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ORIGINAL ARTICLE

Three patients with 46,X,inv(Y)(p11.2q11.2)pat/45,X and their pedigree analysis

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Abstract

The present study aimed to perform chromosome examination and pedigree analysis on three patients with semen abnormality who had undergone in vitro fertilization–embryo transfer (IVF-ET). Peripheral blood cell culture and chromosome karyotyping were performed on 4,200 individuals who had undergone chromosome examination. Among them, 155 pregnant women who had successfully conceived were subjected to amniotic cell culture and chromosome karyotyping and those with abnormal chromosome karyotype were further subjected to C-banding and whole-genome sequencing. Mosaicism for a 46,X,inv(Y)(p11.2q11.2)pat/45,X karyotype was identified in the probands and immediate adult male relatives. The incidence of this mosaicism in the study population was only 0.07% (3/4,200), which is reported for the first time. For the proband of pedigree A, the results of whole-genome sequencing and other tests were normal, and the chromosome karyotype of IVF fetuses was 46,X,inv(Y)(p11.2q11.2)pat. All the male members of three pedigrees have normal phenotypes, with no features of Turner's syndrome (45,X) or hermaphroditism (45,X/46,XY), suggesting that the inverted Y chromosome is extremely unstable and particularly susceptible to loss in somatic cells. So we speculate this karyotype may be a unique type of inverted Y chromosome in somatic cells.

KEYWORDS

in vitro fertilization–embryo transfer, Inv(Y), loss in somatic cells, mosaic

1 | INTRODUCTION

Loss of chromosomes in the early human embryo is thought to cause a large number of spontaneous abortions and can cause tumors when it occurs in a particular cell lineage in older embryos or adults. In addition, it is rare that the loss of the Y chromosome, which occurs in the first few mitoses of a zygote, causes 45,X/46,XY true hermaphroditism, and ~1.7 per 10,000 newborns have such chromosome mosaicism (Hughes, Houk, Ahmed, & Lee, 2006; Yiqi, Huilan, & Hanmin, 1986). In a somatic cell, a male loses a Y chromosome or a female loses an X chromosome, a phenomenon known as sex chromosome loss (SCL); male SCL is also known as Y chromosome loss (LOY) (Bing, Gang, & Jie, 2016). LOY

is a male-specific genetic risk factor. In the present review, LOY is primarily discussed as a mosaic event, with a mixture of cells with and without the Y chromosome in the peripheral blood of normally aging men (Forsberg, 2017).

Somatic and germ cells are of different tissue types and have different modes of division. Somatic mutations are usually caused by environmental factors such as exposure to ultraviolet radiation or certain chemicals. Numerous studies have reported loss of Y chromosome associated with old age, chronic myelocytic leukemia, acute myeloblastic leukemia, other hematological diseases, myeloproliferative diseases, cancer, smoking, urinary incontinence, obesity, diabetes mellitus, hypertension, and other reasons (Bing et al., 2016; Burki, 2015; Duijf, Schultz, & Benezra, 2013; Dumanski et al., 2015; Forsberg, 2017; HesmanSaey, 2014; Lleo et al., 2013; Park, Jeong, & Kim, 2005; Smith, Watson, & Sharma, 1999; Wiktor et al., 1999; Wiktor, Van Dyke, Hodnefield, Passow, & Hanson, 2011; Wong et al., 2008). Because loss of chromosome is a long-lasting process, it exhibits more complex genetic behavior. The aforementioned studies indicate that the Y chromosome is unstable and susceptible to loss in somatic cells, which is a rather complex and common phenomenon, but the loss of the inverted Y chromosome in somatic cells has not been reported so far.

2 | PATIENTS AND METHODS

2.1 | Patients

Peripheral blood cell culture and chromosome karyotyping were performed on 4,200 individuals who underwent in vitro fertilization–embryo transfer (IVF-ET) in the Reproductive Medicine Department of the Second Affiliated Hospital of Hainan Medical University from January 2011 to July 2018. Among them, 155 pregnant women who had successfully conceived were subjected to amniotic cell culture and chromosome karyotyping. Informed consent was obtained from all the patients, and their pedigrees were further investigated.

