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Comprehensive analysis of three female patients with different types of X/Y translocations and literature review

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Abstract

Background X/Y translocations are highly heterogeneity in terms of clinical genetic effects, and most patients lack complete pedigree analysis for clinical and genetic characterization.

Results This study comprehensively analyzed the clinical and genetic characteristics of three new patients with X/Y translocations. Furthermore, cases with X/Y translocations reported in the literature and studies exploring the clinical genetic effects in patients with X/Y translocations were reviewed. All three female patients were carriers of X/Y translocations with different phenotypes. The karyotype for patient 1 was 46,X,der(X)t(X;Y)(p22.33;q12)mat, patient 2 was 46,X,der(X)t(X;Y)(q21.2;q11.2)dn, and patient 3 was 46,X,der(X)t(X;Y)(q28;q11.223)t(Y;Y)(q12;q11.223)mat. C-banding analysis of all three patients revealed a large heterochromatin region in the terminal region of the X chromosome. All patients underwent chromosomal microarray analysis, which revealed the precise copy number loss or gain. Data on 128 patients with X/Y translocations were retrieved from 81 studies; the phenotype of these patients was related to the breakpoint of the chromosome, size of the deleted region, and their sex. We reclassified the X/Y translocations into new types based on the breakpoints of the X and Y chromosomes.

Conclusion X/Y translocations have substantial phenotypic diversity, and the genetic classification standards are not unified. With the development of molecular cytogenetics, it is necessary to combine multiple genetic methods to obtain an accurate and reasonable classification. Thus, clarifying their genetic causes and effects promptly will help in genetic counseling, prenatal diagnosis, preimplantation genetic testing, and improvement in clinical treatment strategies.

Keywords X/Y translocation, Clinical and genetic analysis, Literature review, Re-classified

Background

X/Y translocation is a rare chromosomal abnormality, with approximately 128 patients reported in the literature [1–11], most of which are limited to single patient reports and a few comprehensive analyses of complete families. Aberrations in sex chromosomes can affect gonadal development, leading to complex reproductive and endocrine disorders. In females, it may affect ovarian function and uterine development. In males, it can lead to azoospermia, cryptorchidism, penis or testicular hypoplasia, or it may lead to ovotesticular disorders

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of sex development [12], gynecomastia [10, 11, 13–15]. Although it has been reported in both men and women at birth [2], later diagnoses also occur, which limits possible medical treatments and surgical intervention [16]. Additionally, several studies proved that the presence of Y chromosome material in females leads to an increased risk of gonadoblastoma (10 to 30%) [17, 18].

There are many types of X/Y translocations. Hsu (1994) divided the category of Y/X translocations with der(X) into seven types and further classified the category of Y/X translocations with der(Y) into four types [1]. However, these classifications are complex and cannot be applied to current clinical cytogenetics.

This study conducted a comprehensive analysis of the clinical phenotypes, cytogenetics, and molecular genetics of three patients with rare X/Y translocations and their family members. We also reviewed the relevant published literature, exploring the origin of derivative chromosomes produced by X and Y translocations and the phenotype and fertility of patients carrying this derived chromosome. In addition, we provide suggestions on genetic counseling for patients and reclassify the X/Y translocations into new types based on the breakpoints of the translocated X and Y chromosomes.

Materials and methods

Patients

Three patients and their family members were recruited from the West China Second University Hospital. The patients visited our hospital for infertility or menstrual disorders. The present study was approved by the Medical Ethics Committee of West China Second University Hospital, Sichuan University. Informed consent to participate in the study was obtained from all participants.

Methods

Chromosome G-banding karyotype analysis

Peripheral blood (5 ml) was drawn into a heparin anti-coagulant tube. Blood samples were processed according to *The Association of Genetic Technologists (AGT) cytogenetic laboratory procedures* and analyzed for peripheral blood lymphocyte karyotyping [19]. The diagnosis and results complied with the relevant standards of the *International System for Human Cytogenomic Nomenclature, 2020 (ISCN, 2020)*. The chromosome image analysis system used for karyotyping and image capturing was a Metafer-Automated Slide Scanning Platform and Ikaros from Zeiss.

Chromosome C-banding analysis

Chromosome C-banding preparation was performed according to *The AGT cytogenetic laboratory procedures* [19]. The chromosome dispersion was good and the

length was suitable for splitting the middle chromosome image under a 100×100 microscope and image capture.

Fluorescence in situ hybridization (FISH)

FISH was used to analyze the sex chromosome centromeres. AneuVysion probe sets (Vysis/Abbott, Downers Grove, IL, USA) were used for hybridization of metaphase cells according to the manufacturer's protocol, and the analysis was based on the latest American College of Medical Genetics and Genomics (ACMG) guidelines [20].

Chromosomal microarray analysis (CMA)

Single nucleotide polymorphism-chromosomal microarray analysis was performed using Affymetrix CytoScan 750 K Array chips and Affymetrix Chromosome Analysis Suite (ChAS) software, and the detected structure was analyzed according to the latest ACMG guidelines [21].

Literature review

A literature review was conducted through a targeted search for case reports and original articles on X/Y translocation in English journals archived in PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>) and Chinese medical journals archived in the China National Knowledge Infrastructure CNKI (<http://www.cnki.net>) and WAN-FANG DATA (<http://www.wanfangdata.com>), from January 1978 to April 2022.

Results

Case presentation

Patient 1 (Fig. 1, III-4) was a female (age: 26 years, height: 148 cm, and weight: 44 kg) who was admitted to our hospital for infertility after five years of normal sexual life. When she was 13 years old, her height was about 120 cm, which was shorter than that of her peers (−2 SD), but no treatment was provided; the age at menarche was 13 years, and menstrual cycle was normal. At the age of 25, she underwent preimplantation genetic testing (PGT) at another hospital; 10 eggs were harvested, only one embryo was obtained, and implantation failed. There was no consanguinity in her family, several members were short in stature (140–150 cm; Fig. 1), and none had intellectual disabilities. Two of her cousins (Fig. 1, III-2, III-6) were short in stature, and one (Fig. 1, III-2) had had three biochemical pregnancies and was at 30 weeks of pregnancy at the time of reporting. Detailed clinical information is presented in Table 1. Ultrasonography of the uterine adnexa showed no significant abnormalities. Sex hormone testing showed estradiol (E2): 45.03; progesterone (P): 0.26; luteinizing hormone (LH): 4.34; follicle-stimulating hormone (FSH): 7.34; and Anti-Müllerian Hormone (AMH) (ELISA): 1.96 ng/ml. Clinical materials

