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Chromosomes of Eleven Sexually Abnormal Patients¹⁾

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(With 1 Plate and 2 Tables)

During the last few years, striking advances in cytogenetical techniques for mammalian material have brought a surprising increase in knowledge of human chromosomes. Recently, various types of sexual aberrations in man have been found to be associated with abnormalities of the sex-chromosomes. The present paper deals with the chromosomes in eleven patients showing abnormal sexual development, with special reference to the chromosomal conditions in relation to sex.

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Materials and Methods: Eleven cases of sex abnormalities under study included four cases of Klinefelter's syndrome (nos. 1, 2, 3 and 4), two cases of azoospermia (nos. 8 and 9), one each of female pseudo-hermaphrodite (no. 5), adrenogenital syndrome (no. 6), hypogonadism (no. 7), cryptorchism (no. 10) and retentio testis duplex (no. 11). Diagnoses of those patients, together with sampling of the culture materials for chromosome study, were made in Department of Urology, Hokkaido University, School of Medicine, Department of Urology, Tonan Hospital and Department of Urology, Sapporo Municipal Hospital.

Chromosome observations were carried out on cells from short-term culture of leucocytes separated from the heparinized peripheral blood. The leucocytes in 3-day-culture were exposed to colchicine, and chromosome preparations were made according to the water-pretreatment acetic dahlia squash method, or by the air-drying technique. In one case (no. 5) fibroblasts were obtained from a very small skin biopsy specimen after 38 days of cultivation. Chromosome preparations were made of both leucocytes and fibroblasts by the air-dry method. Chromosome analyses were performed in accordance with the Denver system of nomenclature for the classification of individual chromosomes.

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Table 1. Clinical and diagnostic features in eleven cases of sexual abnormalities under study.

Case no.	Age & sex	Diagnosis	Clinical feature
1	31yr. ♂	Klinefelter's syndrome	Eunuchoid proportions; atrophic testes; atrophic hyalinized seminiferous tubules; arrest of spermatogenesis; aspermia; no obesity; 17-KS: 7.1 mg/day.
2	20yr. ♂	Klinefelter's syndrome	No gynecomastia; very small penis (about 3 cm in length); hypoplastic scrotum and testes; atrophic hyalinized seminiferous tubules; arrest of spermatogenesis; aspermia; no pubic hairs; increase of Leydig cells; gonadotropin: 48 muu/day; 17-KS: 2.6 mg/day; sex chromatin positive.
3	29yr. ♂	Klinefelter's syndrome	Eunuchoid proportions; hypoplastic scrotum and penis; atrophic testes; no pubic hairs; no beard; arrest of spermatogenesis; 17-KS: 5.6 mg/day; gonadotropin: 64muu/day; 17-OHCS: 10.4 mg/day.
4	20yr. ♂	Klinefelter's syndrome	Eunuchoid proportions; no gynecomastia; atrophic testes; left testis: 2 cm; right testis: 3cm; normal developed penis (about 9 cm in length); atrophic hyalinized seminiferous tubules; arrest of spermatogenesis; aspermia; increase of Leydig cells; normal pubic hairs.
5	5yr. ♂	Female pseudo-harmaphrodite	Hypospadias; normal sized and very crooked penis; absence of both testes; internal organs of female type; uterus and ovary present.
6	18yr. ♂	Adrenogenetal syndrome	Bilateral cryptorchism; very small and curved phalus; empty scrotum; testicles absent (not palpated); uterus and ovary present; sex chromatin positive.
7	29yr. ♂	Hypogonadism	Eunuchoid proportions; hypogonadotrophic hypogonadism; small sized penis (4 × 1.5cm); gynecomastia; gonadotropin: 12 muu/day; 17-KS: 2.5-3.5 mg/day; sex chromatin negative.
8	30yr. ♂	Azoospermia	Azoospermia; normal developed penis and scrotum; arrest of spermatogenesis; normal Leydig cells.

9	29yr.	♂	Azoospermia	Azoospermia; normal developed penis and scrotum; normal volume of semen; 17-KS: 7.5 mg/day.
10	6yr.	♂	Cryptorchism	Retentio left testis; other external genitalia of normal male.
11	6yr.	♂	Retentio testis duplex	Both scrotum absence; both testes exist in inguinalis; other external genitalia of normal male.

Results

The diagnostic data of each patient are summarized in Table 1. The results of chromosome counts in those patients are presented in Table 2.

Each of four cases with Klinefelter's syndrome (nos. 1, 2, 3 and 4) showed a consistent chromosome count of 47 (Table 2). The karyotype analyses showed the occurrence of five small acrocentric elements in the complement, which suggested the presence of a Y chromosome, while there were 16 medium-sized submedian chromosomes indicating the presence of two X elements among them (Figs. 1 and 2). From the above findings, it is evident that four Klinefelter's syndrome cases here concerned have an XXY sex-chromosome constitution characteristic to this syndrome.