2.2 | Methods

Heparin-anticoagulated peripheral blood (0.5 ml) was inoculated into Life Jun Cell® Culture (Guangzhou Baiyunshan Baidi Biotechnology) and cultured at 37°C for 72 hours prior to being harvested and subjected to G-banding. After the amniotic fluid was centrifuged, 5 ml of Chang's culture medium was added to the precipitate, mixed well, and then inoculated in a 25-cm^2 culture flask to be cultured openly in a carbon dioxide incubator. The cells were harvested after 8–10 days, and G-banding was performed. The BEION Karyotype Analysis System was used to count 30 mitotic phases, and 3–5 karyotypes were analyzed. Based on abnormal conditions, the counting was further expanded to 100 mitotic phases. Furthermore, confirmation of C-banding, genome-wide detection, and homology detection of the X chromosome were performed. The karyotype description referred to the International System for Human Cytogenetic Nomenclature (2016).

3 | RESULTS

3.1 | New karyotype and clinical diagnosis

One type of human chromosomal karyotype abnormality was in the adult men of three pedigrees, which was 46,X,inv(Y)(p11.2q11.2)pat/45,X. Moreover, no phenotype or symptoms of Turner syndrome (45,X) or hermaphroditism (45,X/46,XY) were observed. No relevant report was found in the Chinese Human Chromosome Abnormality Karyotype Database, the Cytogenetics Database, or the Chinese Human Chromosome Abnormality Nuclei Database. Therefore, the karyotype was included in the Chinese Human Chromosome Abnormal Nuclei Database (Database No. 3574).

3.1.1 | Pedigree analysis

The analysis of the three pedigrees is shown in Table 1. The genealogies of the three pedigrees are shown in Figure 1. The results of cytogenetic examination are shown in Figure 2. Whole-genome sequencing is shown in Figure 3a. Analysis of the X chromosome origin is shown in Figures 3b and 3c.

3.1.2 | Pedigree A

The proband was a 42-year-old man of Han nationality living in Changliu Town, Haikou City (Hainan Province, China). The patient was a civil servant, his height was 175-cm, and he had a normal phenotype. He had one daughter aged 12 years old. His wife was not pregnant after >1 year without contraceptive measures, and the patient was diagnosed with secondary infertility in 2012. In 2013, he underwent assisted reproductive technology (IVF). The chromosome karyotype of peripheral blood was as follows: 46,X,inv(Y)(p11.2q11.2)pat (87)/45,X (13) (Figure 2). The blood type was 0; rhesus macaque blood type D (RHD) and rhesus macaque blood type C (RHC) were positive. Hepatitis B virus test showed that the surface antibodies were positive, while hepatitis C virus was negative; human immunodeficiency virus (HIV), *Treponema pallidum* antibody (TPPA), and antisperm antibody were negative. Furthermore, none of the 17 types of β-thalassemia genotype or three types of α-thalassemia genotype were detected. The results of fluorescence detection of mycoplasma urealyticum nucleic acid amplification (UU-DNA), fluorescence detection of *Chlamydia trachomatis* nucleic acid amplification (CT-DNA), and fluorescence detection of *Neisseria gonorrhoeae*

