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Trisomy 13 with a 13-X Translocation

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INTRODUCTION

Translocations involving the X chromosome are rare events compared to autosomal translocations. The effects of X-autosome translocations on random X inactivation, the extent of this inactivation, and its role in modifying the expected phenotype are of considerable interest. This report describes a 15-month-old girl who has some but not all of the features of trisomy 13. Chromosome analysis with trypsin-Giemsa banding shows a translocation of the major part of the long arm of a no. 13 to the long arm of an X chromosome, making her a partial trisomy 13.

SUBJECTS AND METHODS

Case Report

The patient (BP 050172) is the only child of a 22-year-old mother and a 34-year-old father. There is no history of abortion. The pregnancy was uneventful except for minimal vaginal bleeding in the third month. This full-term infant's delivery was uncomplicated, and her birth weight was 2,675 g. Immediate examination revealed preauricular skin tags on the left and a small supernumerary digit on the ulnar side of the left hand, both of which were removed. Abnormalities of the eyes were noted at birth. At seven weeks there was no report of apneic spells, and the infant's height and weight were less than the tenth percentile; the head circumference was at the tenth percentile (35 cm). Examination of the head revealed the following: prominent metopic suture, narrow bitemporal diameter, epicanthal folds, sloping forehead, large nose, normally situated ears, prominent antihelices with small external auditory meatus on the right, and a high-arched palate without a cleft. A prominent nevus flammeus was present over the occiput and glabella, and there were smaller capillary nevi over the scalp. Ophthalmic examination under anesthesia (Children's Hospital, Los Angeles) revealed microphthalmia with microcornea and aniridia, colobomata of both retinae, optic nerve hypoplasia on the left, and aplasia on the right. The EKG, chest X-rays, and IVP were normal.

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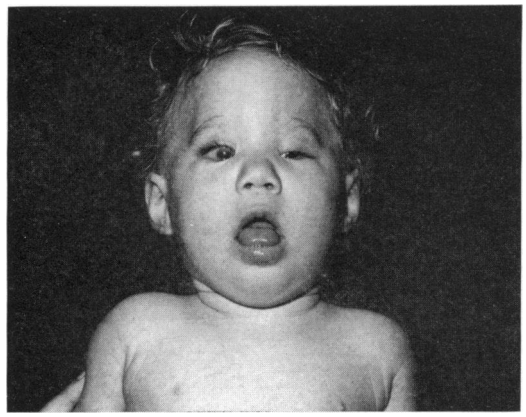

FIG. 1.—Patient at age 13 months. Note epicanthal folds, microphthalmia, microcornea, ptosis (left), and large nose.

When the baby was seen at 13 months of age (fig. 1), repeated myoclonic seizures were present and there was moderate generalized hypertonia. No cardiac abnormality was detected. Her abdomen and external genitalia were normal. There was no prominence of her heels, but her feet showed minimal metatarsus varus. Developmentally, she continues to make slow progress. At chronological age of 57 weeks, gross and fine motor development was at 28 weeks, adaptive and language development at 29 weeks, and personal-social at 36 weeks. Her overall developmental quotient was 53 (normal = 80–100). The infant readily responds to sounds, mouthes and transfers objects, and makes vowel but not consonant sounds.

The family history is noncontributory; the mother had been on birth control pills until 6 months prior to conception.

Methods

Chromosome studies on peripheral blood lymphocytes involved routine studies, quinacrine mustard fluorescence [1], trypsin-Giemsa banding [2], and autoradiography with ^{3}H thymidine [3]. Skin fibroblasts were also studied for their chromosome complement. Sex chromatin studies were carried out on buccal smear cells, hair root sheath cells, and skin fibroblasts. Hemoglobin analyses for fetal hemoglobin (Hb F) were done with alkali denaturation initially, but subsequent samples at 8, 9½, and 13 months used DEAE-sephadex chromatography [4, 5]. The Hb F estimations and the ratios of the two gamma chains ($^{G}\gamma$:$^{A}\gamma$) were determined by the method of Schroeder et al. [6, 7]. Qualitative studies of red cell antigens, red cell enzymes, and serum enzymes used standard methods.