Table 2. Chromosome constitution in eleven cases of sexual abnormalities under study.

Case no.	Chromosome counts						Chromosome constitution	No. of cells obs.
	44	45	46	47	48	75		
1			3	25	2		47/2A+XXY	30
2		1	1	31	1		47/2A+XXY	34
3				33	2		47/2A+XXY	35
4			1	35		1	47/2A+XXY	37
5		1	66				46/2A+XX	67
5*	3	5	41				46/2A+XX	49
6		2	30	1			46/2A+XX	33
7			36				46/2A+XY	36
8		2	37				46/2A+XY	39
9		3	18	2			46/2A+XY	23
10		3	23				46/2A+XY	26
11			14				46/2A+XY	14

* : Fibroblast culture from skin biopsy specimen.

A phenotypically male patient (no. 5) aged 5 years was diagnosed as female pseudo-hermaphrodite (Table 1). Chromosome counts made in 67 well-

spread metaphase cells from blood culture showed that 66 cells had 46 chromosome, while the remaining one cell possessed 45 chromosomes (Table 2). Karyotype analyses of chromosomes in the cells having 46 chromosomes showed that each cell had 4 small acrocentric chromosomes, indicating the absence of the Y, while there occurred 16 medium-sized submedian chromosomes with a sign of the presence of two X elements. A fibroblast culture was established from a very small skin biopsy specimen, and 49 dividing cells were examined. Of these, 41 cells had 46 normal chromosomes, which showed four small acrocentric chromosomes characteristic of the normal female complement (Fig. 3). The remaining 8 cells showing less than 46 chromosomes may be those damaged due to technical failure. It was then evident from both the skin and the blood culture studies that this patient had a normal female complement of chromosomes, consisting of 44 autosomal elements and an XX sex-mechanism. The patient thus was genotypically female.

Diagnosis of a patient, no. 6, was adrenogenital syndrome (Table 1). Exact chromosome counts made in 33 cells revealed that 30 cells had 46 chromosomes. Among the remaining three, two cells possessed 45 and one cell 47 chromosomes, (Table 2). Karyotype analyses made in five cells having 46 chromosomes showed 4 small acrocentric chromosomes and 16 medium-sized submedian chromosomes involving two X elements (Fig. 4). A possible conclusion is that the present case has a normal female chromosome constitution, 44 autosomes and two X's.

Chromosome examination in one case of hypogonadism (no. 7) yielded a consistent count of 46 chromosomes. Karyotype analyses made it clear that they had a normal chromosome complement consisting of 44 autosomes and an XY-sex-constitution (Fig. 5). It is apparent that the patient is genotypically male.

Two cases of patients diagnosed as azoospermia (nos. 8 and 9) indicated that, after careful chromosome counting, they invariably had 46 chromosomes. There were no detectable changes or variations of chromosomes from a normal complement either morphologically or numerically in these cases (Fig. 6): each case consists of 44 autosomes superficially identical to those of a normal complex, and X and Y sex chromosomes.

The two cases, cryptorchism, no. 10, and retentio testis duplex, no. 11, showed no detectable chromosome abnormality under microscopical observations, so far as blood-chromosomes were concerned; each patient possessed 46 chromosomes of an apparently normal complement with the sex-mechanism of XY.

Discussion

Since the first report by Jacobs and Strong (1959), a large number of phenotypic males classified under the general term of Klinefelter's syndrome has been found to possess two X chromosomes and one Y. From that time on numerous confirmatory reports have been published. Recently it has been reported that not all of the chromatin-positive males of Klinefelter's syndrome do in fact represent an XXY condition. Information so far obtained has indicated

that there occur, in the Klinefelter's syndrome with or without associated mental defects, various sex chromosome constitutions such as XX/XXY mosaic, XY/XXY mosaic, XXYY, XXXY, XXXXY conditions and so on (for review, refer to Harnden and Jacobs 1961 and Schoval 1961). Four cases of Klinefelter's syndrome herein dealt with, were found to have 47 chromosomes with an XXY sex-constitution, in complete agreement with those usually known in the vast majority of cases of this syndrome.

In the literature, reference is made to several papers which report that intersex with true- or pseudo-hermaphrodite shows a normal sex chromosome constitution (Hungerford *et al.* 1959, Sasaki and Makino 1960, Makino *et al.* 1960 and others). Recently, mosaicism of cells with different chromosome constitutions has been described to occur in those syndromes (Hirschhorn *et al.* 1960, Warkany *et al.* 1962 and others). Cytological examinations in a case of female pseudo-hermaphrodite here dealt with have revealed on both leucocyte and fibroblast cultures that this patient possessed a normal female chromosome complement without a sign of mosaicism.

