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The X linked recessive form of XY gonadal dysgenesis with a high incidence of gonadal germ cell tumours: clinical and genetic studies

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SUMMARY Five phenotypic females in one family had the genotype 46,XY and all had gonadal germ cell tumours. Studies of the family pedigree suggest that this form of XY gonadal dysgenesis is inherited in an X linked recessive manner.

G banding of elongated metaphase chromosomes from two subjects with XY gonadal dysgenesis and a female carrier showed no aberrations of the X chromosome. The titres of H-Y antigen in three girls with XY gonadal dysgenesis were in the male control range. Thus it appears that, in the X linked form, XY gonadal dysgenesis may be caused by a point deletion or mutation of a gene on the X chromosome, which controls the gonad specific receptor for the H-Y antigen.

Studies of Xg blood groups were uninformative about linkage of *Xg* with the X borne gene causing the XY gonadal dysgenesis.

Dermatoglyphic studies in the girls with XY gonadal dysgenesis and female carriers revealed high *a-b* palmar ridge counts and a tendency for the A mainline to terminate in the thenar area. Both of these features have been described in patients with Turner's syndrome.

XY females with gonadal dysgenesis have streak gonads,[1] but look like normal females who do not develop secondary sexual characteristics at puberty and do not menstruate. They are chromatin negative and have a 46,XY karyotype. They are usually of normal stature and do not have the somatic stigmata of Turner's syndrome. The affected members of one family[2] were unusually tall. Sporadic and familial cases are reported and in the latter the mode of inheritance can be either autosomal recessive or X linked.[3–5] The basic defects causing the failure of male sex differentiation in these disorders have not been elucidated.

A high incidence of germ cell tumours in streak gonads of patients with the XY karyotype was reported by Taylor *et al.*[6]

We describe studies in a family in which XY gonadal dysgenesis appears to have been inherited in an X linked recessive manner, and in which the affected members had a very high incidence of gonadal germ cell tumours.

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Methods

CYTOGENETIC STUDIES

Peripheral blood lymphocytes were set up using a standard whole blood technique stimulated with phytohaemagglutinin. Also, for testing certain family members, in order to achieve the high degree of resolution required to detect small interstitial deletions, elongated prometaphase chromosomes were obtained by a thymidine synchronisation procedure based on those of Viegas-Pequignot and Dutrillaux[7] and Yunis.[8] The cells were G banded using the method of Herbert.[9]

DETERMINATION OF H-Y ANTIGEN

Anti-H-Y antiserum was raised in isogenic Lewis rats by 6-weekly intraperitoneal injections of 20×10^6 male spleen cells into female animals. The

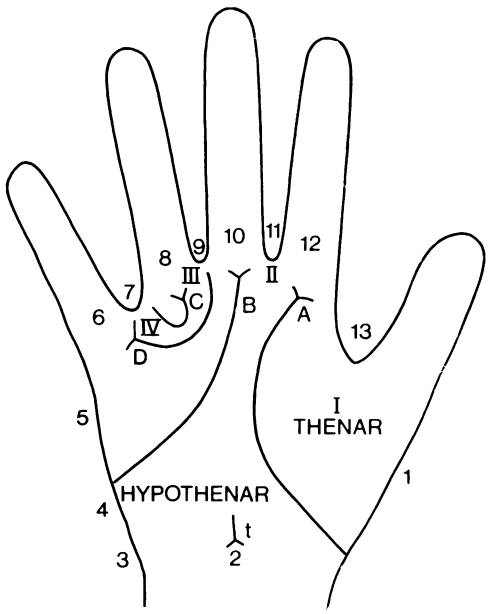

FIG 1 *Diagram of palm showing palmar areas and mainlines.*

A, B, C, D	*Mainlines*
I, II, III, IV	*Interdigital areas*
t	*Axial triradius*
Numbers 1–13	*Numbering system used to indicate position of mainline terminations*

serum was obtained one week after the last injection, inactivated at 56°C for 30 minutes, and absorbed with human female AB erythrocytes, spleen cells of female Lewis rats, and BJAB cells, a female Burkitt lymphoma derived cell line. Of the sera pretreated this way, those showing a clear-cut sex difference in the cytotoxicity test after absorption with male and female control cells respectively were selected for use in the measurements.

