Genetical Studies in Testicular Feminization Syndrome*

KRZYSZTOF BOCZKOWSKI

From the Department of Clinical Endocrinology, Medical Academy, Warsaw, Poland

Testicular feminization syndrome (TFS) represents a well-defined form of male pseudohermaphroditism. The patients are of female legal sex. The habitus is completely and often attractively feminine, with well-developed breasts. There is absence of axillary and pubic hair. The external genitalia are female but with a blind vagina. At laparotomy the uterus and Fallopian tubes are found to be absent, except in a few cases in which a vestigial rudimentary uterus is present. Testes of almost normal size, in some cases with a well-developed epididymis, are found in the abdominal cavity or in the inguinal canals (Goldberg and Maxwell, 1948; Wachstein and Scorza, 1951; Morris, 1953; Hauser, 1963; Morris and Mahesh, 1963; Zourlas and Jones, 1965; Pion and Dignam, 1966).

Analysis of pedigrees shows that this condition, transmitted by normal females to somê of their male descendants, is inherited either as an autosomal dominant male-limited character or as X-linked recessive character. These two possibilities cannot be distinguished by pedigree studies because the affected individuals are sterile.

More than 50 cases have so far been tested cytogenetically and only in a few were chromosomal abnormalities found: a case mentioned by Morris and Mahesh (1963) and Miller (1964), with XO/XY/XX mosaicism, a case with a possible XXXY chromosomal complement (Botella-Llusia, Clavero-Nunez, and Nogales, 1964), a case with XY/XXY/XXY mosaicism (Forsberg, Hall, and Ryden, 1965), a case of 46/47 mosaicism with XXX complement or 21–22 trisomy (Vague et al., 1966), and a case with XO/XY/XXY mosaicism (Uozumi et al., 1967). All other reported cases had an XY sex chromosome pair (see Philip and Sele, 1965; Zourlas and Jones, 1965). Thus chromosomal abnormalities are probably unrelated to the clinical picture of TFS, or at least are not the usual cause of this syndrome.

The question whether TFS is due to an X-linked or an autosomal gene may be approached by means of linkage studies involving X-linked and autosomal marked characters. Of more than 50 conditions which are most likely X-linked (McKusick, 1962), only 2, the Xg blood groups (discovered in 1962 by Mann et al.) and colour-blindness, can, for reason of suitable frequency, conveniently be used.

Subjects and Methods

During the years 1951–1965, 10 propositi with testicular feminization syndrome were examined in the Department of Endocrinology. In 2 cases, no reliable pedigree data were obtained and these are not included in this paper.

Of the remaining 8 families which are the subject of this report, 2 include affected relatives and the total number of cases of TFS in these 8 families is 13. In 7 families blood groups (including Xg) were determined; and in 8 families colour vision was studied with Ishihara's plates. Members of the families who were Xg grouped and all propositi were seen personally by the author.

The nuclear sex of oral mucosa cells was determined in all cases except 2 in family T.M. The sex chromatin was also studied in all sisters (before the onset of menstruation) of cases of TFS.

Cytogenetic studies of white blood cells were done in all cases except Ch.M. and 3 cases in family T.M. The method was that of Moorhead et al. (1960).

The diagnosis of TFS was confirmed by histological examination of the gonads from laparotomy in all cases except 2 in family T.M., 2 in family P.G., and the propositus in family G.I.

Results

A negative sex chromatin pattern and a normal male 46, XY karyotype was found in all 9 cases tested.

None of the 8 patients investigated by laparotomy
had a uterus. All had two testes. Histological examination showed immature seminiferous tubules lined with Sertoli cells, sometimes with degenerative spermatocytes. In six cases foci of Pick's tubular adenoma were found.

**Sex Ratio.** The ratio of affected XY females to normal males to normal females (excluding the propositus in each of the 8 sibships) was 5:15:21 (children who died in infancy were excluded).

**Family T.M.** The pedigree of the family is shown in Fig. 1.

The propositus, III.1, aged 17 years, was admitted to the Endocrine Department because of primary amenorrhoea. The patient had a feminine body build. Her height was 165 cm. and arm span 176 cm., suggesting eunuchoidal body proportions. The breasts were well developed, with normal glandular tissue and large pigmented areolas. There was complete absence of axillary and pubic hair.

The external genitalia were female. In the right labium majorum a gonad protruding from the inguinal canal was palpable. Labia minora were underdeveloped in the lower part; the clitoris was normal. The vagina was 6 cm. long, with elastic walls but rather narrow.

Vaginal smears showed high or marked oestrogenic activity, with presence of androgenic influence. Urinary gonadotrophins were 17 mouse units/24 hr. After laparotomy the gonadotrophins titre rose to 130 and 52 mouse units in consecutive examinations.