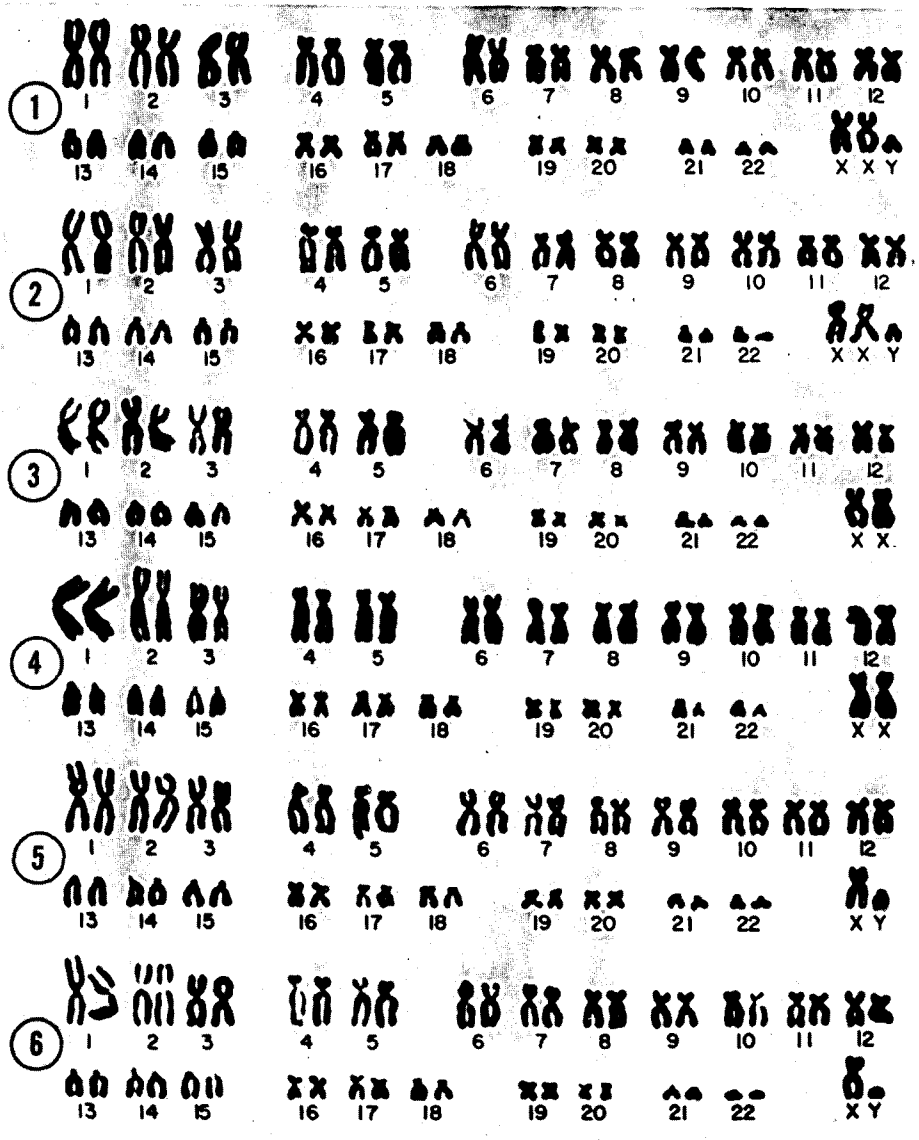
Adrenogenital syndrome has been reported by Makino *et al.* (1962) to be characterized by 46 chromosomes having a normal female sex chromosome constitution. A patient of the same syndrome dealt with in this paper was diagnosed to be a female by the fact that it had a positive sex-chromatin pattern and 46 chromosomes with an XX sex-determining mechanism, while two cases of azoospermia in the present study were of male type having 44 autosomes and an XY sex-chromosomes. Three cases of sexually abnormal individuals with hypogonadism, cryptorchism and retentio testis duplex, all being phenotypically males, were recognized to be males, since they had a normal chromosome constitution with an XY sex-mechanism.

Summary

Eleven cases of sexually abnormal patients were studied with respect to their chromosome constitution. Each of four cases with Klinefelter's syndrome was found to possess 47 chromosomes and XXY sex-complement. Each one of female pseudo-hermaphrodite and adrenogenital syndrome showed 46 chromosomes and an XX sex-mechanism. Two cases with azoospermia and each one of hypogonadism, cryptorchism and retentio testis duplex possessed a normal male chromosome complement.

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Explanation of Plate X

Figs. 1-6. Karyotype analyses of the chromosome complement in patients with sex anomalies. 1, from a patient with Klinefelter's syndrome (no. 3) showing 47 chromosomes with XXY sex-condition. 2, from a patient with Klinefelter's syndrome (no. 4) showing 47 chromosomes with XXY sex-condition. 3, from a patient with female pseudo-hermaphrodite (no. 5), skin culture. 4, from a patient with adrenogenital syndrome (no. 6). 5, from a patient with hypogonadism (no. 7). 6, from a patient with azoospermia (no. 9).