RESULTS

The initial chromosome analysis on the patient revealed a 46,XX,Cq+ complement in all cells studied. The fluorescent karyotype demonstrated that the C-group chromosome bearing the translocation was an X, but did not clarify the source of the translocation. Trypsin-Giemsa studies (fig. 2) demonstrated that the material translocated to the X came from a no. 13 and amounted to about three-fourths of that chromosome. The translocation appears to be reciprocal with probable loss of the distal band of the long arm of the X and the centromere of the no. 13 in the

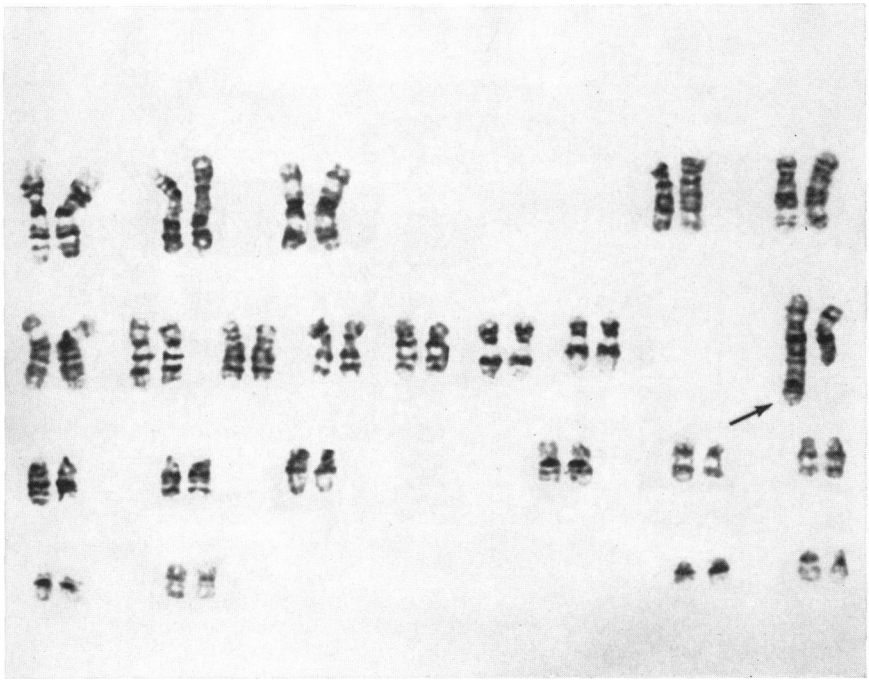

FIG. 2.—Full karyotype with trypsin-Giemsa banding; arrow denotes the Xq+.

reciprocal product (fig. 3). The patient is therefore trisomic for four-fifths of the long arm of the no. 13 chromosome and monosomic for the distal end of the long arm of the X. Chromosome analyses from skin fibroblasts confirmed these findings. Sex chromatin studies revealed a normal female pattern (26%). Although the X-chromatin body sometimes appeared to be larger than normal, particularly in skin fibroblasts, this finding was not consistent. Autoradiographic studies (fig. 4) showed that in the 35 cells counted, the X bearing the translocation (X_t) was always late replicating. Except for a short segment in the proximal part of its long arm, the no. 13 chromosome is also late replicating so that spread of inactivation from the X into the autosomal fragment would be hard to detect. Examination of these karyotypes revealed that 75% of cells had a similar density of grains on the translocated autosomal fragment as its no. 13 homologs. In 25% of cells the X_t was the most heavily grained chromosome; these grains were unevenly distributed throughout the X_t, a pattern which suggests partial inactivation of the translocated no. 13. Chromosome analysis in both parents demonstrated normal karyotypes.