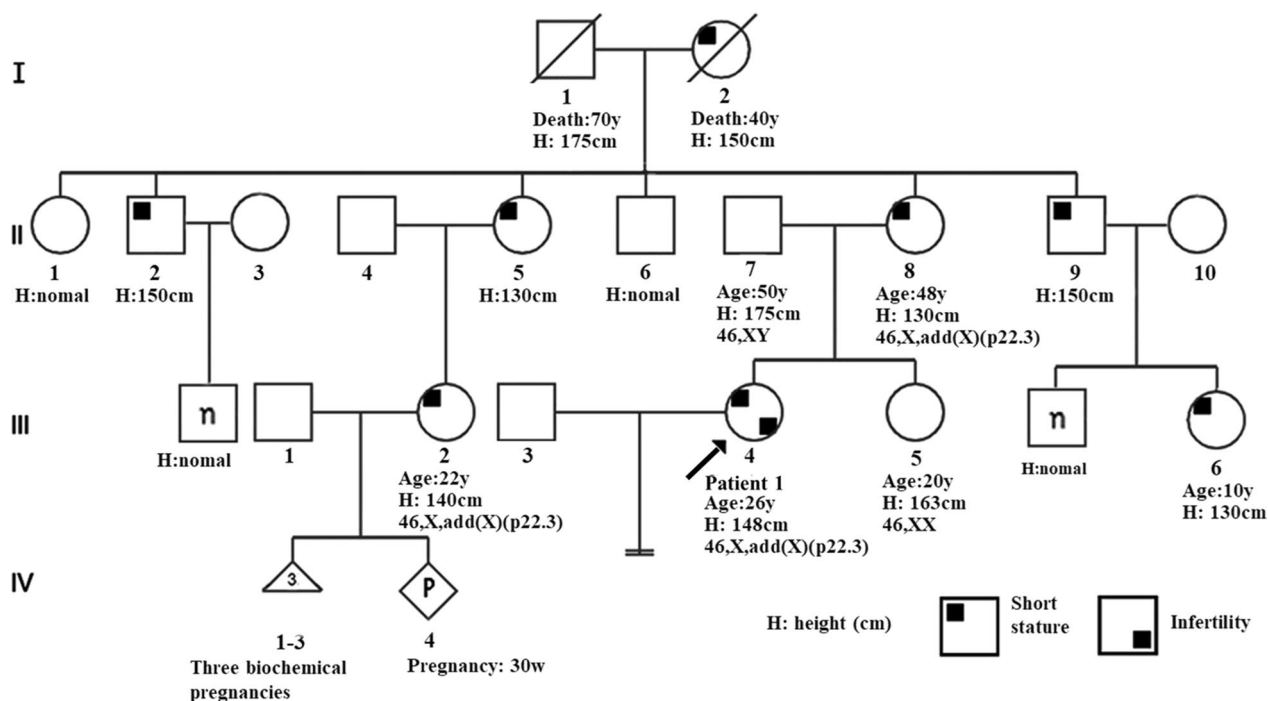


Fig. 1 Pedigree of patient 1. The height of the relevant family members is marked in the figure, showing that most of family members had short stature. Five individuals had chromosomal karyotype results, and three members with short stature (II-8, III-2, and III-4) had the same 46,X,add(X)(p22.3) as the proband, while an individual with normal height (II-8) has normal male karyotype

and laboratory test results are summarized in Table 1. Currently, the patient is planning to undergo adjuvant fertility therapy.

G-banding revealed a derivative X chromosome: add(X)(p22) (Fig. 2a). After C-banding verification, it was found that a long heterochromatin region existed in the unknown segment of der(X) (Fig. 2c). No abnormal findings in FISH analysis. CMA showed arr[GRCh38] Xp22.33(251888_1772154)×1 (1.52 Mb) (Fig. 2e), and no origin of heterochromatin was detected, nor *SRY* or *AZF* genes were identified. Pedigree genetic analysis (Fig. 1) for members with the same clinical manifestations revealed that her mother's (Fig. 1, II-8) G-banding karyotype (Fig. 2b) and her cousin's (Fig. 1, III-2) CMA results (Fig. 2f) were the same as hers (Fig. 1, III-4). The patient's father (Fig. 1, II-7) and sister (Fig. 1, III-5), who had no clinical manifestations, showed normal karyotypes. Her maternal grandfather and grandmother had died and could not be traced. Combined with genetic and clinical analyses, the karyotype and array results were thus interpreted as: 46,X,der(X)t(X;Y)(p22.33;q12)mat.arr[GRCh38] Xp22.33(251888_1772154)×1 (1.52 Mb), whereas the X deleted segment harbored the short-stature homeobox (*SHOX*) gene. Since the Affymetrix CytoScan 750 k chip used in this laboratory had no probe coverage in the Yq12 region, it was impossible to detect the

translocation of this Y chromosome segment; however, combined with the large heterochromatin region shown in the chromosome C-banding results, we suspect that this heterochromatin segment was from the Y chromosome Yq12 region.

Patient 2 was a female (age: 21 years, height: 161 cm, and weight: 57 kg) who had visited our hospital for menstrual disorders for five years and secondary amenorrhea. Menarche began at 13 years of age, menstruation was normal from 13 to 15 years of age, and menstrual thinning started at 15 years of age (1–2 months). Thinning gradually spaced out and amenorrhea developed at 17 years of age. She reported that at the age of 16 years, she was suspected of having polycystic ovary syndrome (PCOS) and was treated symptomatically. At 18 years of age, ultrasonography suggested gonadal dysgenesis (GD). The patient was the only child in her family. Her parents were consanguineous (Fig. 3a), in a good health, and had no similar family history. Gynecological examination revealed internal genital abnormalities. Ultrasonography at 21 years of age showed that the uterus was small and both ovaries were streaks (Fig. 3b). Sex hormone testing showed E2: < 11.8 (low level); P: 0.23; LH: 24.2; FSH: 68.9 (high level); and AMH (ELISA): < 0.06 ng/ml. The patient is currently being treated with hormone replacement therapy (HRT). Clinical materials and laboratory test results are summarized in Table 1.

Table 1 Summary of clinical data and genetic test results for three cases

Cases	Patient 1	Patient 2	Patient 3
Age (year)	26	21	23
Height (cm)	148	168	150
Weight (kg)	44	57	54
Mainly complaints	Primary infertility	Menstrual disorders, secondary amenorrhea	Primary infertility
Sex hormones	FSH(IU/L) (2.5–10.2) 7.34 LH(IU/L) (1.9–12.5) 4.34 T (ng/ml) (0.1–0.5) 0.03↓ E2(pg/ml) (19.5–144.2) 45.03 P (ng/ml) (0.15–1.40) 0.26 PRL(ng/ml) (2.8–29.2) 10.48	68.9↑ 24.2 0.23 <11.8↓ 0.59 8.7	3.4 5.1 0.18 102.3 15.29 14.9
AMH(ELISA)(ng/ml) (2.5–6.3)	1.96↓	<0.06↓	3.97
Ultrasound	Normal uterus (4.3 X 4.5 X 4.4 cm); both ovaries are normal, and left ovaries has 2–3 follicles inside, maximum diameter 0.7 cm; normal bilateral fallopian tubes	Small uterus (the diameter of uterus is 2.4 cm), the endometrial thickness is about 0.15 cm (single layer); bilateral streak ovaries	Normal uterus (3.6 X 4.0 X 4.1 cm); both ovaries are normal; non-visualized bilateral fallopian tubes (surgical removed)
History of pregnancy and childbirth			
Family	G0P0 Some family members have short stature, the mother and cousin's G-banding karyotypes are same as that of the patient, while the father and sister's karyotype are normal	G0P0 Parents are consanguineous, with normal phenotypes, and normal G-banding karyotype	G0P0 The mother had the same karyotype as the patient; and had three miscarriages. The father, sister and two uncles had normal G-banding karyotype,
Genetic test results	46,X,der(X)t(X;Y)(p22.33;q12)mat,ar[GRCh38]Xp22.33 (251888_1772154)X1(1520 kb)	46,X,der(X)t(X;Y)(q21.2;q11.2)dn,ar[GRCh38]Xq21.2q28(86025630_155714301)X1,Yq11.222q12(18443276_26653507)X1	46,X,der(X)t(X;Y)(q28;q11.223)t(Y;Y)(q12;q11.223)mat,ar[GRCh38]Xq28(155077922_155700385)X1,Yq11.223q12(21924024_26653507)X2