TABLE 1 Analysis of the three pedigrees

Item	Pedigree A	Pedigree B	Pedigree C
Region	Changliu Town, Haikou City (HaiNan Province, China)	Lingao County (Hainan Province, China)	Changliu Town, Haikou City (HaiNan Province, China)
Age (year)	42	29	38
Nationality	Han	Han	Han
Gender	Male	Male	Male
Educational level	Undergraduate	Undergraduate	Undergraduate
Occupation	Civil servant	Company employee	Company employee
Pregnancy history of their wives	Gravidity 2 parity 2	Gravidity 2 parity 0	Gravidity 0 parity 0
Height (cm)	175	145	177
Semen examination	Sperm count was 15×10^6/ml, and deformity rate was 90% in 2.0 ml of semen Vitality: A, 0%; B, 41%	No sperm found under the microscope	Sperm count was 3.2×10^6/ml, and deformity rate was 80% in 2.1 ml of semen Vitality: A, 2%; B, 30%
Karyotype of proband	46,X,inv(Y)(p11.2q11.2)pat [87]/45,X [13]	46,X,inv(Y)(p11.2q11.2)pat [9]/45,X [51]	46,X,inv(Y)(p11.2q11.2) pat [44]/45,X [16]
Karyotype of father	46,X,inv(Y)(p11.2q11.2) [79]/45,X [21]	46,X,inv(Y)(p11.2q11.2) [12]/45,X [48]	46,X,inv(Y)(p11.2q11.2) [50]/45,X [10]
Karyotype of little brother	46,X,inv(Y)(p11.2q11.2)pat [79]/45,X [21]	46,X,inv(Y)(p11.2q11.2) pat [11]/45,X [49]	No brother
Karyotype of in vitro fertilization fetus	46,X,inv(Y)(p11.2q11.2)pat	Failed to obtain fertilized eggs	Failed to enter the cycle because of oligozoospermia and physical weakness of his wife
Percentage of 46,X,inv(Y)(p11.2q11.2) pat, %	87	15	73
Percentage of 45,X, %	13	85	27

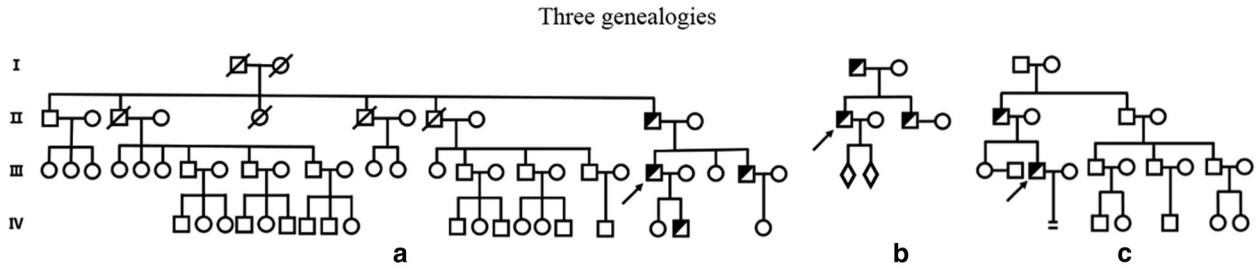

FIGURE 1 Three genealogies. (a) Genealogy of four generations of pedigree A. (b) Genealogy of three generations of pedigree B. (c) Genealogy of four generations of pedigree C

nucleic acid amplification (NG-DNA) were normal. A sperm quality examination was performed. The patient was diagnosed with azoospermia (examination in 2012: sperm count, 52×10^6/ml; deformity rate, 90% in 2.5 ml semen). The vitality revealed the following: A, 1%; B, 32%. An examination in 2013 revealed that the sperm count was 15×10^6/ml, and the deformity rate was 90% in 2.0 ml semen. The vitality revealed the following: A, 0%; B, 41%.

Illumina Human OmniZhongHua-8 BeadChip was used to detect the peripheral blood of the proband of pedigree A, but no known pathogenic chromosomal microdeletion, microrepetition, or distortion was found among the 900,000 single nucleotide polymorphism (SNP) sites covered (Figure 3). For the origin of the X chromosome, haplotype analysis was performed on six sites (44CA, 45CA, 49CA, 50CA, 59CA, and 3′CA) of the DMD gene on the short arm of the X