At laparotomy no uterus or Fallopian tubes were found. Two testes were present: the left, measuring 2.5 × 1.5 × 1.5 cm. with an underdeveloped epididymis, was sited in the abdominal cavity; the right, measuring 5 × 2.5 × 2.5 cm. with a well-developed epididymis, was sited in the inguinal canal. Histological examination of both gonads showed immature seminiferous tubules lined with Sertoli cells.

In generation I there were probably two cases of TFS, but this could not be proved. In generation II there were 2 normal males and 3 normal females and 3 cases of TFS, II.1, II.7, and II.8, who presented with primary amenorrhoea, female body build with good breast development, absence of axillary and pubic hair, and negative sex chromatin pattern. Histological examination of the gonads of II.8 showed them to be testes. All normal males and females except the mother of the propositus had children reported to be normal, but they have not been seen by the author. The mother, II.3, of the propositus had normal axillary and pubic hair. She had one child (the propositus) with TFS and 4 normal girls, all with a positive sex chromatin pattern. The eldest of them, 15 years old, had begun to menstruate. Colour vision in this family was normal; the blood groups are given in the Table.

**Family P.G.** The pedigree of the family is shown in Fig. 2.

In generation II there were two cases of TFS and 1 normal male and 2 normal females. One of the normal females, II.2, has 6 children, all girls and all reported to be normal, but they have not been seen by the author. Another normal female, II.5, has 4 children, 1 with TFS, 1 normal son, and 2 normal daughters both with positive sex chromatin.

The diagnosis of TFS in all 3 cases was established by clinical and cytogenetical examination. Laparotomy was performed on II.3 and two testes with
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--- Propositus.

epididymis were found in positions normally occupied by the ovaries. The right testis was of normal size, the left smaller than normal. Histological examination of both gonads showed immature seminiferous tubules lined only with degenerated Sertoli cells; in both there were foci of Pick's tubular adenoma. The propositus III.1 had been operated on during childhood because of bilateral inguinal hernia.

All 3 cases of TFS (II.3, II.6, and III.1) showed a negative sex chromatin pattern and normal male 46,XY karyotype. Colour vision in this family was normal; the blood groups are given in the Table.

**Family G.E.** The pedigree of the family is shown in Fig. 3.

The propositus, II.9, was 24 years when seen for
the first time. She was admitted to the clinic because of primary amenorrhoea and difficulties in sexual intercourse. The psychosexual orientation was female.

On physical examination she appeared to be a typical case of TFS. The body build was female, but with scanty fat tissue distribution. Her height was 152 cm, and arm span 164 cm., suggesting eunuchoidal body proportions. There was complete lack of axillary and pubic hair. The breasts were well developed but with scanty fat tissue. The external genitalia were of female type with thin and underdeveloped labia minora and very poor pigmentation. The smooth and narrow vagina was only 2 cm. long and ended as a blind pouch. Sex chromatin was negative. Chromosomal analysis showed an apparently normal male karyotype—46,XY.

On laparotomy the uterus and Fallopian tubes were absent and two testes with vasa deferentia were found near the internal orifice of the inguinal canals. Histological examination showed immature seminiferous tubules lined only with Sertoli cells; in both there were foci of Pick’s tubular adenoma.

In the mother, I.2 (aged 70 years) and 1 sister, II.7 (aged 33 years), there was complete lack of axillary hair and little pubic hair. In the sister II.10 (aged 25 years) axillary hair was almost completely absent. The maternal grandmother of the propositus was reported to have a complete lack of axillary hair, but no other case of primary amenorrhoea or TFS is known among her children.

The menarche was late (after 18 years of age) in the mother, I.2, and in the sisters, II.7 and II.10 of the propositus.

None of the sisters showed any clinical abnormalities, they had normal external and internal genital organs of female type, and their sex chromatin was positive. Two older sisters have children; II.4 has 9 and II.7 has 3. All these children are apparently normal (seen by the author or reported). The youngest sister has been married for only a few weeks.

The brothers of the propositus appeared clinically normal, their sex chromatin was negative, and they all have many children who are apparently normal (seen by the author or reported).

Colour vision in this family was normal; the blood groups are given in the Table.

**Family Ch.M.** The pedigree of the family is shown in Fig. 4.

In this family there was one case of TFS (propositus) and one normal brother and one normal sister. The propositus and her normal brother both had deuteranopia. The sex chromatin of both of them was negative. The sister at a general clinical and gynaecological examination was found to be normal. She had normal colour vision and positive sex chromatin pattern. Neither chromosomes nor Xg blood groups were examined in this family.

**Family G.I.** The propositus in this family had

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Fig. 3. Pedigree of family G.E.

