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Familial disorder of sex determination in seven individuals from three related sibships

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Abstract In humans, the sex of an individual is determined by the Y-chromosome-related SRY gene, which causes the differentiation of the undifferentiated gonads into testicular tissue. True hermaphrodites without a Y chromosome and XX males represent a sex determination error in which testicular tissue develops despite the absence of the SRY gene. Familial forms of XX true hermaphrodites and XX males exist in the literature, which also contains the two forms co-existing in the same family. In this report, we present a large family with seven affected individuals with phenotypes ranging from XX male to XX true hermaphrodite with predominance of female characteristics. We suggest that XX maleness and XX true hermaphroditism represent a continuum of the same disorder. We speculate on the mode of inheritance of this disorder in this particular family.

Key words XX Male · XX True hermaphrodite · Sex differentiation · Sex determination · Ovotestis

Introduction

In humans, the sex of an individual is primarily determined by a Y chromosome-testis-determining factor, now known as the SRY gene [31]. If absent, the fetal gonadal tissue develops into ovaries, while if present, it promotes the development of the undifferentiated gonads into testes [6, 14]. Several disorders of sex determination and differentiation involve the development of testicular tissue in an individual lacking the SRY gene such as XX true hermaphrodites and XX males.

A true hermaphrodite is defined as an individual in whom both testicular and ovarian tissue are present, which necessitates that the final diagnosis be based on histological examination of the gonads [4]. Although many gonadal patterns have been observed, the majority of patients present an ovary on one side of the abdomen and a testis or ovotestis on the other side [37]. The grade of gonadal descent seems to depend on the amount of testicular tissue present within the gonad [16, 34, 37]. Ambiguous genitalia are present at birth in 90% of reported cases [5]. The most common chromosomal complement is 46,XX followed by 46,XX/46,XY mosa-

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icism [5, 22]. There is a considerable risk of malignancy with germinal cell tumours being the most frequent and disgerminoma being the most common histological finding [13]. On the other hand, XX males are individuals with normal male phenotype but without ovarian tissue, Mullerian duct derivatives or an evident Y chromosome [8]. In a significant percentage of these individuals a translocated Y chromosome material or mosaicism has been detected [1, 7, 10, 19]. However, there are reports of SRY negative XX males who exhibit full masculinisation [17, 19, 29, 38].

The literature contains several reports of familial cases of true hermaphrodites [2, 11, 12, 18, 20, 30], familial cases of XX males [1, 9, 21, 23, 24, 26, 35, 39] and the two conditions co-existing in the same family [3, 15, 17, 19, 25, 27–29, 32, 33, 38]. Whenever molecular studies were done in families in the last category, most subjects were negative for the presence of Y chromosome material and most of them had genital ambiguity. We here present seven individuals with a spectrum of disorders ranging from XX male to true hermaphrodite with predominance of female phenotype, from three related sibships belonging to an inbred family from Jordan. We speculate on the inheritance pattern in this family.

Case reports

Case 1 (IV.15)

This patient is currently 36 years old and is the one who brought the family to our attention. He was finally diagnosed with true hermaphroditism 2 years ago when a detailed work-up was undertaken, initiated due to 10-year history of infertility. He developed male puberty at the age of 15 years but was short with scanty facial hair and normal pubertal male body hair distribution. He underwent bilateral orchidopexy for bilateral undescended testes at the age of 19 years. A year later, he started developing gynaecomastia which became apparently progressive over the next few years. He married his female first cousin at the age of 25 years, and reports, since then, regular sexual intercourse (2–4 times/week). However, the couple suffered from primary infertility and underwent several investigative procedures for that purpose. The work-up showed his wife to have normal reproductive ability but he had azospermic seminal fluid. At that time, he had a high serum FSH level (44 IU/l, reference range: 1–12 IU/l) and low testosterone. Two testicular biopsies from the left side, done 4 years apart, showed sclerosed testicular tubules and were reported to be consistent with a Sertoli-cell-only picture. His karyotype was 46,XX. During his recent work-up, a pelvic ultrasound showed a small uterine structure. His repeat karyotype showed the same previous results and the SRY was also negative. The results of the hormonal profile are shown in Table 1. He is currently short (156 cm), with normal head circumference (54 cm), and with male physique. He has two small soft testicles that were originally brought down to the scrotum and normal penile size and structure without hypospadias (Fig. 1). Socially, he carries a male name, has been brought up as a male and performs familial male functions such as holding a job and providing the income for the family. He is intelligent and educated and after extensive counselling, he underwent removal of the gonadal tissue, uterus and the breast tissue and started receiving androgen replacement. The right gonad showed both testicular and ovarian structures on microscopy, while the left gonad could not be examined microscopically because of extensive sclerosis that followed the two previous biopsies.