Rabbit complement was selected for low cytotoxicity on RAJI male Burkitt lymphoma cells, which served as targets in the cytotoxicity test.

Fibroblasts and buffy coat blood cells from patients and controls were used for absorption and H-Y antigen was determined according to the methods of Fellous *et al.*[10]

BLOOD GROUPING

Routine serological methods[11] and the monoclonal antibody 12E7 to define the polymorphism related to the Xg groups[12] were used.

DERMATOGLYPHIC ANALYSIS

The techniques of Penrose and Loesch[13] were used, incorporating the modifications suggested by Dennis[14] (see fig 1).

Case report

The proband (V.27, fig 2) was investigated when aged 13 years for short stature and, like a younger sister (V.29) who was short and of low intelligence and had been investigated previously, was found to have a 46,XY chromosome constitution. When she was 14 years 7 months old she developed abdominal pain and a large mass was found arising in the pelvis and extending to the umbilicus. Her height and weight were both just below the 3rd centile. She was of dull intelligence and had no breast development and scanty pubic hair. Under anaesthetic the vulva was found to be well-developed and the vagina of normal capacity but the cervix was small and could not be dilated. At laparotomy a huge unresectable tumour arising in the lower pelvic cavity was found and a biopsy was taken. Histological examination

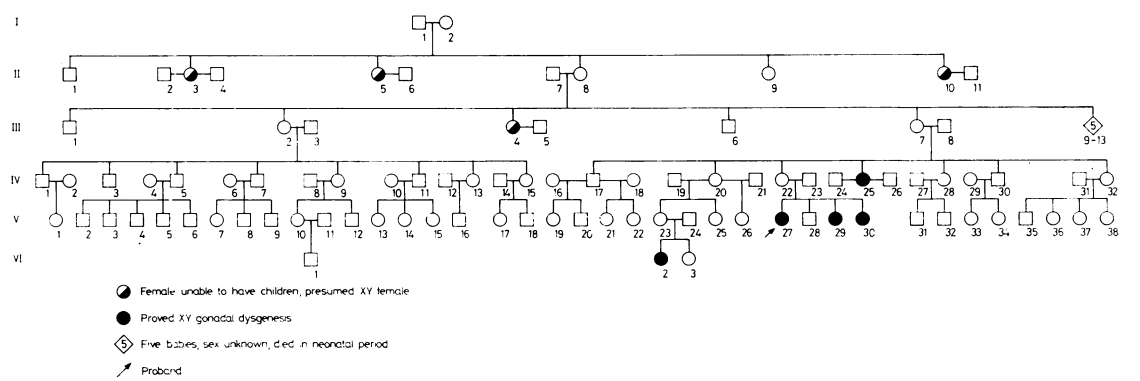

FIG 2 *Family pedigree.*

showed a malignant yolk sac tumour having an epithelial appearance, some papillary areas, Schiller-Duval bodies, and much necrosis. Many acinar spaces were filled with colloid material and some lining cells contained deeply eosinophilic colloid globules. The secretion was thought to be composed partly of alphafetoprotein (AFP).

Further investigations included serum AFP 28 500 U/ml, β human chorionic gonadotrophin (βHCG) 11·0 mIU/l, oestradiol 120 pmol/l, androgens 2·8 nmol/l, FSH >50 U/l, LH 48 U/l, normal radiographs of the chest and skeleton, and normal bone marrow aspirate and biopsy.

Substantial regression of tumour and reduction in serum AFP and βHCG were achieved with vincristine, actinomycin D, and cyclophosphamide and after 11 weeks subtotal excision of a 9×6×6 cm tumour arising from the right side of the pelvis was performed. The vagina was transected and the uterus and fallopian tubes were removed but no gonads were identified. Histological examination revealed much necrotic tumour, some viable areas consisting of yolk sac tumour, and small areas of well differentiated teratoma containing respiratory epithelium, plain muscle, and glial tissue. No gonad was found, but the tumour probably arose in the right dysgenetic gonad.

Postoperatively the serum AFP levels fell further but never reached normal values despite further chemotherapy and radiotherapy. The patient suffered severe vomiting after her drugs, necessitating dose reductions, and, after one year's chemotherapy, when her condition deteriorated and AFP levels rose, she refused further treatment. She died of tumour recurrence 3 months later. There was no necropsy.