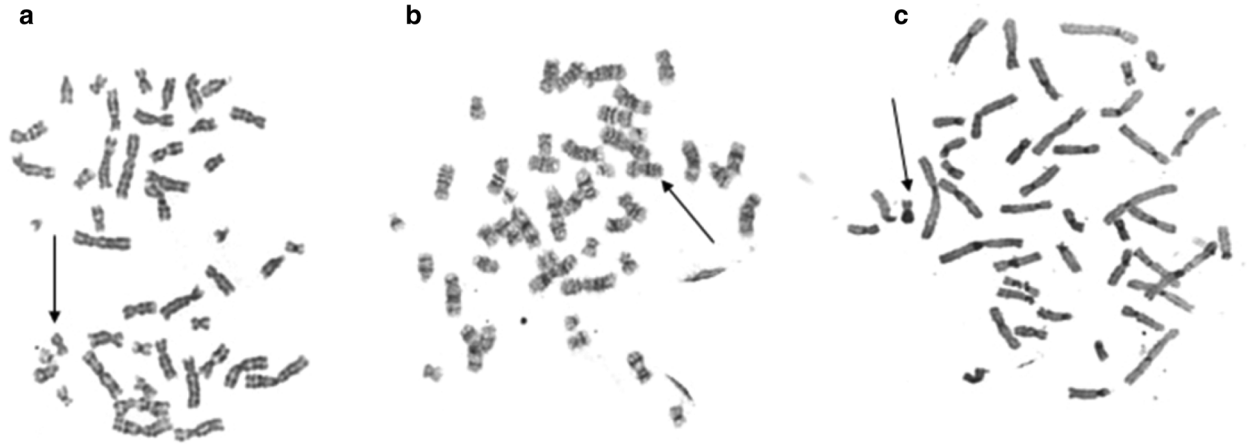

FIGURE 2 The results of cytogenetic examination. (a) G-band diagram: 46,X,inv(Y)(p11.2q11.2)pat. (b) G-band diagram: 45,X. (c) C-band diagram: 46,X,inv(Y)(p11.2q11.2)pat