Case 2 (IV 16)

Case 2 is currently 33 years old and was evaluated 2 years ago around the same time as case 1. He developed male puberty at the age of 14 years with normal pubertal male body and facial hair distribution. He married his female first cousin at the age of 25 years, and reports, since then, regular sexual intercourse (3–4 times/week). However, the couple suffered from primary infertility and underwent several investigative procedures, all showing normal reproductive ability of his wife. One of his small soft testes was biopsied by fine needle aspiration and showed only early-elongated spermatids. His karyotype was 46,XX. During his recent work-up, his repeat karyotype showed the same previous results and the SRY was negative. Pelvic and transrectal ultrasound did not detect any Mullerian duct derivatives. The results of the hormonal profile are shown in Table 1. He is currently of normal height (163 cm), with normal head circumference (57 cm), and with a well-androgenised male physique. He has two small soft testicles (volume ca. 3–4 ml) and normal penile size and structure without hypospadias. He does not have and has never developed gynaecomastia. Socially, he is functioning as a male. He was given the diagnosis of 46,XX male.

Case 3 (IV.22)

This patient is currently 22 years old and was evaluated just recently after having refused the work-up for sometime. He developed male puberty at the age of 14 years with normal pubertal male body and facial hair distribution. Although he is not sexually active, he masturbates with positive ejaculation and his sex partner preference is female. He is engaged to be married to his first cousin. His karyotype is 46,XX and the SRY is negative. The results of the hormonal profile are shown in Table 1. Pelvic ultrasound did not detect any Mullerian duct derivatives, but on the transrectal ultrasound a mass was seen that could be a small uterus. He is currently of normal height (165 cm) with normal head circumference

Table 1 The hormonal profile of affected individuals

Patient	Luteinising hormone (IU/l)	Follicle stimulating hormone (IU/l)	Testosterone (ng/ml)	Oestradiol (pmol/l)	Prolactin (ng/ml)	17-Hydroxy-progesterone (nmol/l)	Dihydro-epiandrosterone (nmol/l)
Reference range	2–12	1–12	1.88–9	< 202	2.2 18.5	1.2–10	
Case 1 (IV.15)	63.13	71.08	1.8		7.5		
Case 2 (IV.16)	27.23	46.61	3.82	210.6	8.6		
Case 3 (IV.22)	20.22	20.92	3.83	129.2	15.5		
Case 4 (IV.25)			0.06	163		11.9	1.3
Case 5 (IV.26)			0.58	417		3.4	2.1
Case 6 (V.5)	0.34	1.81	0.27		12.4	1.6	0.11
Case 7 (IV.10)	17.42	7.3	0.06	222	21.3	3.9	3.8

