida and Lin, 1973). Previously, another case of partial trisomy for the short arm of chromosome 11 was reported (Falk *et al.*, 1973). When the clinical features of our patient are compared to those presented by the one described earlier (Falk *et al.*, 1973), certain characteristics appear to be shared in common, namely: mental retardation, prominent frontal bossing, nystagmus, antimongoloid slant of the eyes, strabismus, broad fingers or toes and high arched or cleft palate. Unusual clinical findings not shared by the 2 cases include enophthalmia, excentric and oval shaped pupils, enlarged clitoris and absent axial triradii. Some of these differences in phenotypic expression may in part reflect differences in the length of the chromosomal segment involved in the 2 patients (in our case the duplication involves bands 11p12 to 11p14, while in the other case it appears to involve bands 11p11 to 11p15). It is hoped that the detailed description of new cases would help delineate a specific syndrome for the partial trisomy of the short arm of chromosome 11.

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Dr. J. J. Yunis
Medical Genetics Division
Department of Laboratory Medicine
and Pathology
Box 198
Minneapolis, Minnesota 55455, USA