Xq- Turner's Syndrome: Reconsideration of Hypothesis that Xp- Causes Somatic Features in Turner's Syndrome

FREDERICK HECHT, DONALD L. JONES, MARLEEN DELAY, and HARVEY KLEVIT

From the Genetics Clinic, Crippled Children's Division, Department of Pediatrics, and the Division of Medical Genetics, University of Oregon Medical School, Portland, Oregon; and the Department of Pediatrics, Permanente Clinic, Portland, Oregon, U.S.A.

Jacobs *et al.* (1961) suggested that a study of individuals with deletions of the X chromosome, 'may help to determine whether genes which influence height are on the short arm of the X chromosome'. Ferguson-Smith (1965) advanced the hypothesis, based on further karyotype-phenotype correlations, that 'deletion of the long arm of the X chromosome . . . is not sufficient by itself to cause the extreme short stature and the multiple stigmata . . .', and that 'monosomy of the short arm of the X chromosome is the decisive factor in the causation of short stature and congenital malformations in Turner's syndrome'. This idea has been generally accepted (*Lancet*, 1965; Jacobs, 1969). To our knowledge, it has not hitherto been substantially challenged.

We wish, therefore, to describe a patient with partial deletion of the long arm of the X chromosome (Xq-), to compare her phenotypically to other patients with Xq- and to patients with XO(45,X), and then reconsider the hypothesis that the genes that affect height and somatic features are on the short arm of the X(Xp).

Case Report

This girl presented at 15 years of age because of short stature, primary amenorrhoea, and lack of secondary sexual development. She had not had peripheral lymphoedema, otitis media, gastro-intestinal bleeding, or renal disease. She had had asthma from age 3 to 8 years. She was of normal intelligence and was doing well in school.

Family. The patient's father was 24 and her mother 23 years of age at her birth. Her father was 175 cm. and her mother 155 cm. tall. Her three sisters experienced normal sexual development with menarche at age 11 years.

Physical examination. At age 15 years the patient was 145.4 cm. tall (Fig. 1). Blood pressure was within normal limits. There was no puffiness over the dorsum of the hands or feet. The fifth fingers were normal in length and shape. The finger-nails were small, hyperconvex, and deep-set at the base. Cubitus valgus was present. Her facial appearance was unremarkable; she did not have epicanthal folds, ptosis of the eyelids,

FIG. 1. The patient at age 15 years showing her short stature, undeveloped breasts, widely-spaced nipples, lack of pubic hair, and cubitus valgus.

Received 3 November 1969.

FIG. 2. Karyotype of lymphocyte metaphase from patient with 46,XXq-. There is a missing C(6-12+X) chromosome and an extra chromosome in the No. 16 position (arrow).

narrow maxilla, acutely arched palate, or a small mandible. Her ears were prominent. The posterior hairline was lower than normal. Her neck was neither short nor webbed. The nipples were widely spaced and inverted and there was no breast development. The chest was rather broad. Heart sounds were normal and no murmur was heard. Femoral pulses were normal. There was little pubic hair development and the labia and clitoris were infantile. She showed more pigmented naevi than her sisters. The distal palmar axial triradii were located more than 35% of the distance up the palms.

X-rays. The fourth metacarpals were hypoplastic, such that a line drawn tangential to the fifth and fourth metacarpal heads passed through the head of the third metacarpal. The fourth metacarpals were also shorter than the combined length of the proximal and distal phalanges by 0.45 cm. on the right and 0.4 cm. on the left. There was no deformity of the medial tibial condyle. The bone age at age 15 years was retarded to the 10 to 11 year level in the wrist and hand and to the 13 to 14 year level in the elbow and pelvis.

Cytogenetic studies. Buccal smears showed a small sex chromatin body in a normal number (25%) of nuclei.

Peripheral blood lymphocyte cultures yielded a total of 386 well-spread metaphases. The modal number of chromosomes per cell was 46. Karyotypes of 24 cells showed a missing chromosome in the C (6-12+X)

group and an extra submetacentric chromosome indistinguishable from chromosome 16 (Fig. 2). No cells consistent with 45,X were observed. The other non-modal cells were karyotypically inconsistent. Neither bone-marrow nor a skin biopsy could be obtained.

Lymphocytes were prepared for autoradiography after continuous late-labelling with tritiated thymidine for 6 hours before harvest. One of the 3 chromosomes

FIG. 3. Partial karyotypes of the No. 16 group chromosomes from 4 cells before and after autoradiography. The chromosome on the left in each group is heavily labelled and is interpreted as Xq-. The partial karyotype in the upper left is from the cell in Fig. 2.

in the No. 16 group was found to be uniformly and heavily labelled (Fig. 3), suggestive of its being the partially deleted X chromosome.

Chromosome studies of the patient's parents and sisters gave normal results.

Extensive blood grouping was consistent with the presumed paternity. The patient and her parents were Xg(a+) and had normal colour vision.

Discussion

Chromosomal diagnosis of Xq-. The patient's karyotype (with a missing C chromosome and an extra chromosome No. 16) is consistent with deletion of one-half to two-thirds of the long arm of the X chromosome. The uniformly late DNA replication of the extra chromosome in the No. 16 position is in keeping with its being Xq-.