FSH Follicle stimulating hormone, LH Luteinizing hormone, T Testosterone, E2 Estradiol, P Progesterone, PRL Prolactin, AMH Anti-Müllerian hormone

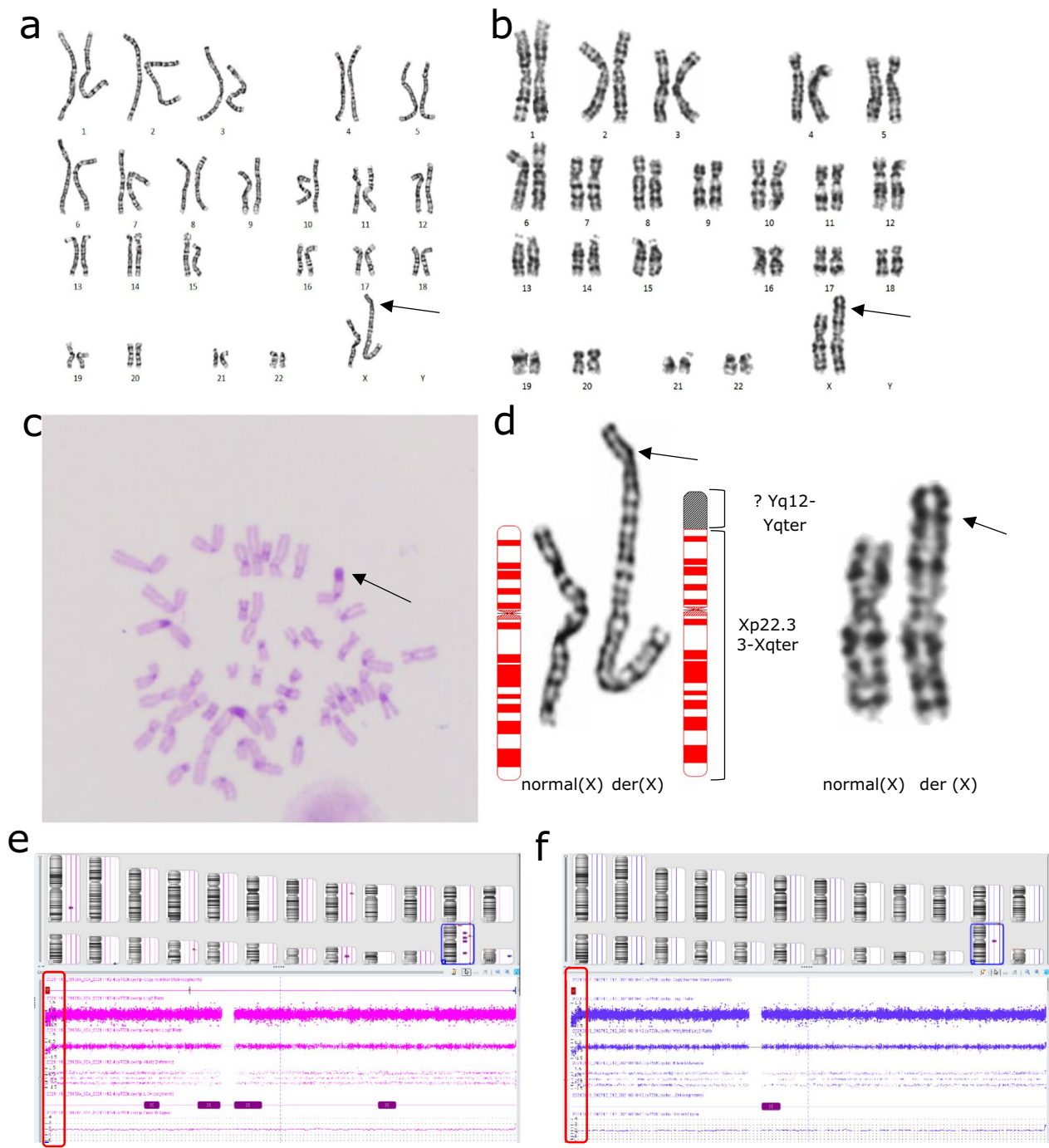


Fig. 2 Cytogenetic and CMA results of patient 1, her mother and her cousin. **a:** G-banded karyogram (550 bands) of the patient, showing der(X) chromosome; **b:** G-banded karyogram (400 bands) of the patient's mother, showing the same der(X) as patient 1; **c:** C-banded metaphase spread showing a large heterochromatin segment (indicated by an arrow) at the end of short arm of the der(X), which is suspected to be a part of chromosome Yq; **d:** Comparison and pattern representation of patient 1 (left) and her mother's (right) X chromosomes. **e:** The results of CMA for patient 1 indicate the deletion of large segment of the X chromosome of 1.52 Mb (red box in e); **f:** The results of the CMA for patient 1's cousin (III-2) is the same as that of patient 1 (red box), and no Y chromosome segments were found. *Note* There were differences in chromosomal banding levels because the patient and his mother did not undergo cytogenetic testing in the same laboratory

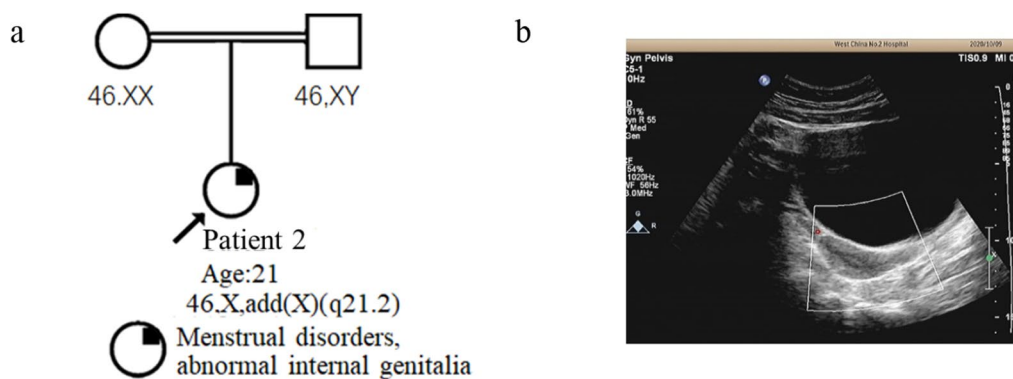


Fig. 3 Pedigree and gynecological ultrasound results of patient 2. **a**: The pedigree shows that the patient's parents are consanguineous and the G-banding karyotype of both parents is normal; **b**: Uterine and appendage ultrasound shows a small uterus, and the bilateral ovaries are unclear

The G-banding karyotype showed a derivative X chromosome: $\text{add}(X)(q21)$ (Fig. 4a). After verification by C-banding, a long heterochromatin region was found in the unknown segment of $\text{der}(X)$ (Fig. 4c). No abnormal findings in FISH analysis. The CMA results were as follows: $\text{arr}[\text{GRCh38}] \text{Xq21.2q28}(86025630_155714301) \times 1$ (69.689 Mb) $\text{Yq11.222q12}(18443276_26653507) \times 1$ (8.21 Mb). There were large genomic homozygous regions (Fig. 4e, f) and the *SRY* and *AZF* genes were not identified. Karyotype analysis of her parents showed no abnormalities (father's karyotype Fig. 4b). The karyotype and array results were thus interpreted as: $46,X,\text{der}(X)t(X;Y)(q21.2;q11.2)\text{dn.}\text{arr}[\text{GRCh38}] \text{Xq21.2q28}(86025630_155714301) \times 1, \text{Yq11.222q12}(18443276_26653507) \times 1$.