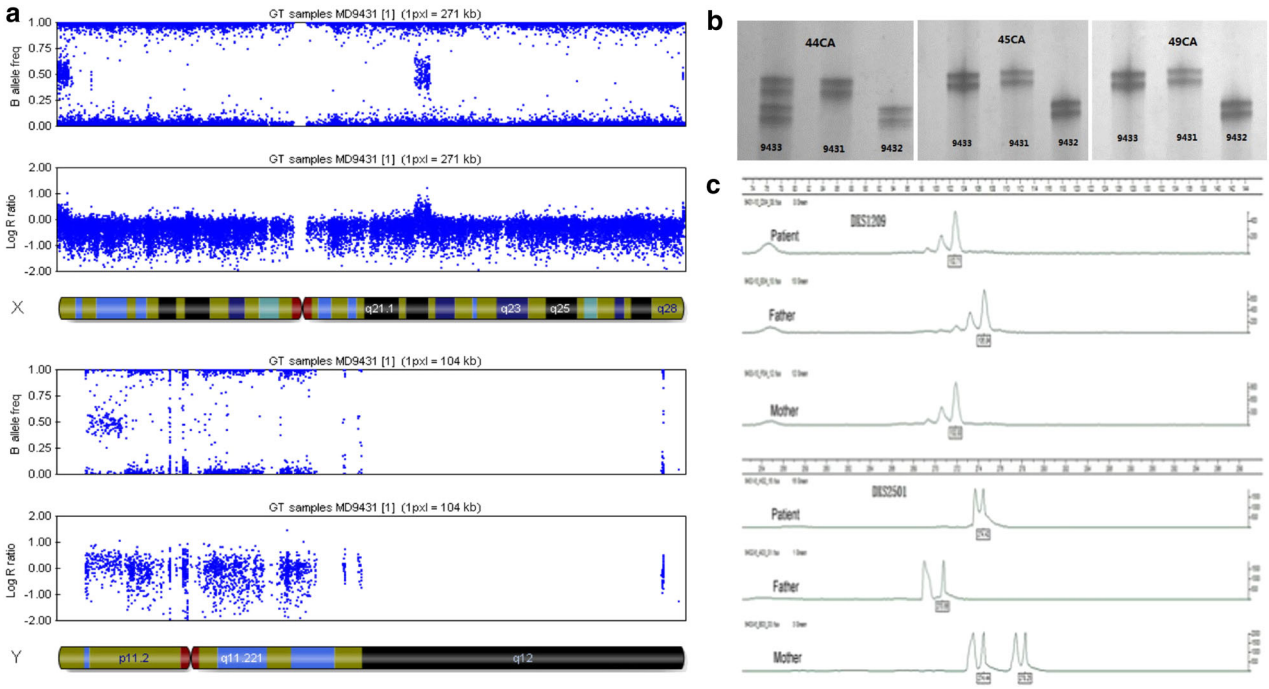

FIGURE 3 Whole-genome sequencing and analysis of X chromosome origin. (a) The proband of pedigree A used Illumina Human OmniZhongHua-8 BeadChip (Chinese human genome single-nucleotide polymorphism [SNP] fiber optic microarray typing technology) to detect, among the 900,000 SNP sites covered, no known pathogenic chromosomal microdeletions and microduplication aberrations were found. (b) The proband of pedigree A (MD9431), father (MD9432), mother (MD9433), and three DMD loci can provide effective genetic information. X chromosome origin was analyzed using X short arm DMD gene 44CA, 45CA, 49CA, 50CA, 59CA, and 3′CA Six CA sites and haplotype analysis of six-point short tandem repeat (STR) loci on the X short arm NDP gene (c). The results showed that the X chromosome of the proband was inherited from the mother; the paternal allele is not transmitted. (c) Two loci in the NDP gene of the probands of pedigree A (DXS1209, DXS2501) can provide effective genetic information. X chromosome origin was analyzed using X short arm DMD gene 44CA, 45CA, 49CA, 50CA, 59CA, 3′CA Six CA sites (b) and haplotype analysis of six-point STR loci on the X short arm NDP gene. The results showed that the X chromosome of the proband was inherited from the mother, an uninherited parent allele [Colour figure can be viewed at wileyonlinelibrary.com]

chromosome and in six short tandem repeat (STR) loci of the NDP gene on the short arm of the X chromosome by PAGE to demonstrate that the X chromosome originates from the mother (Figure 3).

The karyotype in the peripheral blood of his father was 46,X,inv(Y)(p11.2q11.2)pat (79)/45,X (21) (Figure 2). The height of his father was 172 cm. The karyotype in the peripheral blood of his mother was 46,XX. The karyotype

in the peripheral blood of his younger brother was 46,X,inv(Y)(p11.2q11.2)pat (79)/45,X(21) (Figure 2). The height of his younger brother was 176 cm. The karyotype in the peripheral blood of his wife was 46,XX. The amniotic fluid karyotype of the IVF fetus of the proband was 46,X,inv(Y)(p11.2q11.2)pat. The birth weight was 3.55 kg, the Apgar score was 10 points, and no abnormality was observed. The patient was followed up telephonically in 2014 and 2017. The child grew normally and was attending kindergarten. Because the examination was performed only in the clinical laboratory, genital cells or fertilized eggs of the patient could not be obtained to perform gene sequencing. The genealogy is shown in Figure 1a.

3.1.3 | Pedigree B

The proband was a 29-year-old man of Han nationality living in Lingao County (Hainan Province, China). He was a company employee. His height was 145 cm and he had a normal phenotype. He visited the hospital in 2015, and the examination showed that he had hypospadias and short penis. Moreover, the ejaculation of semen was not possible for the patient. The semen routine analysis showed no sperm under a microscope. Testicular biopsy showed active sperm and endocrine hormone examination was normal. The chromosome karyotype in the peripheral blood of the proband was 46,X,inv(Y)(p11.2q11.2)pat (9)/45,X(51) (Figure 2). The blood type was A, and the RHD was positive. Furthermore, UU-DNA, CT-DNA, and NG-DNA were normal. The antisperm antibody was negative and liver and renal functions were normal. The HBVM test revealed chronic hepatitis B. Hepatitis C virus, HIV, and TPPA were negative. The proband rejected further examination, and therefore the whole genome was not sequenced. Thus, it was speculated from the normal phenotype that the patient may be the same as the proband of pedigree A. The karyotype in the peripheral blood of his father was 46,X,inv(Y)(p11.2q11.2)pat (12)/45,X (48) (Figure 2); the karyotype of his younger brother was 46,X,inv(Y)(p11.2q11.2)pat (11)/45,X (49) (Figure 2); and the karyotype of his wife was 46,XX. His wife had recurrent miscarriages twice. In 2016, fertilized eggs could not be obtained from the proband of pedigree B multiple times and, hence, IVF was not successful. The genealogy is shown in Figure 1b.

