J. med. Genet. (1966). 3, 226.

Apparent Deletion of X Chromosome in a Prepuberal Girl*

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Apparent deletion of the short arms of one X chromosome associated with clinically detectable abnormalities, has been reported (Jacobs, Harnden, Court Brown, Goldstein, Close, MacGregor, Maclean, and Strong, 1960; Jacobs, Harnden, Buckton, Court Brown, King, McBride, MacGregor, and Maclean, 1961; de Grouchy, Lamy, Yaneva, Salomon, and Netter, 1961; London, Kemp, Ellis, and Mittwoch, 1964). However, the number of similar recorded cases is limited. The present report concerns an 8-year-old girl in whom chromosomal analysis, combined with radioautography, indicated a possible deletion of the short arms in one X chromosome.

Materials and Methods

Buccal smear. Buccal smears were fixed in 1 : 1 ether/absolute ethanol and stained with 5% cresyl violet.

Chromosomal analysis. Metaphases were obtained from cultures of whole peripheral blood by a method previously described (Steinberger, Smith, Steinberger, and Perloff, 1964). The karyotypes were prepared according to the Denver system of classification proposed in 1960 (see Smith, Steinberger, Steinberger, and Perloff, 1964).

Radioautography. Tritiated thymidine (spec. act. 6·7 c/millimol) was added to three- or four-day cultures in a final concentration of 1 μc/ml. One-half hour later the culture medium was replaced by fresh medium containing a 100-fold concentration of unlabelled thymidine and 1×10^{-6} M colchicine, and the incubation was continued for three hours. Well-spread metaphases were photographed and their location on the slide was recorded. The slides were coated with liquid emulsion (Kodak, NTB-2) and exposed in the dark at 4° C. for 3 to 21 days. Previously photographed metaphases, showing differential labelling, were rephotographed. Thus, karyotypes could be prepared from the same metaphases before and after coating with emulsion.

Case Report

An 8-year-old white girl was examined because of short stature and recent unexplained loss of eyebrows. Her birth and early development were normal. Physical examination revealed a stocky female, height 48·5 in. (122 cm.), weight 71·5 lb. (32·4 kg.). The only abnormalities noted were a high-arched palate and absence of eye-

Received November 9, 1965.

* Supported in part by United States Public Health Service Grant No. HD-00399.

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TABLE I

URINARY LEVELS OF STEROIDS AND GONADOTROPINS IN THE PROPOSITA

Date (1963)	17-ketosteroids (mg./24 hr.)	17-ketogenic Steroids (mg./24 hr.)	Total Gonadotropins (mg./24 hr.)	LH (mg./24 hr.)
Jan. 27	4·8	7·2	—	—
Feb. 2	1·8	11·2	0·066	—
Feb. 3	4·7	14·5	—	—
Feb. 9	6·2	26·7	—	9·1
Feb. 10	5·2	19·7	—	8·8
Feb. 16	3·4	10·7	<0·219	—
Feb. 17	3·3	9·3	—	—
June 1	—	—	—	2·6
June 3	—	—	—	—
Aug. 1	2·0	11·8	—	—
Aug. 15	3·3	8·3	—	—

TABLE II

DISTRIBUTION OF CHROMOSOMAL COUNTS IN THE PROPOSITA, AND RELATIVES

Subject	Chromosomal Counts				Total Number of Metaphases
	<45	45	46	47	
Proposita	0	3	33	0	36
Proposita	3	3	46	0	52
Proposita	2	30	245	5	282
Mother	3	3	46	1	53
Father	2	4	46	0	52
Brother	3	3	46	1	53
Brother	1	4	44	2	51
Paternal grandmother	4	3	47	0	54

brows. The PBI was 6·5 μg./100 ml., cholesterol 143 mg./100 ml. Thyroidal ^{131}I uptake was 10% in 24 hours. Skull X-ray was normal and the bone-age was commensurate with chronological age. Urinary hormone excretion studies are listed in Table I. The 17-ketosteroids and 17-ketogenic steroids were within normal limits. 'Total' gonadotropins, determined by Albert's method (Albert, 1955), were undetectable or extremely low, as is to be expected in an individual of this age. The LH values were raised as determined by the method of Parlow (Parlow, 1958). Study of buccal smears, obtained on three different occasions, revealed sex chromatin body in 28% of cells, but it appeared smaller than normal. The modal number of chromosomes was 46 (Table II). Metaphases with chromosome numbers other than 46 were found to be the result of gain or loss of random chromosomes. Analysis of 25 karyotypes with 46 chromosomes revealed an extra unmatched large acrocentric chromosome and only 15 chromosomes in group X-6-12 (Fig. 1a). Radioautographic studies revealed consistent, heavy labelling of one large acrocentric chromosome (Fig. 1b), occurring late in the period of DNA synthesis.