Patient 3 (Fig. 5, III-4) was a female (age: 24 years, height: 150 cm, and weight: 54 kg) who visited our hospital for infertility. She had a normal sexual life and a history of surgery for an ovarian cyst at 18 years of age and bilateral tubal ligation due to bilateral hydrosalpinx at 23 years of age. No special facial features or menstrual histories were noted. Her parents were not consanguineous and the mother (Fig. 5, II-4) had had three miscarriages (Fig. 5, III-1, III-2, III-5). The older sister (Fig. 5, III-3) was 28 years old, and her menstruation was normal. Recent ultrasonography showed that the uterus and ovaries were normal, and sex hormone testing revealed E_2 : 102.3; P : 15.29; LH : 5.1; FSH : 3.4; and AMH (ELISA): 3.97 ng/ml. The clinical data and laboratory test results are summarized in Table 1.

G-banding karyotyping showed a derivative X chromosome: $\text{add}(X)(q28)$ (Fig. 6a). A long heterochromatin region existed in the unknown region of the derived X chromosome (Fig. 6c). No abnormal findings in FISH analysis. The CMA results were as follows: $\text{arr}[\text{GRCh38}] \text{Xq28}(155077922_155700385) \times 1$ (0.622 Mb), $\text{Yq11.223q12}(21924024_26,653,507) \times 2$ (4.729 Mb) (Fig. 6e, f), and no *SRY* or *AZF* genes were detected. The cytogenetic

analysis of the patient's mother (Fig. 5, II-4) was consistent with that of the proband (Fig. 6b). For the patient's father (Fig. 5, II-3), sister (Fig. 5, III-3), and mother's siblings (Fig. 5, II-1, II-2), the chromosomal karyotyping analysis did not show obvious abnormalities. The karyotype and array results were thus interpreted as: $46,X,\text{der}(X)t(X;Y)(q28;q11.223)t(Y;Y)(q12;q11.223)\text{mat.}\text{arr}[\text{GRCh38}] \text{Xq28}(155077922_155700385) \times 1, \text{Yq11.223q12}(21924024_26653507) \times 2$.

Literature review and reclassification

A total of 81 articles were retrieved, where 128 patients with X/Y translocation were reported, of which, approximately 32 articles analyzed the core family. According to Hsu's report in 1994 [1], X/Y translocations are divided into 11 types (7+4), and the most common types are types 1 and 2. In our study, patients were reclassified according to the location of the breakpoints in the translocated X and Y chromosomes and the centromeric composition of the derived chromosomes. Patients with breakpoints located at $\text{Xp}22$ were categorized into five types (types I-V) based on the composition of the sex chromosome centromere. Type I/type II/type III are consistent with Hsu's type 1/type 2/type 3. Patients with $46,X,\text{der}(X)t(X;Y)(p22;p11)$ were categorized into type IV, and Hsu's type A/type B were merged into type V. Patients with breakpoints located outside of $\text{Xp}22$ were classified as type "other". The reclassifications and phenotypes are summarized in Tables 2, 3, 4.

The patients belonging to type I [$46,Y,\text{der}(X)t(X;Y)(p22;q11)$], having complete absence of $X(\text{pter} \rightarrow p22)$ and two copies of $Y(q11 \rightarrow \text{qter})$, one on the X chromosome and one as a normal Y, were all males (33/33). In these patients, the $\text{der}(X)$ was inherited from their mother (30/33) or was of unknown origin (3/33). Most type I patients had abnormal clinical manifestations, such as short stature and limb anomalies [22], intellectual