3.1.4 | Pedigree C

The proband was a 38-year-old man of Han nationality based in Changliu Town, Haikou City (Hainan Province, China). He was a civil servant. His height was 177 cm and he had a normal phenotype. In 2017, he visited the hospital for IVF-ET because of infertility. The proband and his older sister had follicular occlusion, and the karyotype in the peripheral blood was 46,X,inv(Y)(p11.2q11.2)pat (44)/45,X(16) (Figure 2). His blood type was A, and the RHD was positive. The HBVM test showed positive hepatitis B surface antibodies. Hepatitis C virus, HIV, and TPPA were negative. Moreover, UU-DNA, CT-DNA, and NG-DNA were normal. The antisperm antibody was negative. None of the 17 types of β-thalassemia genotype or three types of α-thalassemia genotype were detected. The patient was diagnosed with oligospermia during an examination in 2017, which showed that the sperm count was 3.2×10^6/ml in 2.1 ml semen, with a deformity rate of 80%. The vitality revealed the following: A, 2%; B, 30%. Because the proband refused further examination, the whole genome was not sequenced. Thus, it was speculated from the normal phenotype that his diagnosis may be the same as that of the proband of pedigree A. The karyotype in the peripheral blood of his father was 46,X,inv(Y)(p11.2q11.2)pat (50)/45,X (10) (Figure 2), and the height of his father was 173 cm. The karyotype in the peripheral blood of his wife was 46,XX. The proband of pedigree C did not enter the cycle because of oligozoospermia and physical weakness of his wife. The patient was followed up telephonically in 2018, and he hoped his wife to conceive naturally. The genealogy is shown in Figure 1c.

4 | DISCUSSION

The genes specific to the Y chromosome not only regulate the spermatogenic function of the testis, but also may have a significant effect on human tissues and organs such as the prostate and brain (Zheng, Xiaobin, & Yixin, 2006). Previous studies (Bernstein, Wadee, Rosendorff, Wessels, & Jenkins, 1986; Schempp et al., 1993) have reported that the inverted Y chromosome does not impact normal fertility. However, in the process of producing germ cells by meiosis, the 46,X,inv(Y)(p11.2q11.2) karyotype forms a unique inversion loop, with inverted band sequence, forming the pericentric inversion of the Y chromosome. Previous studies (Jingmin, Shixiong, Qin, Yifeng, & Ying, 2002; Tomomasa et al., 2000) have reported that inv(Y) can supervene with spermatogenesis hypofunction and sex differentiation abnormality. The reason why the inverted Y chromosome affects male infertility may be that the Y chromosome can cause damage or loss of certain spermatogenesis-related genes in the process of breakage and reconnection. Houzhao, Yan, Fang, and Caihong (2013), Jingmin, Shixiong, Qin, Yifeng, and Ying (2002), Lijuan et al. (2012), and Tomomasa et al. (2000) demonstrated that the inversion of the Y chromosome has an important influence on the formation and growth of sperm, leading to oligoasthenospermia and thus infertility. This indicates that the semen abnormalities in three probands have a certain association with the inverted Y chromosome in the present study.