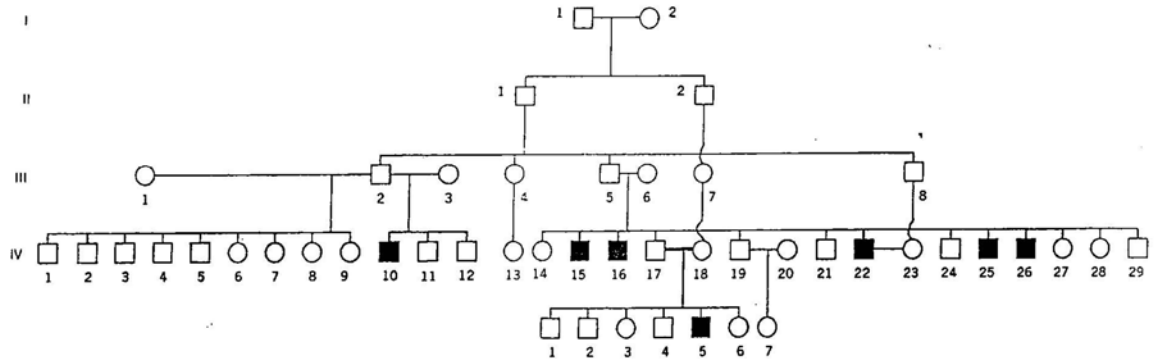

Fig. 1 The pedigree of the family. Besides the affected patients, the following individuals were examined by the authors and had been evaluated at least by chromosomal analysis and SRY status analysis: III.5, IV.1, IV.2, IV.9, IV.11, IV.12, IV.13, IV.17, IV.18, IV.19, IV.20, IV.27, IV.28, IV.29, V.1, V.2, V.7

(56 cm) and with a well-androgenised male physique. He has two small soft testicles (volume ca. 2–3 ml) and normal penile size and structure without hypospadias. He does not have and has never developed gynaecomastia. Socially, he is functioning as a male. Due to all of the above findings, and the uncertainty of the transrectal ultrasound findings, he was given the diagnosis of 46,XX male.

Case 4 (IV.25)

Case 4 is currently 20 years old. He was born with recognised ambiguous genitalia, but was assumed to be a male with hypospadias and bilateral undescended testes and was brought up as such. He was finally diagnosed with true hermaphroditism 2 years ago when a detailed work up was undertaken, initiated by that of his sibling case 1. He developed some male secondary sexual characters at the age of 15 years, with scanty facial and body hair. However, at the age of 16 years he started developing gynaecomastia and cyclic monthly haematuria (Fig. 1). He masturbates without ejaculation and his sex partner preference is female, although he is not sexually active. During his recent work-up, his karyotype was 46,XX and the SRY was negative. The results of the hormonal profile are shown in Table 1. He is currently of normal height (168 cm) with normal head circumference (54 cm) and with general male physique. He has a normal penile size and structure with peno-scrotal hypospadias. Socially, he carries a male name and was brought up as a male. After counselling, he decided to maintain his male gender and underwent removal of the gonadal tissue, uterus and the breast tissue and started receiving androgen replacement. Both gonads showed both testicular and ovarian structures on microscopy (ovotestes).

Case 5 (IV.26)

This patient is currently 18 years old. He was born with recognised ambiguous genitalia, but was assumed to be a male with hypospadias and bilateral undescended testes and was brought up as such. He was finally diagnosed with true hermaphroditism 2 years ago when a detailed work up was undertaken, initiated by that of his sibling case 1. He developed some male secondary sexual characteristics at the age of 14 years, with scanty facial and body hair. However, at the age of 15 years he started developing gynaecomastia with final well-developed breasts and cyclic monthly haematuria. He masturbates without ejaculation and his sex partner preference is female, although he is not sexually active. During his recent work-up, his karyotype was 46,XX and the SRY was negative. The results of the hormonal profile are shown in Table 1. He is currently of normal height (159 cm) with microcephaly (52 cm) and with a general male physique. He has a small penis, which seems normal in structure, but with peno-scrotal hypospadias. Socially, he carries a male name and was brought up as a male. After counselling, he decided to maintain his male gender and underwent removal of the gonadal tissue, uterus and the breast tissue and started receiving androgen replacement. Both gonads showed both testicular and ovarian structures on microscopy (ovotestes) with a vas deferens and an epididymus on one side (Fig. 1).

Case 6 (V.5)

Case 6 is currently 4 years old. He was born with recognised ambiguous genitalia, in the form of a small penis, peno-scrotal hypospadias and bifid scrotum. The right gonad was felt in the scrotum but the left was assumed undescended. He underwent surgical exploration when the right gonad was biopsied and found to be an ovotestis, although a vas deferens was present and attached. The left vas deferens and epididymus were not attached to the left gonad, which was biopsied and found to contain only testicular tissue. There was no obvious uterine structure but there was a cervical remnant and a blind vagina with an urethro-vaginal fistula. The fistula was also seen on cystoscopy. The karyotype was 46,XX and the SRY was negative. The results of the hormonal profile are shown in Table 1. The two gonads were fixed inside the scrotum and a right inguinal hernia was repaired. The final gender assignment is male as requested by his parents.