There was no evidence of a second line of cells. Though mosaicism can never be excluded in any person, extensive lymphocyte studies gave evidence only for Xq-.

Phenotypic findings. We have found reports of 5 other patients with Xq- without evidence of mosaicism. The Table lists their findings and those of the present patient.

It should be noted that our patient and 2 other patients with Xq- had 'short stature', being less than 152.4 cm. tall (Table), and that at least one of the remaining 3 patients was also somewhat short, being only 155 cm. in height as an adult (Court Brown *et al.*, 1964). It is also noteworthy that individuals with Xq- may have the other somatic stigmata of Turner's syndrome such as short

fourth metacarpals, increased numbers of pigmented naevi, and hypoplastic nails.

Comparison between 46,XXp- and 45,X. The Table lists the phenotypic findings in Xp- and 45,X together with the findings in Xq-. Only cases of Xp- and Xq- without known mosaicism have been included, since mosaic cases could confuse such a comparison. Similarly, cases with isochromosomes for the X long arm (Xqi) chromosomes have been omitted, since they are not only monosomic for one arm of the X, but trisomic for the other as well.

The paucity of data on Xp- and Xq- is apparent in the Table. More cases with Xp- or Xq- need to be described, preferably from chromosome surveys of newborns, to provide a fuller picture of the phenotypes associated with Xp- and Xq-.

Hypothesis reconsidered. Ferguson-Smith (1965) pointed out that individuals with Xq- show fewer somatic stigmata of Turner's syndrome than individuals with 45,X or Xp-. If this is correct, what could be the basis for it? Ferguson-Smith (1965) suggested one possibility, namely, that Xp- is responsible for the somatic features of Turner's syndrome. Another possibility is biased ascertainment. The X chromosome is one of the longest, most metacentric chromosomes in the C group. Penrose (1964), pooling data from various laboratories, concluded the 'discrimination between X and No. 6 by metrical means is not possible'. Turpin and Lejeune (1965), using cells prepared without

TABLE
COMPARISON OF PHENOTYPIC FINDINGS

Findings	This Case*	Xq- Other Cases†		All Cases	Xp-	45,X	
Short stature‡	+	2/5	3/6	(50%)	4/4	(100%)	105/105 (100%)
Shield chest	+	0/2	1/3	(33%)	1/5	(20%)	29/36 (80%)
Webbed neck	-	0/5	0/6	(0%)	1/5	(20%)	63/117 (54%)
Lymphoedema	-	0/3	0/4	(0%)	0/5	(0%)	37/94 (39%)
Short fourth metacarpal	+	0/5	1/6	(17%)	0/0	(0%)	34/59 (58%)
Hypoplastic nails	+	0/5	1/6	(17%)	0/0	(0%)	20/26 (77%)
Pigmented naevi	+	2/4	3/5	(60%)	1/5	(20%)	32/62 (52%)
Congenital heart disease	-	0/5	0/6	(0%)	0/5	(0%)	18/87 (21%)
Menstruation	-	1/5	1/6	(17%)	1/4	(25%)	7/83 (8%)
Streak gonads	O	3/3	3/3	(100%)	1/1	(100%)	23/25 (92%)
Severe mental defect	-	0/5	0/6	(0%)	0/5	(0%)	7/86 (8%)
References					§		¶

* + = present; - = Absent; O = no data.

† Becker, Paris, and Albert (1963) and Becker (1964, personal communication to Ferguson-Smith (1965). Court Brown *et al.* (1964) and D. J. Mantle (1964, personal communication to Ferguson-Smith (1965); Ferguson-Smith (1965); Grouchy *et al.* (1961); and Grouchy (1964, personal communication to Ferguson-Smith (1965)); Polani (1963; 1964, personal communication to Ferguson-Smith (1965), and P. E. Polani, personal communication to the authors, 1967).

‡ Short stature = less than 152.4 cm.

§ Atkins, Santesson, and Voss (1965); Jacobs *et al.* (1961); Lejeune *et al.* (1966); Steinberger *et al.* (1966); Tveterås (1965).

¶ Ferguson-Smith (1965).

colchicine, ranked the X between chromosomes Nos. 5 and 6, whereas Bender and Kastenbaum (1969) placed it between chromosomes Nos. 7 and 8. Xp- may be more difficult to detect cytologically than Xq-. An individual with Xp- and a mild somatic phenotype might be more easily missed than an individual with a comparable phenotype and Xq-. Xq- might make that chromosome more metacentric than other chromosomes in the C group and thus allow its detection with relative ease. Comparable deletions of the short arm might serve only to hide that chromosome (Xp-) among the smaller, less metacentric C chromosomes. Thus, there may be a tendency to investigate only cases with Xp- with relatively flagrant somatic stigmata of Turner's syndrome.