Fig. 4. Pedigree of family Ch.M.
only 1 sib, a normal brother. The propositus was operated on during childhood because of right inguinal hernia. Both breasts had well-developed glandular tissue but the left one was smaller. The axillary hair was absent and the pubic hair was very scanty (Fig. 5). Over a period of 6 months large doses of androgens were given, but there was no significant growth of pubic hair nor any signs of clitoral enlargement. The propositus had a negative sex chromatin pattern and a normal male 46,XY karyotype. The mother of the propositus, who had menstruated normally from the age of 15, had no axillary hair and only scanty pubic hair. Colour vision was normal in this family; the blood groups are given in the Table.

The propositus G.I. is a swimming champion. She does not know of the chromosomal sex situation, but her mother has been informed and advised to discourage her from further competitive swimming.

Family S.A. The propositus showed a negative sex chromatin pattern and a normal male 46,XY karyotype. She had 1 normal brother and 3 normal sisters who were chromatin positive. She had no axillary hair and her pubic hair was scanty. After administration of large doses of androgens during four months, no significant growth of pubic hair nor any signs of clitoral enlargement occurred.

The mother of the propositus menstruated normally and had normal axillary and pubic hair. The eldest sister of the propositus was 36 years old, the two younger were 14 and 13. The eldest sister had the menarche when 15 years old but has always menstruated irregularly at intervals of 30–38 days. She has been married for eight years, but has no children and has complained of infertility which is probably caused by lack of ovulation. She has female body proportions. Her breasts began to develop during puberty. She has no axillary hair on the left side and scanty on the right side. Pubic hair is scanty. Colour vision was normal in this family; the blood groups are given in the Table.

Family B.B. In this family there was one case of TFS (propositus), 2 normal sisters, and one normal brother. Both sisters of the propositus were chromatin positive. The propositus showed a negative sex chromatin pattern, and a normal male 46,XY karyotype. Colour vision was normal in this family. The blood groups of the propositus, her mother, brother, and younger sister are given in the Table.

Family K.I. In the sibship of the propositus in this family there was one normal brother, and one normal sister who had a positive sex chromatin pattern. The propositus showed a negative sex chromatin pattern and a normal male 46,XY karyotype. Colour vision was normal in this family; the blood groups are given in the Table.

Discussion

Linkage Studies. The published linkage data between X-linked genes and TFS are scanty. Stewart (1959) described a family with 2 members having TFS; one was colour-blind and the other had normal colour vision. Their normal brother was also colour-blind. Another recessive X-linked trait, haemophilia, was reported by Nilsson et al. (1959) in a pseudohermaphrodite patient (most probably TFS) and in the brother who was normal.

The Xg blood groups of two families with TFS have been published (McKusick, 1962; Philip and Sele, 1965). The combined score analysis of these two families and of those which give linkage information in the present series (P.G., G.E., G.I., and B.B.) does not give any indication that the locus for TFS is within measurable distance of that for Xg (R. Sanger and R. R. Race, 1965, personal communication).

In family Ch.M. the propositus and her normal brother were both deuteranopic. If the gene for
TFS is X-linked, there must have been recombination between the TFS and deuteranopia genes.

The fact that these and other data exclude close or fairly close linkage between TFS and Xg does not imply that the gene for TFS is not carried on the X, for the X is a long chromosome and several known X-linked genes have not been demonstrably linked with the Xg(a) locus (Sanger, 1965).

In respect of 5 of the 8 families here reported some linkage information is recorded in respect of autosomal blood group markers (family P.G.—ABO, Rh, and Kell; family G.E.—ABO, MNSs; family B.B.—Rh; family G.I.—MNSs; family S.A.—ABO, Rh, and Duffy). All that can be said of the contribution of the present families on their own is that they exclude close linkage with ABO, MNSs, Rh, Kell, and Duffy (L. R. Sanger and R. R. Race, 1965, personal communication).

Whether or not linkage studies will solve the problem of the inheritance of TFS will only be known from more data. It is hoped that in reports on such families the blood groups will, whenever possible, be included.

Sex Ratio. It has been reported by different investigators that the number of affected males exceeds the number of normal males in the families (Pettersson and Bonnier, 1937; Taillard and Prader, 1957), but this was later shown (Lenz, 1959) to be due to the way in which the families had been selected. In our 8 families, excluding propositi, the number of normal males (15) exceeds the number of affected (5). However, when only the two families with familial occurrence are considered, the number of affected (5) exceeds the number of normal males (4). The ratio of females to the total number of XY individuals does not differ in our material from the expected (1:1), which is in accordance with previous observations (Taillard and Prader, 1957; Grumbach and Barr, 1958).