Results of studies on the family members

After the diagnosis was made in the proband all the available family members were examined and studied. The family pedigree is shown in fig 2. It appears that the condition was inherited in an X linked recessive manner, that is, manifest in XY females but transmitted by presumed carrier females. Both of the patient's younger sisters had XY gonadal dysgenesis, so their gonads were removed prophylactically. An aunt (IV.25) had been treated for bilateral 'ovarian' dysgerminomas and we found her chromosomes to be 46,XY. Investigation of the family led to the

TABLE 1a *Clinical features of subjects with XY gonadal dysgenesis.*

Family member	*Age when XY gonadal dysgenesis confirmed (yr)*	*Height (cm)*	*Weight (kg)*	*Vagina, uterus, fallopian tubes*	*Secondary sexual development*	*Age when gonads removed (yr)*	*Histology of gonads*	
							Right	*Left*
IV.25	31·6	160	70	Apparently normal female	Amenorrhoea. Normal breasts, axillary, and pubic hair. Deep voice.	23·5	Dysgerminoma	Dysgerminoma
V.27	13·2	145	37·5	Apparently normal female	Scanty pubic hair. No breast development	14·9	Yolk sac tumour and areas of differentiated teratoma	Not found
V.29	5·0	99	19·0	Apparently normal female	None	13·5	Gonadoblastoma Dysgerminoma	Gonadoblastoma
V.30	0·5	Not recorded then but subsequently height on 10th and weight on 50th centiles		Apparently normal female	None	8·4	Gonadoblastoma Dysgerminoma	Gonadoblastoma Dysgerminoma
VI.2	1·25	78	9·0	Apparently normal female	None	1·7	Gonadoblastoma Dysgenetic	Dysgenetic

TABLE 1b *Results of investigations of subjects with XY gonadal dysgenesis.*

Family member	*Serum hormones (before gonads removed)*				*Serum AFP (U/ml)*	*Serum βHCG (mIU/ml)*	*H-Y antigen*		
	LH (U/l)	*FSH (U/l)*	*Oestradiol (pmol/l)*	*Androgens/ testosterone (nmol/l)*			*Blood*	*Fibroblast culture*	*Other*
IV.25	—	—	—	—	—	—	—	Positive	Epileptic
V.27	48	>50	120	Androgens 2·8	28 500	11	—	—	Dull intelligence (reading age 10 yr)
V.29	25	38	16	Testosterone 1·5	<11	<2	Positive	—	Educationally subnormal (IQ 54)
V.30	—	—	—	—	<15	<2	—	—	—
VI.2	—	—	—	—	—	—	—	Positive	—

diagnosis of V.12, whose gonads were therefore removed. Further details about the five members proved to have XY gonadal dysgenesis are shown in table 1. All had gonadal tumours. Four phenotypic females from previous generations were said to have been infertile, but all had died so could not be investigated. One (III.4) was said to have been unusually tall.

CYTOGENETIC STUDIES

The following phenotypic females were found to be 46,XX: IV.22, V.17, V.25, V.26, V.36, V.37, V.38, VI.3; whereas IV.25, V.27, V.29, V.30, and VI.2 were 46,XY.

G banding on elongated chromosomes from IV.22 (carrier female) and V.29 and V.30 (females with XY gonadal dysgenesis) showed no abnormalities, in particular no deletions in their X chromosomes.

H-Y ANTIGEN

The results of the determinations of H-Y antigen on three subjects with XY gonadal dysgenesis (IV.25, V.29, and VI.2) are shown in fig 3. All had titres in the male control range.

BLOOD GROUPING

All the family members tested (IV.20, IV.22, IV.23, IV.25, IV.32, V.17, V.23, V.25, V.27, V.29, V.30, V.36, V.37, V.38, VI.2, VI.3) were Xg(a+). The cells of all these relatives were also tested and found positive with the monoclonal antibody 12E7[12] defining the polymorphism related to the Xg blood groups. Results for 12 other blood group systems are available on request.