Dermatoglyphics in the patient showed both palmar axial triradii in the t position and two arches and three ulnar loops on the right with four arches and one ulnar loop on the left. Neither plantar pattern showed fibular S arches. The parents both have palmar axial triradii in the t position and unremarkable digital patterns. Hemoglobin electrophoresis in the parents showed 98% Hb A and 2%

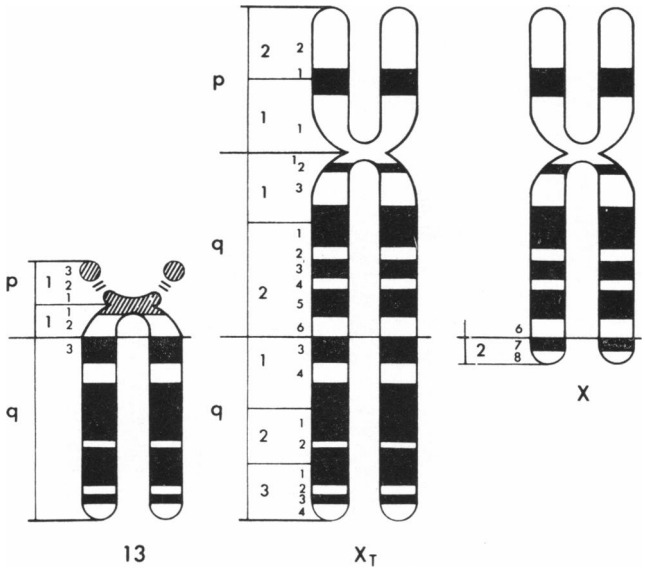

FIG. 3.—Diagram of formation of 13-X translocation. The break in the no. 13 appears to be through the no. q12 band, and that on the X, through the q27 band. The translocation (46,XX, t[13;X][q12;q27]) appears to be reciprocal.

Hb A_2; Hb F estimations by alkali denaturations were normal. At 7 weeks, blood smears from the patient did not show an increase in nuclear projections from polymorphonuclear leukocytes. Gene marker studies were carried out to see whether an additional allele could be detected in the HL-A, Hp, Rh, and AcP systems; none was found. The Xg typing was not informative.

DISCUSSION

The patient described here had some of the clinical signs of trisomy 13 resulting from the translocation of approximately three-fourths of that chromosome to an X. Although trisomy 13 has a wide spectrum of malformations, review of 30 reported cases showed that each of 12 phenotypic changes were present in approximately 50% or more of patients [8, 9] (table 1). Four of the reported cases had four of these changes, four had five, two had six, and the largest number, nine, had seven of them. Only two of these abnormalities were noted in our patient; the absence of a cardiac defect, survival beyond 1 year of age, and the level of the developmental quotient were particularly significant. There seems little doubt that the modified trisomy 13 phenotype in our patient resulted from an incomplete trisomy, but whether it was due to partial inactivation of the translocated fragment or to the partial trisomy is uncertain.

Searle [10] noted the rarity of translocations involving the X chromosomes in radiation-induced translocations in mice. This was confirmed recently by Seabright [11], who reported not only the rarity of structural changes of the X chromosome