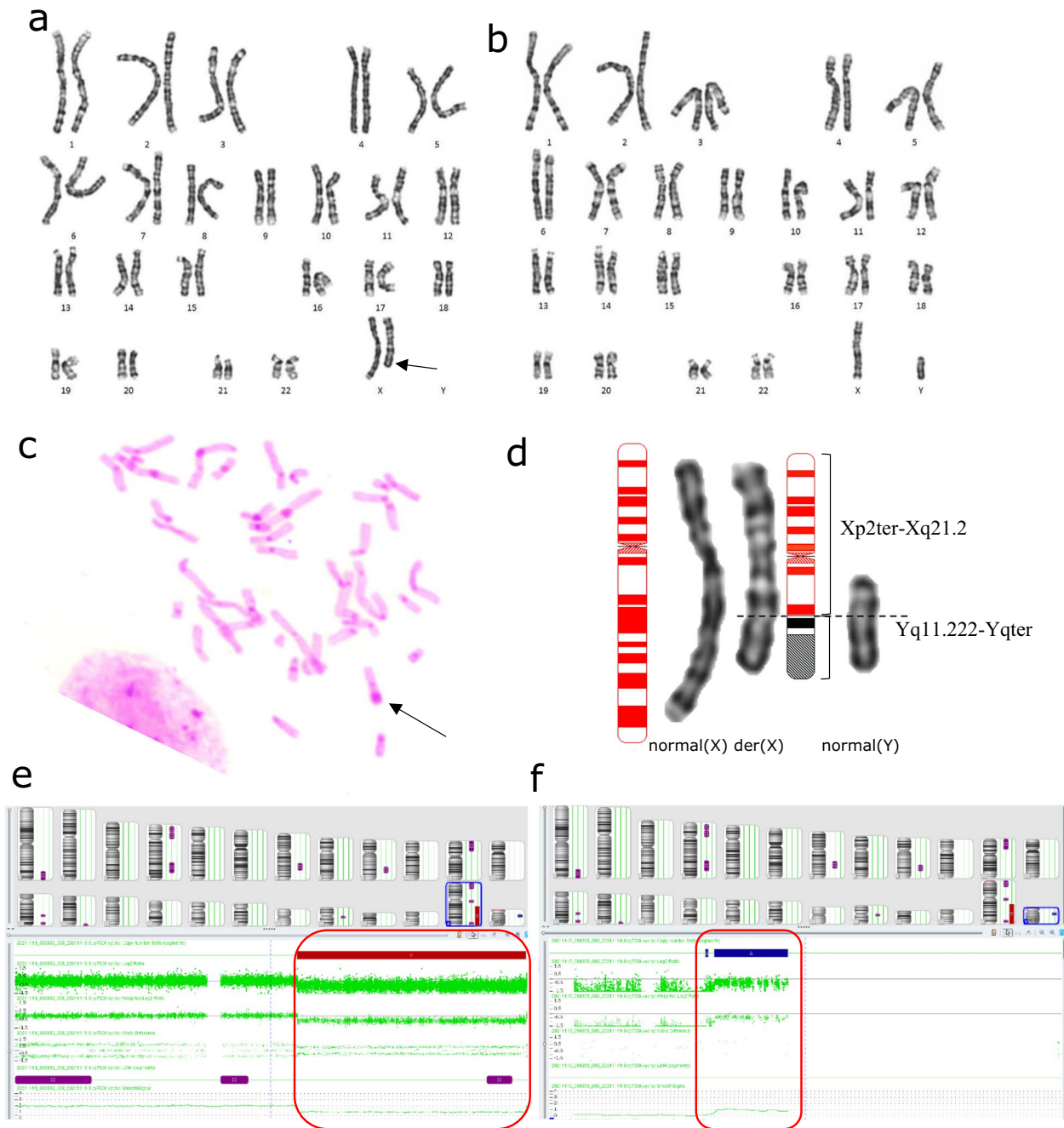


Fig. 4 Cytogenetic and CMA results of patient 2. **a**: The results of the G-banded karyogram (550 bands) of patient 2 (a derivative X chromosome is indicated by an arrow); **b**: The result of the G-banded karyogram (550 bands) of the patient's father: a normal male karyotype; **c**: Fragment of C-banded metaphase spread of patient 2 (photomicrography), showing a large heterochromatin region at the end of the long arm of derivative X chromosome; **d**: patient 2 X chromosome (left) and her father's Y chromosome (right) comparison chart, the results show that the Xq21.2 (of der(X)) unidentified source segment of the band are more consistent with the father's Yq11.2 band; **e, f**: CMA results show that a large 69.689 Mb deletion of the long arm of the X chromosome (red box in e), and a partial duplication of the long arm of the Y chromosome (red box in f), as well as multiple regions with AOH (red regions in the figure)

disability [11], and may have gonadal abnormalities (eg. cryptorchidism) [22, 23]. Those with type II [46,X,der(X)t(X;Y)(p22;q11)], type III [46,X,psu dic(X;Y)(p22;p11)],

and type IV [46,X,der(X)t(X;Y)(p22;p11)] had an X(pter → p22) single copy. In type II patients the majority were females and have a single copy of Y(q11 → qter)

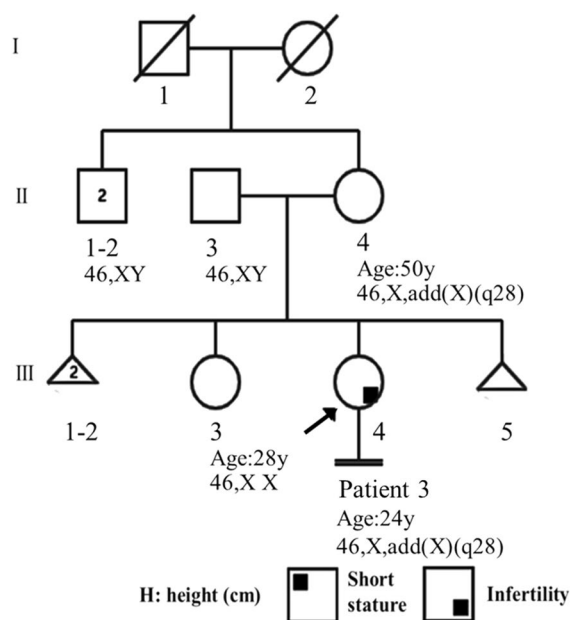


Fig. 5 Pedigree of patient 3. Six family members underwent G-banding karyotyping; the mother's karyotype results were consistent with patient 3, and the other results were normal. The sex of the three aborted embryos is unknown

(53/55). Types III and IV patients had a single copy of Y(p11 → qter) or Y(p11 → pter), respectively. The phenotypic sex of reported patients depends on the presence of SRY gene, however, three patients (one from type III and two from type IV) were presenting with a female phenotype despite having SRY gene [24–26]. Type V [46,X,der(Y)t(X;Y)(p22;q11)] patients had X(p22 → qter) and Y(pter → q11) single copies, and an extra copy of X(p22 → pter), and all patients were males (6/6). The details are presented in Table 3.

Type “other” included 21 patients, of which, 15 were females and 6 were males. Patients with type “other” were more likely to have gonadal abnormalities (14/21). Almost all patients had at least one complete X-chromosome segment (details shown in Table 4) [5–8, 27–40].

Discussion

The inheritance of structurally altered X and Y chromosomes differs from that of autosomes, and it is difficult for X/Y balanced translocation carriers to have a descendant with a balanced chromosomal structure. Translocation between the X and Y chromosomes can impact the pairing of sex chromosomes during meiosis and result in different patterns of X chromosome inactivation [41, 42], which can affect growth and development.

In the Patient 1 with X chromosome deletion followed by der(X)t(X;Y), the deleted region (Xp22.3) contains

SHOX gene required for normal bone formation. Its haplo-insufficiency can result in short stature and Leri-Weill dyschondrosteosis, which usually has a more severe phenotype in females [43, 44]. The patient (Fig. 1, III-4), her mother (Fig. 1, II-8), and cousin (Fig. 1, III-2) showed symptoms of short stature. As no genetic testing was available for male patients in this family, it was impossible to identify whether the short male patients in the family (Fig. 1, II-2, II-9) and the cousin (Fig. 1, III-6) carried the same der(X); however, based on the pedigree, we speculated that the original patient (Fig. 1, I-2) may have passed the der(X) to her sons (Fig. 1, II-2, II-9) and daughters (Fig. 1, II-5, II-8), then to her granddaughters (Fig. 1, III-2, III-4, III-6). The proband's female-specific hormones had no significant abnormalities, except for a decrease in AMH to 0.98 ng/ml, indicating a mild decrease in ovarian reserve function. After a year of treatment and good condition in daily life, the latest AMH level was 1.96 ng/ml, indicating that her ovarian reserve function showed a good recovery. Her mother had given birth to two children, with no history of miscarriage, and began experiencing irregular menstruation and prolonged menstrual cycles around the age of 40 years. She did not undergo hormonal profiling, so the possibility of premature ovarian failure (POF) cannot be ruled out. Other women with short stature in this family (Fig. 1, II-5, II-8), who may carry der(X), have all been pregnant. Patient 1 and her cousin still have a chance of becoming pregnant, although they experienced recurrent spontaneous abortion (RSA) (Fig. 1, III-2) or infertility (Fig. 1, III-4), which may be result from recombination changes of der(X) during meiosis. Genetic counseling was provided for the patient with information on the nature, mode of inheritance, the genetic risk for offspring, and prenatal testing issues. Currently, Patient 1 has pregnancy desire and assisted reproductive technology (ART) has been proposed for the infertility treatment.