DERMATOGLYPHIC CHARACTERISTICS

Four subjects with XY gonadal dysgenesis, three obligatory carriers, six other blood relatives, and three relatives by marriage were studied. No abnormal patterns were seen in their fingers or palms (tables 2 and 3). In IV.20 the relatively uncommon radial hypothenar arch pattern was present on the right hand and IV.32 had a displaced axial triradius on the right hand, though no true arch was formed.

The formulae for the mainline endings are included in table 3. There was a tendency for the A mainline to terminate in area 1, the thenar area, especially in the XY gonadal dysgenesis subjects and their mothers. The B mainline showed a tendency to terminate in area 5. The C and D mainlines showed no trends, although there were four instances of a missing *C* triradius giving an O termination for the C mainline.

The palmar ridge counts are given in table 4. The *a-b* ridge counts, particularly for the left hand, were higher for the XY gonadal dysgenesis subjects

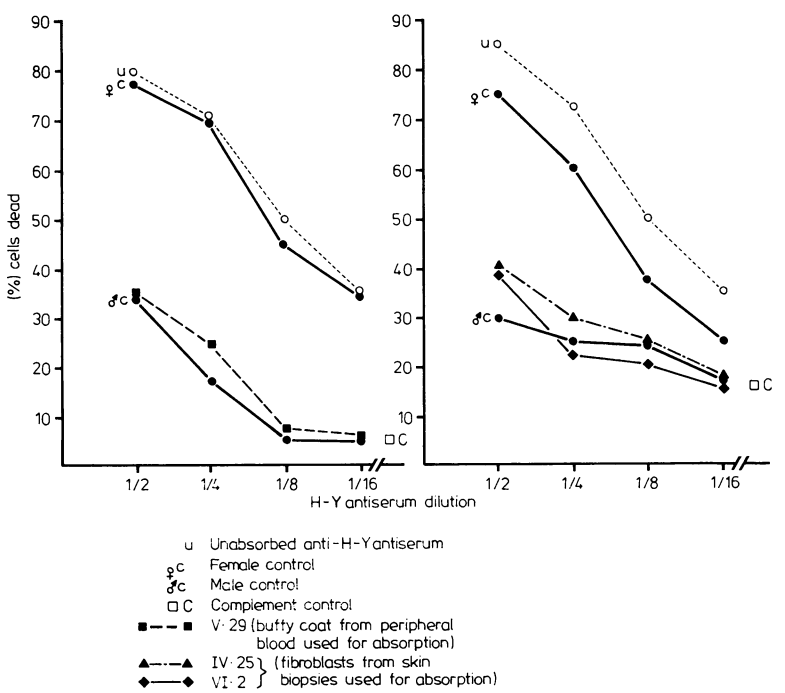

FIG 3 *Results of the Raji cell cytotoxicity test on cells from patients with familial XY gonadal dysgenesis.*

TABLE 2 *Digital patterns.*

Subject		*Right hand*					*Left hand*				
		1	*2*	*3*	*4*	*5*	*1*	*2*	*3*	*4*	*5*
XY gonadal dysgenesis	IV.25	dl	l^u	l^u	l^u	l^u	l^u	l^u	l^u	l^u	l^u
	V.29	l^u	l^u	l^u	l^u	l^u	l^u	l^u	l^r	l^u	l^u
	V.30	l^u	l^u	l^u	l^u	l^u	l^u	l^u	l^u	l^u	l^u
	VI.2	l^u	l^r	w	w	l^u	l^u	w	w	w	l^u
Obligatory carriers	IV.20	l^u	l^u	l^u	l^u	l^u	l^u	l^u	l^u	l^u	l^u
	IV.22	l^u	l^u	l^u	l^u	l^u	l^u	l^u	l^u	l^u	l^u
	V.23	dl	w	w	dl	l^u	l^u	l^u	dl	dl	dl
Other blood relatives	V.25	l^u	l^r	A	l^u	l^u	l^u	A	A	l^u	l^u
	V.26	w	l^u	l^u	l^u	w	dl	l^u	l^u	l^u	w
	V.32	dl	l^u	l^u	l^u	l^u	l^u	l^u	l^u	l^u	l^u
	V.36	w	l^u	l^u	w	l^u	l^u	l^u	l^u	w	l^u
	V.37	dl	l^u	l^u	w	l^u	dl	l^u	dl	w	l^u
	V.38	dl	dl	l^u	—	—	—	—	—	—	—
Non-blood relatives	IV.23	l^u	l^u	l^r	l^u	l^u	l^u	w	l^u	l^u	l^u
	V.24	l^u	l^r	l^u	l^u	l^u	l^u	l^u	l^u	w	l^u
	IV.31	dl	l^r	dl	w	w	dl	l^r	dl	w	w

A = arch, l^u = ulnar loop, l^r = radial loop, dl = double loop, w = whorl.