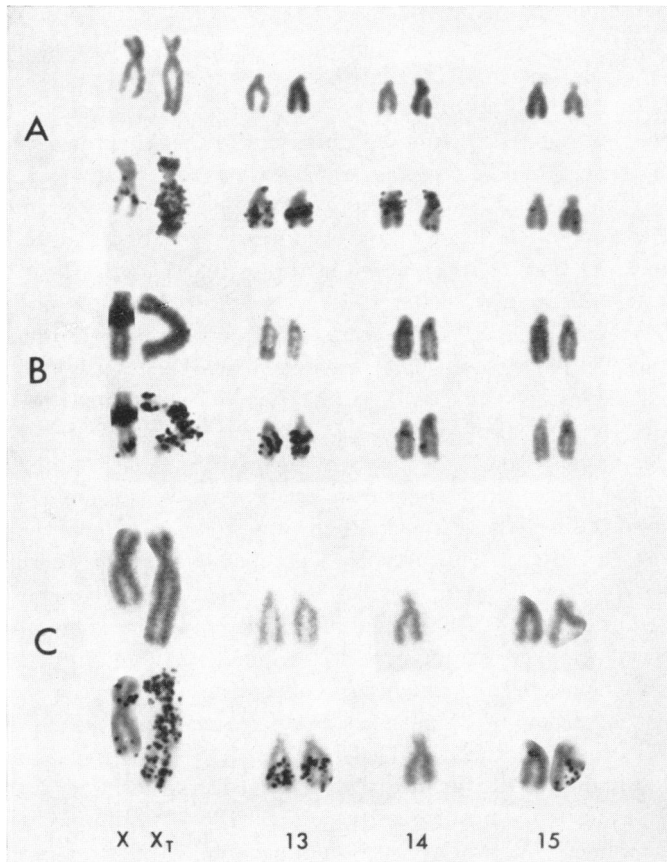

FIG. 4.—Autoradiograph of X chromosomes and no. 13, 14, and 15. The X_t was late labeling in all cells examined. In the majority of cells, the grains on the no. 13 and X_t were generally of equal density. (A no. 14 is missing in partial karyotype *C*.)

TABLE 1

FINDINGS IN 30 CASES OF D TRISOMY COMPARED TO OUR PATIENT

Abnormality	Frequency	Our Patient
1. Death prior to 6 months	28/30	—
2. Distal palmar triradius	12/13	--
3. Polydactyly	22/30	+
4. Cardiac abnormality	19/28	--
5. Microphthalmia and/or coloboma	20/30	+
6. Single palmar or simian crease	13/18	—
7. Cleft lip or palate	18/30	--
8. Apneic spells	17/30	—
9. Hyperconvexity of nails	17/30	—
10. Low set ears (± malformations)	16/30	—
11. Lose skin folds of neck	14/30	—
12. Scalp defect	13/30	—

but also the isolation of the X from interchanges with autosomes. Whether this reflects conservation of the X chromosome [12] or selection against such rearrangements is not known. There are only about 16 reports of X-autosome translocations in man. Six of these were translocations of material from the X to an autosome, and nine were from an autosome to the X chromosome [13, 14].

The possible effect of X-autosome translocations on random X inactivation and the role of the latter in contributing to the phenotype is an intriguing one. An exception to random X inactivation occurs with an abnormal X chromosome (isochromosome, deletion, or ring) which is always inactivated. All of the reported patients with translocation of material from the X to an autosome have shown inactivation of the normal X chromosome (X_n). With one exception, the structurally abnormal X and its autosomal fragment have been active, and separation of the fragment from the X-inactivation center has been postulated as the reason, despite the fact that one translocation involved the short arm and the remainder involved the long arm of the X. The patient reported by Cohen et al. [13] showed inactivation of the translocated fragment in one-third of cells examined, in addition to X_n inactivation. All of these translocations appeared to be balanced, and except for the last report, patients had normal phenotypes or primary amenorrhea.

When material is translocated from an autosome to an X chromosome, the X carrying the translocation (X_t) is invariably inactivated, usually in all the cells examined. A very pertinent finding is that, with one exception, all of these translocations appear to have been unbalanced. This suggests a selective factor in that complete X_t inactivation in a balanced translocation would result in a partial monosomy. The case reported by Thelan et al. [15] appears to be the single exception: this patient with an apparent balanced translocation (46,X,t[Xq+; 18q—]) had physical findings suggestive of the 18q— syndrome; 80% of cells showed X_t and the rest X_n inactivation. Another point of interest is that in six of the nine reported cases, the entire X_t was inactivated; and in the remainder, X_t inactivation did not appear to involve the autosomal fragment. Although proximity to the X-inactivation center has been suggested to explain this spread of inactivation, it is also possible that the type of translocation may be a factor. For example, complete inactivation of the X_t might occur in an insertional but not in a reciprocal translocation, the former being analogous to Cattanach's translocation in mice [16]. We suggest that the type of translocation determines the extent of inactivation on the X_t. The trypsin-Giemsa banding studies in our patient demonstrated a probable reciprocal translocation involving the last band of the X and the proximal band of the no. 13 chromosome. However, we could not be certain from the autoradiographic studies that inactivation of the autosomal fragment had not occurred, although the abnormal phenotype and high Hb F levels would argue against this.