Clinical course. Although thyroid function was within normal limits, a therapeutic trial with desiccated thyroid (60 mg. daily) was instituted. After six months, the patient's eyebrows reappeared and she showed further growth. She is now 10 years of age, height 51·5 in. (130 cm.); span 50 in. (127 cm.); crown-pubis 28·5 in. (72·4 cm.); floor-pubis 23 in. (58·4 cm.) and weight 83 lb. (37·6 kg.). There are no signs suggestive of onset of puberty.

Discussion

Several reports postulating deletion in one X chromosome have been published. Jacobs *et al.* (1960) described a 37-year-old woman with primary amenorrhoea, scanty axillary and pubic hair, no breast development, and infantile external genitalia. A laparotomy revealed 'streak' gonads similar to those seen in ovarian dysgenesis. A small sex chromatin body was observed in 7% of cells from a buccal smear; no drumsticks were seen in blood leucocytes. Chromosomal analysis revealed 46 chromosomes with an apparent deletion in one X chromosome. Jacobs *et al.* (1961) reported a second case of sexual hypoplasia and apparent deletion of the short arms of one X chromosome. No laparotomy was performed in this case. Two women with partial deletion of the long arms of one X chromosome, resulting in a chromosome of similar size and shape as those in pair 16, were described by de Grouchy *et al.* (1961). Both these patients had primary amenorrhoea and ovaries similar to those found in gonadal dysgenesis. In none of the above described cases was radioautography performed to determine whether the abnormal chromosome was a part of the late-labelling X chromosome.

London *et al.* (1964) described a 28-year-old woman who complained of infrequent menses. She was short ((57 in.) (144 cm.)) and stocky ((105 lb. (47·6 kg.)), with poor breast and nipple development, and a high-arched palate. An infantile uterus and atrophic ovaries, containing chiefly stromal tissue, were found at laparotomy. Sex chromatin body was found in less than 1% of cells in buccal smear. Chromosomal analysis of cells obtained from peripheral blood, bone-marrow, skin, and ovary, revealed a mosaic constitution. 70% of metaphases were 45/XO, 19% were 46/X plus a large acrocentric chromosome similar to the chromosomes in group D. Radioautography revealed late heavy labelling of one large acrocentric in the metaphases containing 46 chromosomes. The authors interpreted the extra acrocentric to be a deleted X chromosome. The possibility of trisomy in group D was considered unlikely because of absence of clinical findings usually associated with such chromosomal abnormality.

Our case similarly reveals a single X chromosome and an extra large acrocentric chromosome that is late-labelling. Short stature has been found to be associated with absence of short arms of X chromosome (Jacobs *et al.*, 1961). In our case, short stature is also part of the clinical picture. Furthermore, there are no congenital anomalies of the type asso-