Patient 2 exhibited X chromosome deletion (q21.2-qter)(86025630_155714301)×1 and translocated Y(q11.2-qter)(18443276_26653507)×1 region followed by der(X)t(X;Y). The deleted region X(q21.2-q28) included multiple dosage-sensitive genes that may cause diseases. The Y region contains AZF factors that are required for spermatogenesis that are not relevant to the female phenotype. The parents were consanguineous, and their karyotypes were normal; therefore, the source of der(X) was an abnormal recombination between X and Y during the first paternal meiosis [7], forming a sperm with a derivative X (Fig. 7). The patient had abnormal reproductive system development, including a small uterus and streak ovaries, and her sex hormones showed relatively high levels of FSH and low E2. The AMH level (ELISA) was extremely low, indicating ovarian dysfunction. Currently,

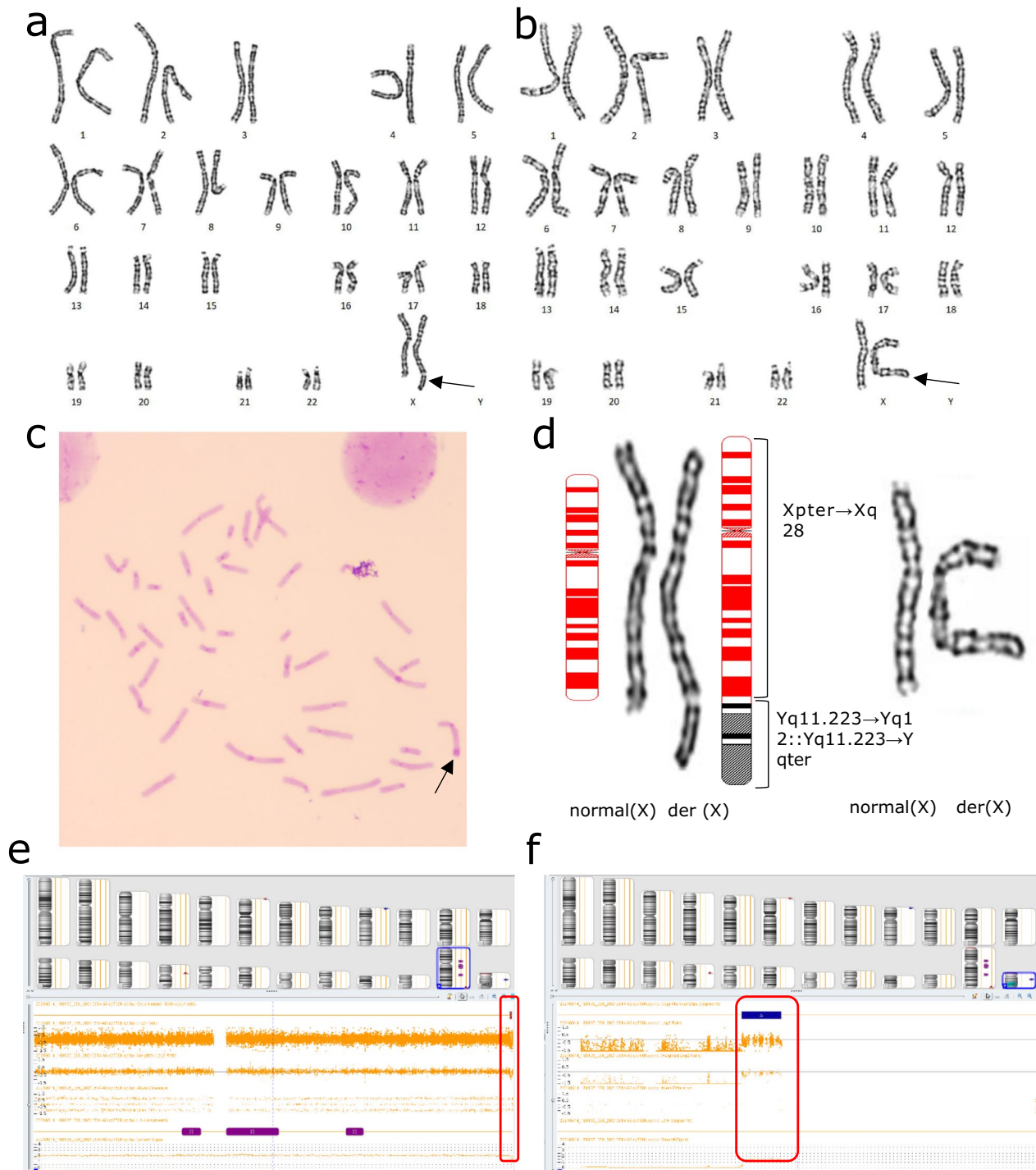


Fig. 6 Cytogenetic and CMA results of patient 3 and abnormal X chromosome. **a:** The results of the G-banding (550 bands) of patient 3, there is a derivative X chromosome (arrow); **b:** The mother's G-band karyotype (550 bands) shows the same der(X) (arrow) as in patient 3; **c:** C-banding of patient 3, showing larger heterochromatin segments in the long arm end segments of the der(X); **d:** Comparison of X chromosomes of patient 3 (left) and her mother (right). **e, f:** CMA results showing deletions of large segment at the end of the long arm of chromosome X (red box in e) and two copies of the segments of the long arm part of the chromosome Y (red box in f)

Table 2 Summary of the two classifications

New types			Hsu's types	
Basis	Type	Karyotype	Type	Karyotype
Xp22	type I	46,Y,der(X)t(X;Y)(Xqter → Xp22::Yq11 → Yqter)	type 1	46,Y,der(X)t(X;Y)(Xqter → Xp22::Yq11 → Yqter)
	type II	46,X,der(X)t(X;Y)(Xqter → Xp22::Yq11 → Yqter)	type 2	46,X,der(X)t(X;Y)(Xqter → Xp22::Yq11 → Yqter)
	type III	46,X,psu dic(X;Y)(Xqter → Xp22::Yp11 → Yqter)	type 3	46,X,psu dic(X;Y)(Xqter → Xp22::Yp11 → Yqter)
	type IV	46,X,der(X)t(X;Y)(Xqter → Xp22::Yp11 → Ypter)	type 4	46,X,der(X)t(X;Y)(Xqter → Xp11.2::Yq11 → Yqter)
	type V	46,X,der(Y)t(X;Y)(Ypter → Yq11::Xp22 → Xpter)	type 5	46,X,der(X)t(X;Y)(Xpter → Xq22::Yq12 → Yqter)
Not-Xp22	type other	–	type 6	46,X,der(X)t(X;Y)(Xpter → Xq22::Yq11 → Yqter)
			type 7	46,X,psu dic(X;Y)(Xpter → Xq22::Yp11 → Yqter)
			type A	46,X,der(Y)t(X;Y)(Ypter → Yq11.2::Xp22.1 → Xpter)
			type B	46,X,der(Y)t(X;Y)(Ypter → Yq11.23::Xp22.1 → Xpter)
			type C	46,X,der(Y)t(X;Y)(Ypter → Yq11.21::Xp21 → Xpter)
			type D	46,X,der(Y)t(X;Y)(Ypter → Yq11.23::Xq28 → Xqter)