Prior to completion of the trypsin-Giemsa studies, support for the diagnosis of trisomy 13 in our patient came from routine hemoglobin electrophoresis. Although the level of Hb F of the normal child is of the order of 5% at 6 months [17], the percentage in our patient was 18% at 13 months. The adult level of Hb A_2 is 2.0%–3.5% and is reached by the normal child at about 3 months of age [18].

The value found in our patient is only at the lower limit of this range at 13 months of age. The $^{G}\gamma$ and $^{A}\gamma$ chains are the products of nonallelic structural genes and differ in the presence of a glycyl or an alanyl residue at residue 136 of the γ chain [7]. At birth, the $^{G}\gamma$:$^{A}\gamma$ ratio is about 3:1, approximates 2:3 by the age of 6 months, and is also about 2:3 in the traces of Hb F in the adult [17]. However, this "adult" ratio of 2:3 varies between about 1:2 and 1:1. Consequently, the ratio of 1:1 in our patient at $9\frac{1}{2}$ months is approximately normal despite the high percentage of Hb F. Few cases of D trisomy survive beyond 3 months, but three patients followed by Huehns [19] had Hb F levels of 6.4%, 5.9%, and 2.6% at $2\frac{1}{8}$ years, $2\frac{1}{2}$ years, and $4\frac{3}{4}$ years, respectively. Trisomy D appears to be the only chromosomal abnormality with increased levels of Hb F. This specificity is further supported by the report of an adult with erythroleukemia and trisomy D in bone marrow culture who had clones of red cells containing Hb F [20]. The fact that both the level of Hb F and the proportions of the two types of γ chain are reverting, although abnormally slowly, to the adult pattern suggests that this is not due to a structural gene in triplicate but to a regulatory mechanism controlling the switch from γ to β chain production. The level of Hb F in our patient indicates that the distal three-fourths of this chromosome is involved in hemoglobin maturation.

The relationship of the no. 13 chromosome to eye defects is also of interest. Eight patients with retinoblastoma have been reported with a partial deletion of the no. 13 chromosome. A recent study with trypsin-Giemsa banding identified an intercalary loss of material between the q22 and q32 bands on the no. 13 chromosome in a patient with retinoblastoma [21]. The spectrum of eye abnormalities seen in trisomy 13 includes cyclops, anophthalmia, microphthalmia, optic and retinal agenesis, and apparently normal eyes. These findings suggest the presence of a locus controlling retinal development on the long arm of the no. 13 chromosome. Examination of partial trisomies could be helpful in localizing this locus, but so far none has been accurately identified with differential staining.

SUMMARY

A child of 13 months with some of the clinical findings suggestive of trisomy 13 was found to have a 13-X translocation resulting in a partial trisomy. Autoradiographic studies confirmed that the X bearing the translocation was always inactivated, but it is uncertain whether the modified phenotype is the result of partial inactivation of the translocated autosome or of the incomplete trisomy.