Case 7 (IV.10)

This individual is currently 19 years old. He was born with recognised ambiguous genitalia, but was assumed to be a male with hypospadias and bilateral undescended testes and was brought up as such. The subject was finally diagnosed with true hermaphroditism 2 years ago when a detailed work-up was undertaken, initiated by that of his cousins. At the age of 15 years he started developing gynaecomastia with final well-developed breasts (Fig. 1) and cyclic monthly haematuria and female physique. His external genitalia showed an enlarged clitoris, fused labia, perineal hypospadias and female distribution of the pubic hair. He masturbates without ejaculation and his sex partner preference is female, although he is not sexually active. During his recent work-up, a pelvic ultrasound showed a uterus and a cervix. His karyotype was 46,XX and the SRY was negative. The results of the hormonal profile are shown in Table 1. He is currently of normal height (171 cm) with normal head circumference (54 cm). Socially, he carries a male name and was brought up as a male. After counselling, he decided to maintain his male gender and underwent removal of the gonadal tissue, uterus and the breast tissue and started receiving androgen replacement. Both gonads showed both

testicular and ovarian structures on microscopy (ovotestes), and the ovarian tissue showed follicles at different maturation stages and a corpus luteum.

Materials and methods

The family and all of the available members were ascertained at the clinical service provided by the National Centre for Diabetes, Endocrinology and Genetics, Amman, Jordan. The extended pedigree showing the relationship of the three sibships is shown in Fig. 2. All patients had a hormonal profile done in the laboratory of the National Centre for Diabetes, Endocrinology and Genetics, Amman, Jordan, which included LH, FSH, prolactin, oestradiol, testosterone, and DHEA. Four individuals had 17-hydroxyprogesterone measured to exclude congenital adrenal hyperplasia.

Cytogenetic studies

Chromosomal analysis was performed twice using standard techniques from peripheral blood lymphocytes from all individuals mentioned in the legend of Fig. 2. For each individual, 50 metaphases were analysed.

Molecular studies

Genomic DNA was extracted from peripheral blood by standard techniques from all individuals mentioned in the legend of Fig. 2. For SRY gene amplification, two primers Xcs 11 (5'GTCGCACTCTCCTTGTTTTTGAC3') and Xcs 15 (5'CCGATTGTCCTACAGCTTTGTC3'), which amplify a 648 bp fragment, were used in a standard PCR reaction. The annealing temperature used in the PCR cycles was 65 °C. As a positive control, co-amplification of the marker DXS1684 (CA repeat, 128–148 bp, Xq28) was performed. After amplification, the amplified products were electrophoresed in a 2% agarose gel stained with ethidium bromide, visualised by UV light and photographed on a Polaroid film. Two normal unrelated males and two normal unrelated females were used as controls.

Results

All individuals mentioned in the legend of Fig. 2 as examined, other than the affected individuals, had a chromosomal analysis and SRY status that corresponded to their clinically assigned sex. The available results of the hormonal tests are summarised in Table 1. A summary of the clinical features is shown in Table 2.

Discussion

There are seven affected individuals in this extended family coming from three sibships and from two generations. The range of sex determination abnormality in the affected members of this family is rather wide, from what seems to be XX males (cases 2 and 3) to true hermaphrodite with predominance of female characteristics (case 7). This variability in the expression of the same disorder is quite evident in their hormonal profiles, especially for the testosterone levels (Table 1). The two individuals who are suspected to be XX males (cases 2 and 3) did not have a gonadal biopsy, but the assumption was made based on their clinical phenotype, pelvic ultrasound, hair distribution and hormonal profiles. In some of the families in the literature, with both XX males and XX true hermaphrodites, the XX males did not have a gonadal biopsy [17, 33]. In addition, the absolute exclusion of true hermaphroditism cannot be ascertained except after the examination of all gonadal tissue. Based on our observations and those from published series, we believe that XX males and XX true hermaphrodites, at least in the familial cases, are manifestations of the same pathogenetic process, representing a spectrum of testicular tissue development. Previously, three unrelated XX males were reported to have Mullerian duct derivatives and various degrees of gonadal dysgenesis, despite the absence of Y related sequences [36]. These three individuals provided a link between SRY negative XX males and SRY negative XX true hermaphrodites [36]. The affected individuals in our family exemplify the presence of this continuum. The variability in the extent of testis development can be dependant on other factors, whether genetic or environmental, or is more probably a random process.