TABLE 3 *Palmar patterns and mainline endings.*

Subject		*Thenar*		*Interdigital*		*Hypothenar*		*Mainline formulae*	
		R	*L*	*R*	*L*	*R*	*L*	*R*	*L*
XY gonadal dysgenesis	IV.25	—	—	III	IV	—	—	4, 7, 9, 11	1, 5, 7, 9
	V.29	—	—	IV	IV	—	—	1, 5, 5, 7	1, 5, 5, 7
	V.30	—	—	IV	IV	$\hat{H}$	—	3, 5, 5, 7	1, 3, 5, 7
	VI.2	—	—	IV	IV	—	—	3, 5, 7, 9	3, 5, 7, 9
Obligatory carriers	IV.20	—	—	III^T	III^T	HRA	$\hat{H}$	1, 7, 7, 11	1, 7, 0, 11
	IV.22	—	I	III	III	—	—	3, 7, 9, 11	1, 5, 9, 9
	V.23	—	—	III^T	IV	—	—	3, 7, 7, 11	1, 5, 5, 7
Other blood relatives	V.25	—	—	III^T	IV	$\hat{H}H$	$\hat{H}H$	4, 5, 0, 9	3, 5, 7, 9
	V.26	—	—	IV	IV	$\hat{H}H$	$\hat{H}H$	1, 5, 5, 7	1, 5, 5, 7
	IV.32	—	—	III	III^T	—	H	1, 7, 9, 11	3, 7, 7, 11
	V.36	I	I	III	—	—	—	5, 7, 0, 11	3, 5, 0, 9
	V.37	—	—	—	—	$\hat{H}H$	$\hat{H}$	1, 7, 0, 11	3, 5, 0, 9
	V.38	—	—	IV	—	—	—	Not read	
Non-blood relatives	IV.23	—	—	IV	IV	HRA	—	1, 5, 5, 7	3, 5, 5, 7
	V.24	—	—	III	IV	H^r	—	4, 7, 9, 11	4, 7, 7, 11
	IV.31	—	—	III	III	H^r	$\hat{H}$	4, 7, 9, 11	4, 7, 9, 11

I = peripheral thenar loop, III^T = tented arch in 3rd interdigital area, H = hypothenar peripheral loop, HRA = hypothenar radial arch, III, IV = peripheral loops in interdigital areas, $\hat{H}$ = hypothenar central loop, H^r = hypothenar radial loop.

TABLE 4 *Palmar ridge counts.*

Subject		*Right*				*Left*				
		a-b	*b-c*	*c-d*	*RTOT*	*a-b*	*b-c*	*c-d*	*LTOT*	*TPRC*
XY gonadal dysgenesis	IV.25	39	27	34	100	50	23	38	111	211
	V.29	53	34	44	131	57	26	47	130	261
	V.30	49	41	48	138	60	38	49	147	285
	VI.2	42	20	36	98	48	19	34	101	199
Obligatory carrier	IV.20	39	17	45	101	42	20	43	105	206
	IV.22	58	32	45	135	62	36	45	143	278
	V.23	40	24	39	103	41	28	34	103	206
Other blood relatives	V.25	34	26	33	93	45	18	36	99	192
	V.26	32	23	36	91	43	21	33	97	188
	IV.32	36	30	30	96	44	22	37	103	199
	V.36	42	26	26	94	43	.... 60		103	197
	V.37	46	.... 39		85	38	.... 38		76	161
	V.38	38	27	17	80	No ridge count			—	—
Non-blood relatives	IV.23	38	38	40	116	42	38	40	120	236
	V.24	44	23	34	101	44	20	34	98	199
	IV.31	39	21	35	95	45	18	32	95	190

and for the obligatory carriers than for the unaffected female relatives. These *a-b* ridge counts affected the total palmar ridge counts, which were consequently higher in the affected members of the family.