Evolution and the X chromosome. The hypothesis that Xp- is responsible for the somatic stigmata of Turner's syndrome implies that genes influential in the development of stature and other somatic features are clustered on Xp (Ferguson-Smith, 1965; Jacobs, 1969). The limitation of somatic information to Xp is not in keeping with the view that the X chromosome evolved from an autosome and that the former autosomal loci on it were conserved virtually without loss during evolution (Ohno, 1967). As we have suggested, biased ascertainment and small numbers of cases may be responsible for the apparent differences between the phenotypes associated with Xp- and Xq-.

The idea that either Xp- or Xq- may give rise to short stature and the other somatic stigmata of Turner's syndrome would thus fit better with current concepts on the evolution of the X chromosome. If correct, it would suggest that X-linked genes of an 'autosomal nature' (such as haemophilia A and B, Duchenne muscular dystrophy, colour-blindness, and glucose-6-phosphate dehydrogenase) might be on either the short or the long arm of the X chromosome.

Summary

A patient is described with partial deletion of the long arm of the X chromosome (Xq-). She presented with primary amenorrhoea, lack of secondary sexual development, short stature, and other somatic abnormalities associated with Turner's syndrome.

Comparison of her phenotype with that of other Xq- patients indicates that deletions affecting the long arm of the X chromosome may produce short stature and other somatic stigmata of Turner's syndrome, though not so frequently as with 45,X.

The question is raised: Does the Xq- phenotype differ from that with Xp-? Small numbers and possibly biased ascertainment of cases presently preclude answering this question. Restriction of most loci affecting somatic development to the short arm of the X is in conflict with the view that the X chromosome was once a primitive autosome and that former autosomal loci on the X have been retained essentially intact during evolution (Ohno, 1967). The location of 'autosomal' segments on the X chromosome has important implications for the map of the X chromosome.

Supported by USPHS grant CA 07941 and by a grant from the Children's Bureau to the Crippled Children's Division for a Genetics Clinic. D.L.J. was a research fellow under Human Genetics Training Grant I-TOI-HD-0016 from the National Institute of Child Health and Human Development. We thank Dr. Everett W. Lovrien of the University of Oregon Medical School and Dr. Howard Cann of Stanford University School of Medicine for blood grouping.

REFERENCES

- Atkins, L., Santesson, B., and Voss, H. (1965). Partial deletion of an X chromosome. *Annals of Human Genetics*, **29**, 89-95.
- Becker, K. L., Paris, J., and Albert, A. (1963). Ovarian dysgenesis due to deletion of the X chromosome. *Proceedings of the Staff Meetings of the Mayo Clinic*, **38**, 389-394.
- Bender, M. A., and Kastenbaum, M. A. (1969). Statistical analysis of the normal human karyotype. *American Journal of Human Genetics*, **21**, 322-351.
- Court Brown, W. M., Harnden, D. G., Jacobs, P. A., Maclean, N., and Mantle, D. J. (1964). Abnormalities of the sex chromosome complement in man. *Medical Research Council. Special Report Series*, No. 305, p. 130.
- Ferguson-Smith, M. A. (1965). Karyotype-phenotype correlations in gonadal dysgenesis and their bearing on the pathogenesis of malformations. *Journal of Medical Genetics*, **2**, 142-155.
- Grouchy, J. de, Lamy, M., Yaneva, H., Salomon, Y., and Netter, A. (1961). Further abnormalities of the X chromosome in primary amenorrhoea or in severe oligomenorrhoea. *Lancet*, **2**, 777-778.
- Jacobs, P. A. (1969). Structural abnormalities of the sex chromosomes. *British Medical Bulletin*, **25**, 94-98.
- , Harnden, D. G., Buckton, K. E., Court Brown, W. M., King, M. J., McBride, J. A., MacGregor, T. N., and Maclean, N. (1961). Cytogenetic studies in primary amenorrhoea. *Lancet*, **1**, 1183-1188.
- Lancet (1965). Making sense of Turner's syndrome (Leading article). **2**, 529-530.
- Lejeune, J., Doumic, J. M., Berger, R., and Rethoré, M. O. (1966). Sur un cas de dysgénésie ovarienne XX_{del}. *Annales de Génétique*, **9**, 132-133.
- Ohno, S. (1967). *Sex Chromosomes and Sex-linked Genes*. Springer-Verlag, Berlin.
- Penrose, L. S. (1964). A note on the mean measurements of human chromosomes. *Annals of Human Genetics*, **28**, 195-196.
- Polani, P. E. (1963). Sex-chromosome anomalies in phenotypic females. In *Proceedings of the Second International Congress on Human Genetics (Rome)*, Vol. 2, pp. 1135-1144. Istituto G. Mendel, Rome.
- Steinberger, E., Steinberger, A., Smith, K. D., and Perloff, W. H. (1966). Apparent deletion of X chromosome in a prepubertal girl. *Journal of Medical Genetics*, **3**, 226-229.
- Turpin, R., and Lejeune, J. (1965). *Les Chromosomes Humains*. Gauthier-Villars, Paris.
- Tveterås, E. (1965). Gonadal dysgenesis with deleted X chromosome. *Acta Paediatrica Scandinavica*, Suppl. No. 159, pp. 131-132.