Case Reports


A Masculinizing Syndrome Associated with a Doubly-satelitied Extra Chromosome

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An extra chromosome bearing satellites on both arms was reported by Ellis, Marshall, and Penrose (1962) in a 13-year-old girl who had poor physical development, kyphosis, epilepsy, and slight mental retardation. The patient had no signs of Down's syndrome and the dermal ridge patterns were not unusual. The chromosome number was 47 due to an extra chromosome which could be distinguished from the normal acrocentric chromosomes, because satellites were seen on both ends and the long arms were not divergent. Parental chromosomes were normal. The authors suggested that the abnormal chromosome might have resulted from a single cross-over in the loop between a pair of homologous group-G chromosomes which were heterozygous for a pericentric inversion. F. J. Dill and J. R. Miller (1964, personal communication) observed a similar extra acrocentric chromosome with double satellites in an institutionalized male who had moderate mental retardation. The patient's father was dead and the mother had normal chromosomes.

This note records a third case in which a doubly-satellited extra chromosome was present in all analysed cells of a woman admitted to hospital for investigation of suspected Cushing's syndrome. The case differs from those mentioned above in that she was not mentally retarded and the aberrant chromosome was smaller and metacentric.

Case Report

A 58-year-old Negro woman, born July 2, 1906, was referred to the genetics laboratory after extensive endocrine studies failed to establish the cause of her masculinizing syndrome. Menarche had occurred at the age of 14, and the menstrual periods were typically scanty and irregular, and remained so in spite of cyclical hormone therapy. Because of intense hirsutism she has had to shave her face and chest daily since the age of 16. Gynaecological examination at that time disclosed an 'infantile uterus'. She has been married three times, the first at the age of 28. Despite frequent intercourse she did not become pregnant. She had an uneventful menopause at the age of 47. A sub-total thyroidectomy for a nodular goitre was performed in 1956. Her parents, two brothers, and three sisters had died from a variety of unrelated causes. The only living relative, a sister with diabetes mellitus, was not available for study. None of the family members were known to have had gross physical deformity, hirsutism, or sexual disturbances.

The patient (Fig. 1 and 2) was an obese, bearded woman who measured 65 in. (165 cm.), had an arm-span of 70.5 in. (179 cm.), and a pubis-to-sole length of 35 in. (90 cm.). She weighed 215 lb. (99.7 kg.).

The blood pressure was 170/115 mm. Hg. She had generalized hirsutism, a cervico-dorsal fat pad, striae of inner arms and thighs, large pendulous breasts, attached ear lobules, and short incurved fifth fingers. There was marked clitoral hypertrophy, a normal introitus, and a small uterus with attached leiomyoma. Endometrial biopsy showed a benign polyp.

Radiographs demonstrated moderately advanced
generalized osteoarthritis and partial destruction of the lower lumbar spine. Skull films were normal. Most fasting blood sugars were normal, but there was a diabetic glucose tolerance test response. Urinary follicle-stimulating hormone levels exceeded 100 mouse units per 24 hr. Normal pituitary and adrenal responsiveness was shown to the administration of dexamethasone ('Dexameth'), ACTH, and SU4885 ('Metopirone'). Finger-prints showed ulnar loops on all digits except the left thumb (whorl). The corrected total ridge count was 113. The fourth interdigital areas had loops. Total maximum adi angle and the right and left axial t heights were 90°, 21.8%, and 12%, respectively.

**Cytogenetic Studies.** Sex-chromatin was observed in 38% of buccal nuclei. Chromosomal studies of cultured lymphocytes (Rohde, 1963), revealed that in 29 of 30 suitable C-mitoses there were 47 chromosomes. Fifteen cells were karyotyped and each showed a normal female complement plus an additional small chromosome which was seen to have satellites on both arms (Fig. 3). This extra chromosome was slightly smaller than those in group G, measured 1.86 μ in length, and had a centromeric index of 50. The satellites were symmetrical and in some plates both satellites were in association. The large and small acrocentric chromosomes appeared normal, and in occasional spreads all three possessed satellitid short arms.

**Discussion**

The extra chromosome in this patient is possibly an isochromosome which originated during meiosis from the satellited short arm of an unknown donor chromosome. By definition, isochromosomes have a centromeric index of 50 ('mediocentric') and the two arms are mirror images of one another. While metacentric chromosomes may also arise from pericentric inversion or from 'centric fusion' of similarly-sized whole-arm fragments, the former is excluded in this case, and on the whole the isochromosome origin of the doubly-satellited chromosome in this patient is favoured by its exhibition of complete symmetry. Since satellites could be observed on all members of the D and G group chromosomes, and neither mosaicism nor the co-isochromosome of the long arm were detected, the extra chromosome must have arise extremely early in development and in all likelihood before fertilization.

Since very little is known about the genetic content of the satellited short arms of the acrocentric chromosomes, the causal relationship of this aberrant chromosome to the masculinizing features is uncertain until additional cases with the same association are discovered. In normal persons the variability of the short arms of the acrocentrics is so great that Penrose (1964) suggested that 'logically it seems only possible to arrange them according to the measurements of their longer arms'. That D/G and presumptive G/G translocation carriers are phenotypically normal suggests that the genetic role of at least certain satellited short arm fragments must be almost negligible.

In addition, Gustavson (1964) was not able to discern a phenotypic difference between cases of mongolism with standard trisomy or with translocations.

The doubly-satellited extra acrocentric chromosomes observed by Ellis *et al.* (1962) and F. J. Dill and J. R. Miller (1964, personal communication) would, if their interpretations are correct, constitute double trisomies of the short arms of an homologous pair (? of small acrocentrics). The presence of mental retardation in their two patients suggests that significant genetic content may be present, and the similarities between the two cases argue against a fortuitous association of
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Mental deficiency with the aberrant extra chromosomes.

The patient described herein is thought to have a short arm tetrasomy which may well be responsible for the phenotypic disturbances. It is suggested that this case likely represents a new chromosomal syndrome of masculinization with normal intelligence that is due to a partial autosomal tetrasomy. No previous case has been reported of an extra autosome in man in which mental retardation has not occurred.

Summary

The clinical and genetical findings in a woman with sterility, hirsutism, and additional features of Cushing’s syndrome are presented. Except for an abnormal glucose tolerance test, the endocrine studies were normal.

Cytogenetic study of cultured lymphocytes disclosed the presence of an additional small aberrant chromosome which was doubly satellited. The origin and significance of the extra chromosome are discussed.

REFERENCES


Corrigendum

September issue, p. 186.

Formula in third line of second column should read:

\[ x = \frac{P(z_1 \mid y_1)}{P(z_2 \mid y_2)} \]