Discussion

The presence of the H-Y antigen appears to be essential for the organisation of the mammalian testis, and the structural gene for H-Y antigen is believed to be autosomal.[15] Production of the antigen is thought to be regulated by genes on the Y chromosome, whereas genes on the X chromosome have a suppressing effect. The X chromosome also appears to possess a gene for a gonad specific receptor for H-Y antigen[15] without which the virilising effects of the antigen are not expressed.

Studies in the Scandinavian wood lemming have assisted the understanding of the interaction between the genes involved in sex determination. In this species two morphologically different X chromosomes exist, X and X*. The X* chromosome is slightly shorter than the wild type X, presumably owing to a deletion in the short arm.[16] The X* chromosome is generally correlated with a female phenotype, even in the presence of a Y chromosome, only XY animals showing a male phenotype (X*XY subjects, showing a phenotypic range from male to female, will not be discussed here). Other genotypes which occur in wood lemmings, XX, X*Y, X*O, X*X, and XO, are all fertile females. An area on the short arm (deleted in the X* genotypes) appears to contain the gene for the gonad specific receptor of the H-Y antigen (and also for its suppressor).[15 17]

In the family we report the genetic situation resembles that of the X*Y wood lemming female, that is, the autosomally mediated production of H-Y antigen is normal because the regulatory gene on the Y chromosome is functioning, but the X chromosome lacks the presumed gonad specific receptor gene, so differentiation of the testis does not occur. The affected subjects thus develop as females but, unlike the X*Y lemming, have dysgenetic gonads and are not fertile. This parallels the XO condition resulting in fertile females in rodents, but in sterile females with dysgenetic gonads in the human. Subject IV.25 in our pedigree, however, had spontaneous breast development, but never menstruated.

The analogy with the X*Y wood lemming would have been strengthened had we been able to demonstrate a deletion on the X chromosome of our patients and the obligatory carriers who were tested. However, we cannot exclude the presence of a point mutation or deletion.

Previous studies of H-Y antigen in XY gonadal dysgenesis have involved mostly sporadic cases, and familial occurrence only in sibs of one generation, and some showed normal titres whereas others did not.[18] Thus there appears to be genetic heterogeneity in the disorder and the precise mechanisms involved are not yet fully understood for all the variants.

The H-Y suppressor gene in man seems to be closely linked to the loci on Xp22·3→Xpter required for the expression of steroid sulphatase and the Xg blood group antigen.[19–21] Since, in the wood lemming, the suppressor gene and the receptor gene appear to be affected by the same deletion, they should be in close proximity. If this linkage group was conserved in evolution, the receptor gene should be close to Xp22·3 in the human. However, all the family members tested were Xg(a+) and therefore uninformative about linkage with the X borne gene causing gonadal dysgenesis.

It has become apparent that the only subjects with intersex states who are particularly prone to gonadal tumours are those with a Y chromosome line.[22] Thus, there is little increased risk in girls with 45,XO Turner's syndrome whereas the risk for gonadoblastoma or dysgerminoma, arising usually in the second and third decade, had been estimated to be in the order of 20 to 30% for 45,XO/46,XY mosaics (male intersex with Turner phenotype) and girls with X linked gonadal dysgenesis.[22] Gonadal tumours are rare in true hermaphrodites but an increased risk of perhaps 10% is present in karyotype 46,XY testicular feminisation subjects. Tumours have been described in XY gonadal dysgenesis as early as 7 years of age.[23] Gonadal tumours in girls with XY gonadal dysgenesis who express the H-Y antigen have been reported and it has been postulated that H-Y negative subjects may have a lower risk of tumours.[5] However, further pedigrees of H-Y negative cases have not yet been studied to establish whether this is so.

As reported in another study,[24] the dermatoglyphic prints revealed no abnormalities in the finger or palm patterns. However, in the girls with XY gonadal dysgenesis and in female carriers there were high *a-b* palmar ridge counts and a tendency for the A mainline to terminate in the thenar area. Both of these features have been described as characteristics of patients with Turner's syndrome,[25] but further studies are needed to clarify this possible similarity in the features present in XY and XO dysgenesis.

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Reference to the results of the determination of H-Y antigen in the subjects with XY gonadal dysgenesis has been published previously.[15 17]

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