Absence of Axillary and Pubic Hair. Only 2 of the 13 cases of TFS reported in this paper (G.I. and S.A.) had any pubic hair and none had any axillary hair. The absence of axillary and pubic hair is one of the characteristic signs of TFS. It is worth mentioning here, however, that cases of TFS with excellent breast development and female external genitalia without signs of masculinization, but with sparse pubic hair, have been described by Jones and Scott (1958) and McKusick (1962).

The administration of large doses of androgens did not produce any significant growth of axillary or pubic hair in patients with TFS (Wilkins, 1957; Morris and Mahesh, 1963). In 8 of our cases the oestrogens in doses 50–100 mg. monthly, in some cases with progesterone (30 mg.), were given one to two years or even longer. These doses always induce growth of axillary and pubic hair in cases of pure gonadal dysgenesis, both with male and female karyotype (Boczkowski and Teter, 1966; Boczkowski, 1968). In our cases of TFS we have not noticed any significant growth of axillary or pubic hair after administering these hormones. It is also important that after administration of large doses of androgens to cases of TFS, clitoral enlargement was not observed in our cases or in those of Wilkins (1957) or Morris and Mahesh (1963).

It appears, therefore, that in TFS there may be insensitivity of some target organs (hair and clitoris) to all sex hormones. There is no hair growth after administration of androgens or oestrogens with progesterone and no clitoral enlargement after androgens.

Testicular Feminization Syndrome as a Sex-modified Trait. Decreased axillary and pubic hair in otherwise normal females in TFS families as described above has been reported by a number of authors (Schultze, 1930; Mishell, 1938; Spurzy and Ulm, 1958; Scharplatz, 1958; Kessler, 1959; Gayral et al., 1960; Pion et al., 1965). In two families a delayed menarche was also reported (Beatty, Champ, and Swyer, 1953; Puck, Robinson, and Tijo, 1960).

The lack of, or very scanty, axillary and pubic hair in females in three families reported in this paper (G.E., G.I., and S.A.) may indicate that the gene responsible for TFS is not entirely inert in heterozygous females. The question arises whether this supports the X-linked or sex-limited autosomal hypothesis. Sex limitation is only the extreme example of control of the expression of a certain genotype by sex. When the genotype is expressed in both sexes but in a different manner in each, we can speak of the sex-controlled, or sex-modified, gene expression (Stern, 1960).

For the lack of, or very scanty, axillary and pubic hair in females from TFS families the sex-modified expression is the best explanation. On such an hypothesis in XY individuals the TFS gene might determine abnormal hormonal production by the testes and absence of axillary and pubic hair. In females, however, it might cause only absence of, or scanty, axillary and pubic hair, as there could be no question of anomaly of testicular hormonal production in normal females.

Some Clinical Considerations. It should be stressed that the presence of female external genitalia
and normal male karyotype in a girl is not sufficient to diagnose TFS with certainty in a female before puberty. We do not know whether or not the breast development and absence of axillary and pubic hair will occur during adolescence. This is why we cannot accept the case of Gropp et al. (1963), with a large Y chromosome, and the twins with XXY karyotypes described by German and Vesell (1966), as proved cases of TFS. These cases may be similar to those in which there is absence of breast development coupled with female external genitalia (Schlegel et al., 1966; Boczkowski and Teter, 1968). Another possibility is that in these cases signs of virilization may develop during puberty.

In all our cases the body build was feminine and there was good breast development, both of which are characteristic of TFS. It is worth mentioning, however, that in almost all cases the arm span was greater than the height (sometimes more than 10 cm) which is a characteristic sign of eunuchoid body proportions.

In our cases the labia minora were underdeveloped and thin. This sign was stressed in TFS by Morris and Mahesh (1963) and in other cases of intersexuality by Boczkowski and Teter (1965, 1966).

The presence of foci of Pick's tubular adenomas in six cases of TFS presented in this report is not an indication for early removal of testes. These adenomas are benign lesions, and we remove testes as a rule only after puberty. As none of our patients had malignant gonadal tumours we are of the opinion that the danger of malignancy before the age of 25–30 is not as high as suggested in some previous papers.

Summary

Studies were carried out in 8 families where there were in all 13 patients with testicular feminization syndrome (TFS). The ratio of affected XY individuals to normal males to normal females (excluding the propositus) was 5:15:21, respectively. In 9 cases of TFS, cytogenetic studies were performed and in all normal male 46,XY karyotypes were found. In all 8 families colour-blindness tests were done, and in 7 families blood groups (including Xg) were determined. The data do not give any indication that the locus for TFS is within measurable distance of those for Xg or colour-blindness. They exclude also close linkage with autosomal marked blood groups—ABO, MN, Rh, Kell, and Duffy. In 3 families absent axillary and very scanty pubic hair were encountered in otherwise normal females. This finding suggests that TFS is a sex-modified rather than a male-limited trait.

It is stressed that as a rule we cannot diagnose TFS before puberty.

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