The mode of inheritance of this disorder in this family is not straightforward but it appears to be monogenic. Despite the presence of a limited number of consanguinity loops in the shown pedigree, the family is highly inbred for generations and individuals III.2 and III.3 and III.5 and III.6 are from the same extended family and are thus related but further than second cousins. The nature of the pedigree, the relation between the three sibships with affected individuals, the unaffected parents, the presence of multiple affected individuals in

Table 2 Summary of the clinical and pathological findings, chromosomal analysis and SRY status of the affected individuals

Patient	Age at diagnosis (years)	Gynaecomastia	Hypospadias	Crypt-orchidism	Ovotestis	Chromosome analysis	SRY status
Case 7 (IV.10)	17	Present	Present	Bilateral	Present	46,XX	Negative
Case 1 (IV.15)	34	Present	No	Bilateral	Present	46,XX	Negative
Case 2 (IV.16)	31	Absent	No	No	Not available	46,XX	Negative
Case 3 (IV.22)	22	Absent	No	No	Not available	46,XX	Negative
Case 4 (IV.25)	18	Present	Present	Bilateral	Present	46,XX	Negative
Case 5 (IV.26)	16	Present	Present	Bilateral	Present	46,XX	Negative
Case 6 (V.5)	3	Not applicable	present	Unilateral	Present	46,XX	Negative

