

Inheritance of Testicular Feminization Syndrome: Some Negative Linkage Findings

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Testicular feminization is a rare condition: estimates of the incidence vary from 1 in 20,000 to 1 in 130,000 births. Those affected show a normal female physique and orientation: however, they have a short vagina but no uterus, and their gonads are testes which are to be found in the abdomen or in the inguinal canal. The karyotype is male, XY (Jacobs *et al.*, 1959).

Testicular feminization is clearly inherited, though the exact manner of inheritance is in doubt: it could be an X-linked recessive character or an autosomal dominant character which is expressed only in males (Grumbach and Barr, 1958). Other XY intersexual conditions with similar patterns of inheritance, such as male pseudohermaphroditism or X-linked hypospadias, are not included in this report.

Linkage Tests

Hopes were that linkage tests might decide the manner of inheritance: measurable linkage between testicular feminization and an X-borne marker such as colour blindness or the Xg groups would establish X-linkage; measurable linkage with an autosomal marker would establish the autosomal alternative. With this in view the Blood Group Research Unit was, during the past six years, sent samples of blood from 49 propositi and 170 of their relatives, but no positive result has emerged. If the *tf* locus be on the X it is too far away from Xg for linkage to be measured. If *tf* be on an autosome the data are enough to show that it is not close to the loci for ABO, MNSs, Rh, Duffy, or Kidd. Slimmer data are just enough to show that *tf* is not *very* close to the loci for P, Lutheran, Kell, Dombrock, or secretor.

The sums of the lod scores (Maynard-Smith, Penrose, and Smith, 1961) are given in the Table.

Families were scored only when there was evidence of the condition in the sibs or ancestry of the mother of the propositus or, failing this, when the propositus had an affected sib. A single affected member in a family may represent a new mutation and being so could give no linkage information.

Some of the families have already been published (McKusick, 1962; Philip and Sele, 1965; Boczkowski, 1968; Bartlett *et al.*, 1968) and others probably will be.

The distribution of the Xg groups among the 49 phenotypically female propositi is, as expected, that of males:

	Observed	Male Expectation	Female Expectation
Xg(a+)	26	32.29	43.32
Xg(a-)	23	16.71	5.68

Indeed the Xg distribution is somewhat ultra-male (χ^2 for 1 d.f. = 3.6, $p = 1$ in 17), but we suppose this to be a chance of sampling and will be surprised, not to say nonplussed, if the tendency persists: the deviation from the female distribution is beyond question (χ^2 for 1 d.f. = 59.7, $p = 1$ in many millions).

So far, linkage tests using blood groups as markers

TABLE
TESTICULAR FEMINIZATION: LINKAGE ANALYSIS

	No. of Scoring Families	Recombination Fraction, θ				
		0.05	0.1	0.2	0.3	0.4
Xg	13	-4.885	-2.320	-0.471	+0.036	+0.082
ABO	8	-7.199	-4.231	-1.642	-0.502	-0.026
MNSs	12	-3.849	-1.728	-0.221	+0.147	+0.116
P	1	-0.584	-0.340	-0.138	-0.052	-0.012
Rh	11	-4.554	-2.545	-0.944	-0.348	-0.111
Lutheran	1	-0.536	-0.305	-0.121	-0.045	-0.010
Kell	1	-0.721	-0.444	-0.194	-0.076	-0.018
Secretor	1	-0.584	-0.340	-0.138	-0.052	-0.012
Duffy	11	-3.807	-2.075	-0.730	-0.261	-0.090
Kidd	5	-1.093	-0.396	+0.074	+0.153	+0.092
Dombrock	2	-0.051	+0.122	+0.175	+0.115	+0.037

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leave the problem of the precise manner of inheritance of testicular feminization where it was. However, the recent interpretation by McKusick (1967) of a family reported by Gayral *et al.* (1960) makes X-linkage look the better guess.

Summary

Those with the syndrome of testicular feminization are to outward appearance females but their karyotype is XY. The condition is inherited through the mother, but it is not clear whether the gene responsible is X-linked or is autosomal and only able to express itself in the male.

Demonstrable linkage with the X-borne blood group Xg or with an autosomal blood group would settle the question one way or the other. However, tests on a series of families give no hint of linkage either with Xg or with the autosomal blood groups, so the problem remains as it was.

The distribution of the Xg groups in 49 propositi is, as expected, that of males.

The substance of this paper is entirely due to the following physicians and cytogeneticists who, with the linkage problem in mind, sent samples of blood from cases of testicular feminization and from their relatives: Dr. A. Adam of Tel Hashomer, Dr. C. N. Armstrong of Newcastle, Dr. L. Aubert of Toulon, Dr. K. Boczkowski

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