Table 3 Summary of reported Xp22;Yq11 and Xp22;Yp11 translocation

The exception type		Type I		Type II		Type III		Type IV		Type V	
		M	F	M	F	M	F	M	F	M	F
Category	Gender	M	F	M	F	M	F	M	F	M	F
	Number	33	0	2	53	2	2	7	2	6	0
Origin	Pat	0	0	0	1	0	0	0	0	0	0
	Mat	29	0	0	8	0	0	0	0	0	0
	De novo	0	0	1	8	1	0	2	1	2	0
Stature	Unknown	4	0	1	36	1	2	5	1	4	0
	Short	26	0	0	42	2	1	4	0	2	0
	Normal	6	0	2	10	0	0	3	1	0	0
Limbs	Unknown	1	0	0	1	0	1	0	1	4	0
	Short	12	0	0	8	0	0	2	1	4	0
	Normal	21	0	2	45	2	2	5	1	2	0
Gonad	Unknown	0	0	0	0	0	0	0	0	0	0
	Abnormal	10	0	1	9	2	1	3	0	3	0
	Normal	1	0	0	27	0	0	1	1	0	0
Psychomotor movements	Unknown	22	0	1	17	0	1	3	1	3	0
	Abnormal	10	0	0	4	0	0	0	0	3	0
	Normal	22	0	2	49	2	2	7	1	3	0
Mental	Unknown	1	0	0	0	0	0	0	1	0	0
	Abnormal	13	0	0	4	0	0	0	0	2	0
	Normal	17	0	2	47	2	2	7	1	4	0
Facial deformities	Unknown	3	0	0	2	0	0	0	1	0	0
	P	15	0	1	7	0	0	1	0	3	0
	P	1	0	0	2	0	0	0	1	0	0
Eye abnormalities	P	12	0	0	1	0	0	1	0	0	0
	P	6	0	0	1	0	0	1	0	0	0
	P	9	0	0	4	0	1	1	0	2	0

M male, F female, P positive, patients present with this clinical phenotype, Pat paternal, Mat maternal. Unknown: There is no mention of the relevant circumstances in the text

Table 4 Summary of type “other” (new) for Y/X translocation

Detailed results	Gender	Short stature	Mental retardation	Head and face retardation	Limbs retardation	Optic abnormalities	L-W Chondrosclerosis	Psychomotor abnormalities	Gonad abnormalities
46,X,der(X)t(X;Y)(q22;q11)dn [5]	F	–	–	–	–	–	–	–	+
46,X,psu dic(X)t(X;Y)(q22;p11) [6]	F	–	–	–	–	–	–	–	+
46,X,der(X)t(X;Y)(p11.2;q11)dn [27]	F	+	–	–	–	–	–	–	+
46,X,der(X)t(X;Y)(q25;q12) [28]	F	–	–	–	–	–	–	–	+
46,X,der(X)t(X;Y)(q26.2;q11.223) [29]	F	–	–	–	–	–	–	–	+
46,X,der(X)t(X;Y)(q26.2;q11.223)mat [29]	F	–	–	–	–	–	–	–	+
46,X,der(X)t(X;Y)(q26.3;q11.223) [30]	F	n	–	–	–	–	–	–	–
46,X,der(X)t(X;Y)(q28;q11.2)dn [31]	F	–	–	–	–	–	–	–	+
46,X,der(Y)t(X;Y)(p21.1;q11)dn [32]	F	+	+	+	–	–	–	–	n
46,X,der(Y)t(X;Y)(p21.2;p11.3) [33]	F	+	–	+	–	–	–	+	+
46,X,der(Y)t(X;Y)(q13.1;q11.223) [34]	F	–	–	–	–	–	–	–	+
47,X,Y,der(Y)t(X;Y)(p21.1;p11.2)* [35]	F	n	–	+	–	+	–	–	+
46,X,der(Y)t(X;Y)(q28;q11.23)dn [36]	M	–	–	+	–	–	–	+	+
46,X,der(Y)t(X;Y)(p21.3;q11.21) [36]	M	–	–	+	+	+	+	+	+
46,X,psu dic(X;Y)(p11.3;p11.1) [37]	F	+	–	–	–	–	–	–	n
47,X,der(X)t(X;Y)(p11.4;p11.2)X2[65%]/46,X,der(X)(p11.4;p11.2)[35%]mat [38]	F	+	–	–	–	–	–	–	n
45,X[25%]/46,X,der(X)t(X;Y)(p11.4;p11.2)[75%] [37]	F	+	–	–	–	–	–	–	–
46,X,psu dic(X;Y)(p22;q11)dn [38]	M	+	–	–	–	–	–	+	n
45,der(X)t(X;Y)(p22.3;p11.2)[8]/46,t(X;Y)(p22.3;p11.2)[12] [7]	M	–	–	–	–	–	–	–	+
46,X,dic(X;Y)(p22.33;p11.32)/45,X/45,dic(X;Y)(p22.33;p11.32) [8]	M	–	n	–	–	–	–	–	+
45,der(X)t(X;Y)(p22;p11.3)ins(X;Y)(p22;q12)[[80]/45,X[20] [40]	M	+	–	+	–	–	–	–	n

“+”: with an exception in this regard; “–”: there is no anomaly in this regard; n: this aspect is not described

Type “other” include types 4\5\6\7, type C\D and other karyotypes

M male, F female

*: This patient is a sex reversal case report

across eight articles, nine patients had the Xq/Yq translocation, including a family study where phenotypes varied in severity and included menstrual disorders, primary/secondary amenorrhea, POE, streak gonads, and non-pregnant chorionic carcinoma [29, 31]. Studies by Tharapel et al. showed that deletion of different regions of the long arm of the X chromosome can be associated

with GD or POE. Women with X(q13-qter) region deletion were more likely to develop complete ovarian failure, whereas women with X(q24-qter) deficiency may have symptoms of POE [45]. Researchers have speculated that X(q13-q26) is the “critical area” for ensuring normal ovarian function, which conforms to the observations made for Patient 2 [46, 47]. Baronchelli et al. studied a family

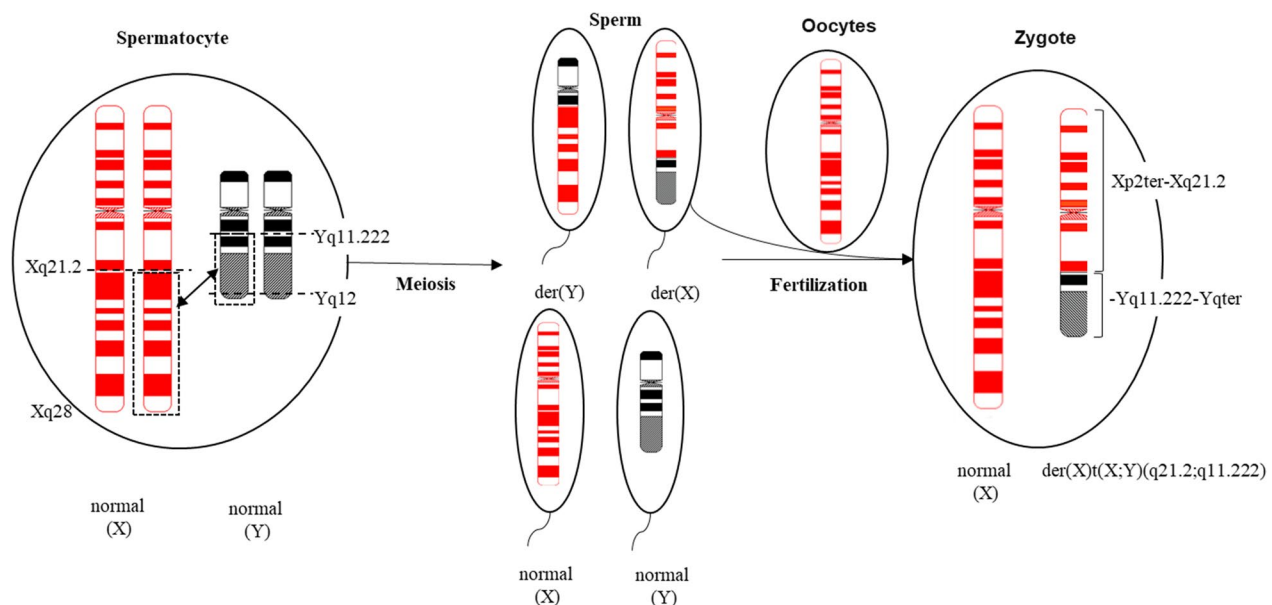


Fig. 7 The chromosomes X and Y pair and recombine at the meiosis, and fertilization. It is speculated that the patient 2's der(X) is derived from the abnormal recombination of X chromosome Xq21.2 and Y chromosome Yq11.222 during meiosis of paternal spermatocytes, with an ideogram of 550 band