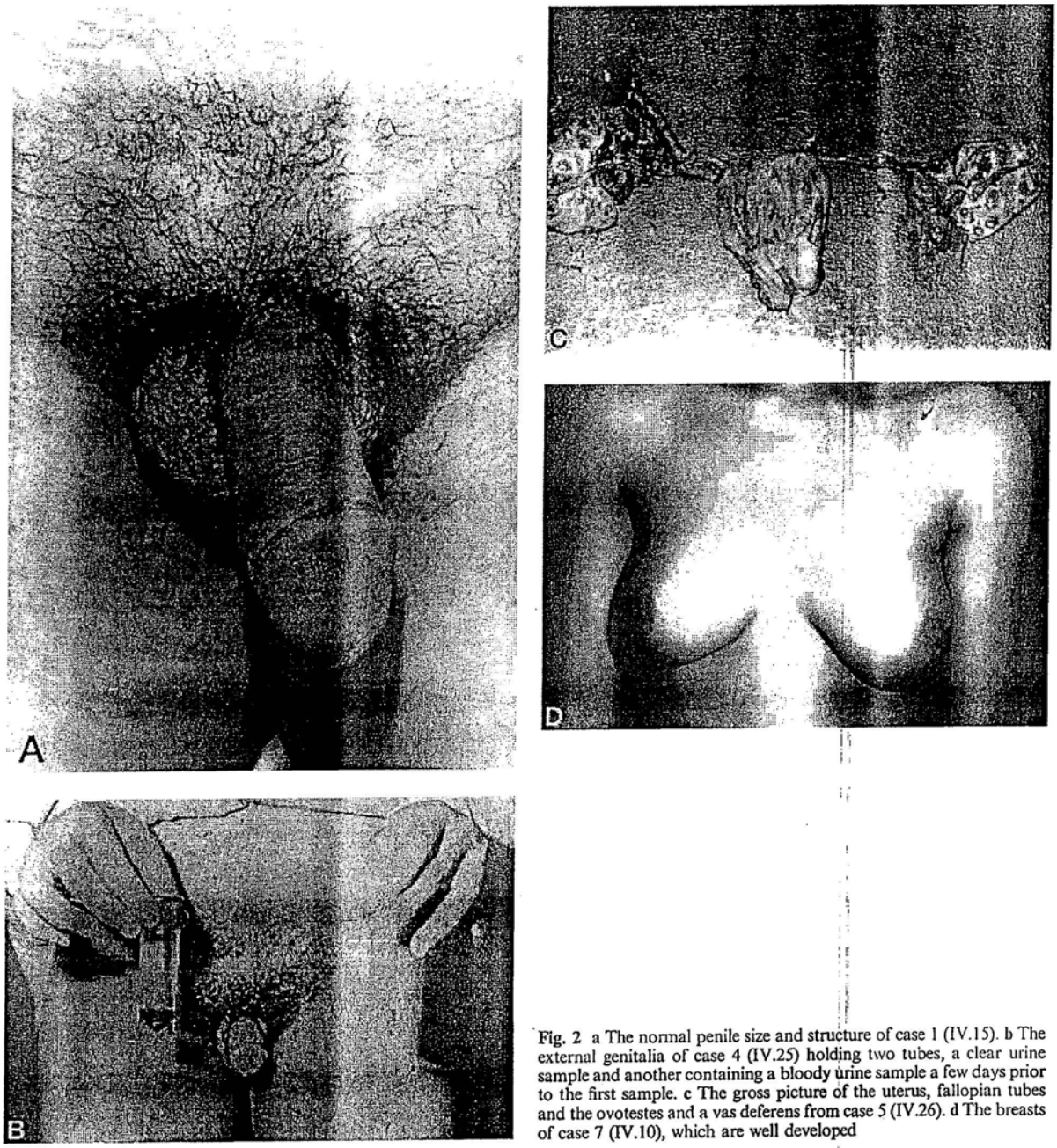

Fig. 2 a The normal penile size and structure of case 1 (IV.15). b The external genitalia of case 4 (IV.25) holding two tubes, a clear urine sample and another containing a bloody urine sample a few days prior to the first sample. c The gross picture of the uterus, fallopian tubes and the ovotestes and a vas deferens from case 5 (IV.26). d The breasts of case 7 (IV.10), which are well developed

one sibship, all point towards autosomal recessive inheritance with sex limitation. It is to be assumed that the phenotype is penetrant only in homozygous 46,XX individuals, while homozygous 46,XY individuals are protected by the presence of the Y chromosome, and are thus non-penetrant. Two observations strengthen the autosomal recessive hypothesis. First, individual III.2 has married twice and the nine offspring from one marriage, to an unrelated wife, are completely normal. The other marriage from a related wife produced one affected individual out of three. Second, the sibship V.1 to V.6 has one affected member out of six, with normal and consanguineous parents. One observation does not conform to the autosomal recessive hypothesis, which is that 5 out of 13 individuals are affected in one sibship, while the expected should be only 1/8th of the members, due to the sex limitation and thus the reduced penetrance of the phenotype. However, this can be explained

by chance or by the father III.5 being homozygous non-penetrant and the inheritance is actually pseudodominant in this sibship. Autosomal dominant inheritance of the disorder with sex limitation is unlikely, as III.5 did not have affected offspring from one marriage. Also, the presence of the affected child in the last generation does not agree with this pattern. The probability of X-linked inheritance seems unlikely as the three sibships are related through the fathers (male lineage). However, there is the remote possibility that the three mothers of the three sibships are carriers of the disorder and the presence of the Y chromosome protects against the manifestation of the disorder in cytogenetic males. Recessive inheritance of a pseudo-autosomal gene alteration, escaping X-inactivation, but also with sex limitation, might be a plausible mode of inheritance in this family. It could provide an explanation for the excessive number of affected individuals in the sibship in which 5 out of the13 sibs are affected.

A hypothesis involving a regulatory cascade for sex determination has been suggested before, in which the SRY gene is said to repress expression of a gene termed Z [19]. The wild type expression of this gene is a negative regulator of male sex determination and is functional in wild type females. A homozygous mutation in this hypothetical gene in an XX individual will allow for expression of male characteristics while a heterozygous mutation should still be functional in suppressing male characteristics. Our reported family strengthens this hypothesis, in case the suggested mode of inheritance is correct, by providing a larger family size that helps in reaching the same conclusions.

The observation that all affected individuals had and decided to keep the male gender could be probably be explained by the cultural background of this family. In general, the Jordanian culture, being part of the wider Arabic culture, is dominated by men and parental preference for having boys is quite evident. This could explain the parents' choice of rearing the children with ambiguous genitalia as boys. For the child who was identified at a young age (case 5), the parents chose to rear him as a boy. However, all affected members of this family, with the exception of the youngest, had females as sexually preferred partners with no homosexuality reported.

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