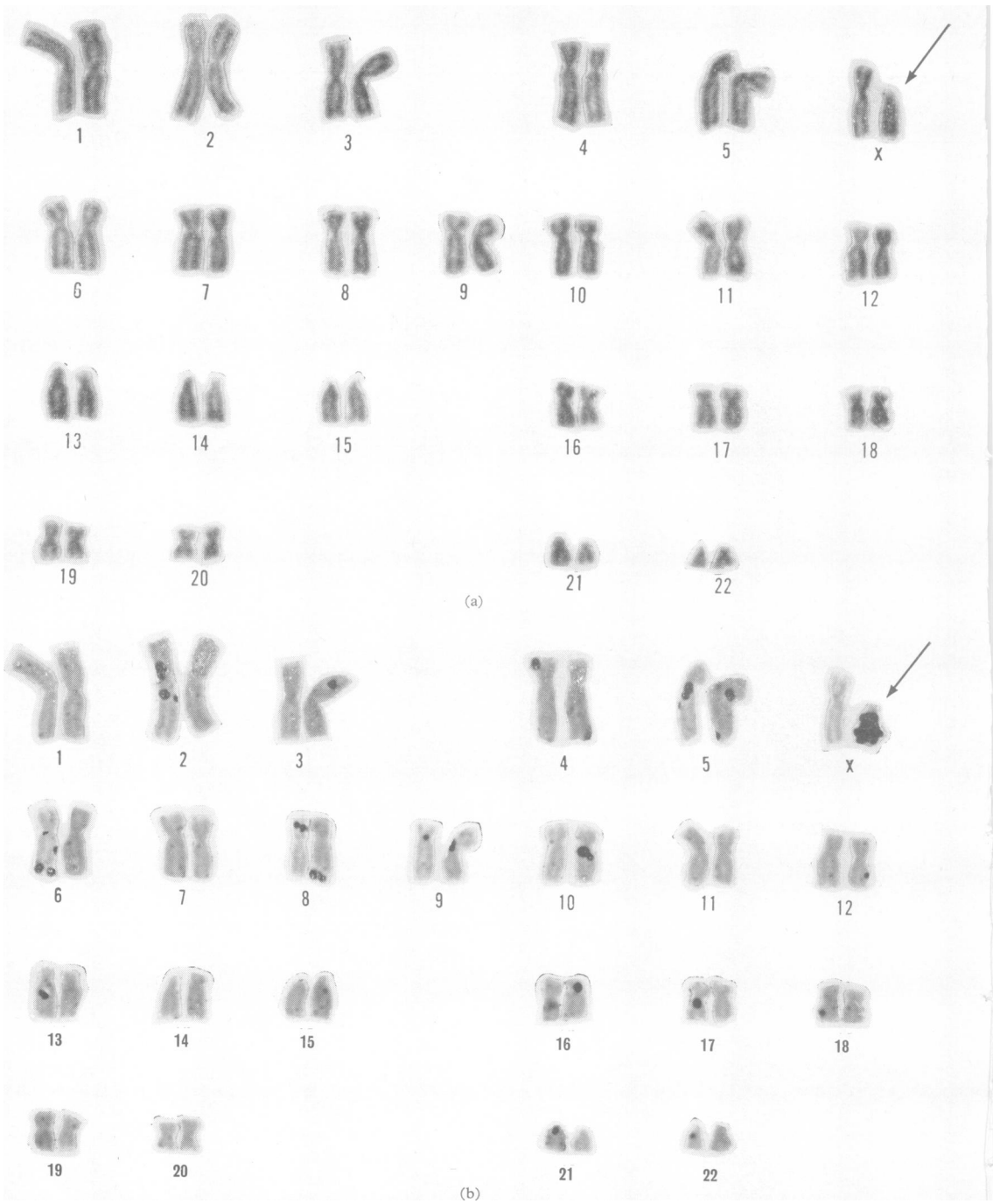

FIG. 1. Karyotype of proposita, from culture of peripheral blood. Chromosomes arranged according to the Denver system. Arrow points to the unpaired, acrocentric chromosome. (*a*) Karyotype from a metaphase photographed before coating with photographic emulsion. (*b*) Karyotype from the same metaphase photographed after developing the photographic emulsion. Note heavy labelling of the unpaired acrocentric chromosome, which is thought to be a deleted X.

ciated with group D trisomy. Thus, we consider the unpaired acrocentric chromosome to be a deleted late-labelling X chromosome. This conclusion is based on the findings of German (1962), Morishima, Grumbach, and Taylor (1962), and Gilbert, Muldal, Lajtha, and Rowley (1962) who report that one X chromosome in normal females becomes labelled later during the DNA synthetic period of the cell. Correlations of clinical findings with the degree of deletion of the late-labelling X chromosome should contribute to the mapping of genes on this chromosome.

Summary

Chromosome analysis was performed on an 8-year-old girl with short stature, high-arched palate, and unexplained loss of eyebrows. Karyotypes obtained from cultures of peripheral blood revealed 46 chromosomes with one X chromosome, and an extra large acrocentric chromosome in group D. Radioautography, using ^{3}H-thymidine, revealed one large acrocentric chromosome to be late-labelling. It is suggested that this chromosome represents a deleted late-labelling X chromosome.

Addendum

Since the submission of this paper for publication, a report of a case very similar to ours has come to our attention (Atkins, Santesson, and Voss, 1965). Atkins *et al.* found in a sexually immature 14-year-old girl of short stature, a deletion involving the short arms of one X chromosome. Radioautography showed comparatively heavy late labelling of the deleted X chromosome.

The authors wish to thank Miss Irene Bronstein for her assistance in the preparation of karyotypes.

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