in which the daughter's der(X)t(X;Y)(q26.2;q11.223) came from the mother, and both the mother and daughter had symptoms of POF [29]. This indicated that it is still possible to have children with X(q26.2-qter) deletion. However, the breakpoint in our patient is more proximal and thus it was associated with a more severe phenotype. Premature ovarian failure 2A (POF2A) was described to result from deletion or mutation in the *DIAPH2* gene on chromosome Xq22 (OMIM# 300108). The patient's parents were consanguineous, and CMA indicated multiple regions with absence of heterozygosity (AOH), which did not completely exclude the patient's clinical correlation with these regions. Genetic counseling was provided for the patient with information on the nature, and the risk of implications about gonadoblastoma. Patient 2 was now treated with HRT and followed up clinically.

Patient 3 had X chromosome deletion (Xq28) (155077922_155700385)×1 followed by der(X)t(X/Y). Xq28 is a gene rich region that contains many pathogenic loci that have X-linked recessive inheritance. The patient's mother (Fig. 5, II-14) also carried the same der(X), with regular menstruation and menopause at 50 years of age and without abnormal phenotype. The 0.622 Mb deletion region in our patient did not involve POF susceptibility genes. Therefore, Patient 3 and her mother did not have manifestations of ovarian dysfunction. Family analysis revealed that her mother (Fig. 5, II-4) had three spontaneous abortions (Fig. 5, III-1, III-2, III-5), and did not

give birth to a boy. The mother's X chromosome origin could not be traced, as her maternal grandfather (Fig. 5, I-1) and grandmother (Fig. 5, I-2) had passed away, and both uncles (Fig. 5, II-1, II-2) had a normal male karyotype. However, Delon et al. reported a karyotype of 46,X,der(X)t(X;Y)(q28;q11.2)dn in a 28-year-old female patient with infertility similar to our Patient 3 [31]. Therefore, based on the pregnancy history of the patient's mother, we speculated that this der(X) may undergo recombination changes during meiosis, which results in the failure to produce normal embryos. Alternatively, multiple pathogenic genes in the deletion region of the X chromosome, such as *RAB39B* (OMIM 300774) and *TMLHE* (OMIM 300777) have an XLR inheritance and nullosomy of which can lead to a severe phenotype in the male fetus, causing miscarriage or embryo lethality [48]. The gained Y(q11.223q12) segment in which no *SRY* or *AZF* genes were detected; therefore, this region has no clinical correlation in this female patient. Genetic counseling was provided for the patient with information on the nature, the genetic risk for offspring and prenatal testing issues. Currently, the patient has pregnancy desire and ART has been proposed because her bilateral fallopian tubes have undergone ligation surgery.

In most of studies related to X/Y translocation (Tables 3 and 4), breakpoints in the X/Y translocation are located in Xp22/Yq11 (type I/type II/type V, approximately 77.19%). However, it is worth

mentioning that only one patient with definitive child-bearing has been reported among all male patients [9], while many women have had children. Patients with Xp22/Yq11 translocations tend to complain of short stature. Some patients with the Xp22/Yq11 translocation also have Leri-Weill dyschondrosteosis, which is characterized by Madelung deformity. Male patients may also have contiguous gene deletion syndrome manifestations, such as intellectual disability, skeletal anomalies, psychomotor abnormalities, gonadal abnormalities, facial deformities, chondrodysplasia punctata (ARSE gene deletion) [49], ichthyosis (STS gene deletion) [50], and other symptoms, which are usually absent or less intense in female patients [3].

A small number of breakpoints were located at Xp22/Yp11 (type III/type IV, approximately 8.77%). Although a bias may occur due to the small number of patients, it is interesting to note that none of the patients with Xp22/Yp11 translocation had significant signs of deformity, except for one patient with induced fetal abortion due to an upper extremity abnormality [23]. Male patients with Xp22/Yp11 translocation in types III and IV have karyotypes of 46,X,psudic(X;Y)(p22;p11) and 46,X,der(X)t(X;Y)(p22;p11) and 45,der(X)t(X;Y), respectively. Both types have a deletion of the chromosome Y segment, resulting in phenotypic effects related to disorders of sexual development. Three female patients with type III and type IV had verified *SRY* gene in der(X) [24–26]. This could be partly explained by the inactivation of der(X), which may spread into the translocated Yp segment, resulting in the *SRY* gene expression being suppressed or completely inhibited [33, 35, 42, 51]. Female patients with type IV had milder phenotypes than those with other types, indicating that Yp may compensate for the Xp22 partial gene deletions, which also matches the presence of a pseudoautosomal region (PAR1) in Xp and Yp [52, 53]. However, they still had gonadal abnormalities, which is consistent with previous studies showing that two normal X chromosomes are essential for normal ovarian function [54].

Breakpoints rarely occur at other locations such as Xp21, Xp11, and Xq (Table 4, approximately 14%), and the karyotype is mostly 46,X,der(X)/46,X,der(Y) among female patients. The two reported male patients had severe phenotypic effects [36], illustrating that the insufficient gene dosage of chromosome X may affect male survival. The incidence of gonadal abnormalities was significantly higher in female patients.

All patients in the above classifications contained at least one normal X chromosome, except for those with type I. Patients with type I also had a higher probability of nervous, gonadal, and bone dysplasia than those

with other types, indicating that the complete human genome is essential for human development.

Conclusion

X/Y translocation is complex in both clinical presentation and classification, and we reviewed this category of cases by performing systematic clinical and cytogenetic analyses of three patients with different phenotypic presentations. This information will further improve understanding of the clinical and genetic aspects of X/Y translocations.

Abbreviations

FISH	Fluorescence in situ hybridization
CMA	Chromosomal microarray analysis
PGT	Preimplantation genetic testing
E2	Estradiol
P	Progesterone
LH	Luteinizing hormone
FSH	Follicle-stimulating hormone
AMH	Anti-Müllerian hormone
ELISA	Enzyme linked immunosorbent assay
GD	Gonadal dysplasia
PCOS	Polycystic ovary syndrome
ART	Assisted reproductive technology

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Author contributions

SL, XZ and HW contributed to the study conception and design. Material preparation, data collection and analysis were performed by SL, JZ, XL, YL, XZ, TH, and YY. The first draft of the manuscript was written by SL and XZ, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Medical Ethics Committee of West China Second University Hospital, Sichuan University (Approval Number: 2021–157). Informed consent was obtained from all subjects involved in the study.

Consent for publication

Written informed consent has been obtained from the patients to publish this paper.

Competing interests

The authors declare that they have no competing interests.

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