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REFERENCES

1. Caspersson T, Zech L, Johansson C: Analysis of the human metaphase chromosomes set by aid of DNA-binding fluorescent agents. *Exp Cell Res* 62:490–492, 1970

2. SEABRIGHT M: A rapid banding technique for human chromosomes. *Lancet* 2:971–972, 1971
3. SCHMID W: DNA replication patterns of human chromosomes. *Cytogenetics* 2:175–193, 1963
4. HUISMAN THJ, DOZY AM: Studies on the heterogeneity of hemoglobin. IX. The use of tris (hydroxymethyl) aminomethane-HCl buffers in the anion-exchange chromatography of hemoglobin. *J Chromatog* 19:160–169, 1965
5. DOZY AM, KLEIHAUER EF, HUISMAN THJ: Studies on the heterogeneity of hemoglobin. XIII. Chromatography of various human and animal hemoglobin types on DEAE-sephadex. *J Chromatogr* 32:723–727, 1968
6. SCHROEDER WA, HUISMAN THJ, SHELTON JR, WILSON JB: An improved method for quantitative determination of human fetal hemoglobin. *Anal Biochem* 35:235–243, 1970
7. SCHROEDER WA, HUISMAN THJ, SHELTON JR, SHELTON JB, KLEIHAUER EF, DOZY AM, ROBBERSON B: Evidence for multiple structural genes for the Y chain of human fetal hemoglobin. *Proc Natl Acad Sci USA* 60:537–544, 1968
8. TAYLOR AI: Autosomal trisomy syndromes: a detailed study of 27 cases of Edward's syndrome and 27 cases of Patau's syndrome. *J Med Genet* 5:227–252, 1968
9. SNODGRASS GJAI, BUTLER LJ, FRANCE NE, CROMA L, RUSSELL A: The "D" (13–15) trisomy syndrome: an analysis of 7 examples. *Arch Dis Child* 41:250–261, 1966
10. SEARLE AG, BEECHEY CV, EVANS EP, FORD CE, PAPWORTH DG: Studies on the induction of translocations in mouse spermatogonia. IV. Effects of acute gamma irradiation. *Mutat Res* 12:411–416, 1971
11. SEABRIGHT M: High resolution studies on the pattern of induced exchange in the human karyotype. *Chromosoma* 40:333–346, 1973
12. OHNO S: The mammalian genome in evolution and conservation of the original X-linkage group, in *Comparative Mammalian Cytogenetics,* edited by BENIRSCHKE K, Berlin, Springer-Verlag, 1969, pp 18–29
13. COHEN MM, LIN C-C, SYBERT V, ORECCHIO EJ: Two human X-autosome translocations identified by autoradiography and fluorescence. *Am J Hum Genet* 24:583–597, 1972
14. SARTO GE, THERMAN E, PATAU K: X inactivation in man: a woman with t(Xq−; 12q+). *Am J Hum Genet* 25:262–270, 1973
15. THELEN TH, ABRAMS DJ, FISCH RO: Multiple abnormalities due to possible genetic inactivation in an X/autosome translocation. *Am J Hum Genet* 23:410–418 1971
16. OHNO S, CATTANACH BM: Cytological study of an X-autosome translocation in mus musculus. *Cytogenetics* 1:129–140, 1962
17. SCHROEDER WA, HUISMAN THJ, BROWN AK, UY R, BOUVER NG, LERCH PO, SHELTON JR, SHELTON JB, APELL G: Postnatal changes in the chemical heterogeneity of human fetal hemoglobin. *Pediatr Res* 5:493–499, 1971
18. WILSON MG, SCHROEDER WA, GRAVES DA, KACH VD: Hemoglobin variation in D-trisomy syndrome. *N Engl J Med* 277:953–958, 1967
19. HUEHNS ER, HECHT F, KEIL JV, MOTULSKY AG: Developmental hemoglobin anomalies in a chromosomal triplication: D_1 trisomy syndrome. *Proc Natl Acad Sci USA* 51:89–97, 1964
20. CEPPELLINI R: Genetic control mechanisms in mammals, in *Proceedings 2d International Conference on Congenital Malformations,* New York City, July 1963, New York, International Medical Congress, 1964, pp 199–204
21. WILSON MG, TOWNER JW, FUJIMOTO A: Retinoblastoma and D-chromosome deletions. *Am J Hum Genet* 25:57–61, 1973