Unstable karyotype may be associated with poor prognosis. Newberg et al. (1998) analyzed the cytogenetic status of somatic cells and sperm in one patient with 46,XY/45,XO mosaicism and moderate oligoasthenospermia, and found that the frequency of mutated sperm composed of aneuploid chromosomes was significantly higher than that of somatic cells, suggesting that even if an individual with mosaicism can produce offspring, the risk of producing offspring with abnormal chromosome numbers is higher than that in the general population. Sex chromosome mosaicism leads to important differences in phenotype, ranging from almost normal males to females with Turner syndrome and those with uncertain gender. The differences in gender and phenotype are mainly due to the appearance of 45,X cell line and its proportion, and 45,X cell line mosaicism is considered to be a crucial factor in the development of gonads (Des Groseillier, Beaulieu, Brochu, Lemyre, & Lemieux, 2006). In this study, among adult males in three pedigrees, the proportion of 45,X mosaicism was 13% for the proband of pedigree A, 85% for the proband of pedigree B, and 27% for the proband of pedigree C. The dose effect makes the proband of pedigree B appear short in stature and exhibit hypogonadism, immature testicular interstitial cells, seminiferous tubules, and azoospermia, depending on the proportion of 45,X. In pedigrees A and C, 45,X accounted for a small proportion, and only manifested as oligoasthenospermia.

The use of gene chips to detect molecular mutations not only accurately identifies the mutation site and type, but also detects multiple genes or even entire genomes for analysis of DNA variations and polymorphisms on a large scale (Ryu & Nam, 2000). Phenotypes of different individuals mainly differ in SNPs, and Illumina Human OmniZhongHua-8 BeadChip was used to investigate the peripheral blood of the proband of pedigree A, but showed no known pathogenic chromosomal microdeletion, microrepetition, or distortion (Figure 3). Haplotype analysis was performed on six sites of the DMD gene on the short arm of the X chromosome and in six STR loci of the NDP gene on the short arm of the X chromosome by PAGE to demonstrate that the X chromosome originates from the mother (Figure 3).

In 2013, chromosome karyotyping of the fetus of the proband of pedigree A was confirmed by amniotic cell culture to be 46,X,inv(Y)(p11.2q11.2)pat, without 45,X karyotype, and a male baby with normal phenotype was born. Yunyuan (2007) considered that the loss of chromosome that occurs in the process of meiosis will produce (n-1) gametes, which will form a certain type of monosomy after fertilization, often leading to embryonic death and thus miscarriage. If it occurs in the process of mitosis, two types of somatic cells, (2n-1) and (2n), will be formed, producing a patient with chromosomal mosaicism. Because the mosaic cannot be passed from the father to the son in the form of a mosaic, the level of the mosaic must be reset to 100% for each fertilization event, thereby indicating that the zygote of the proband of pedigree A only carries the inverted Y chromosome. Because all the male members of the three pedigrees are adults, it is speculated that their SRY genes are intact, so the probands and adult male members of the immediate families of the three pedigrees have normal phenotypes.

Because of the complex palindromic structure and other repeated sequences inside the Y chromosome, they themselves will undergo homologous recombination, and self-renewal of the Y chromosome as well as loss of the middle part in the process of homologous recombination of self-repeated sequences may be the cause of loss of the Y chromosome. Danielsson et al. (2019), Yuting (2015), and Zeqing (1976) considered that loss of the Y chromosome may be associated with hematological tumors, which may be the cause or result of tumorigenesis, or it may be due to the physiological loss of normal somatic cells, although as with other solid tumors, the physiological loss of the Y chromosome makes the occurrence of hematological tumors highly susceptible.

Matsuguchi, Goto, Fukumoto, Okamura, and Niho (1992) reported a case of male aplastic anemia, in which all bone marrow cells had 45,X karyotype, showing loss of Y chromosome in all bone marrow cells, and peripheral blood examination revealed that the 45,X karyotype accounted for 10%. In the present study, the probands of the three pedigrees showed a different percentage of retention of the inverted Y chromosome in terms of chromosome karyotype for peripheral blood, specifically 87% in the proband of pedigree A, 15% in the proband of pedigree B, and 78% in the proband of pedigree C. This indicates that, when mosaicism is observed in the chromosome karyotype of peripheral blood in the adult male members of the immediate relatives of the three pedigrees (namely, probands, fathers, and brothers in pedigrees A, B, and C), the inverted Y chromosome was lost from certain cells after fertilization. It has been demonstrated that the inverted Y chromosome is remarkably unstable and is particularly susceptible to loss in somatic cells (Shurong, Yisheng, & Hong, 1999). Its mechanism may be loss of heterozygosity or loss of a functional allelic gene with normal heterozygous loci, possibly due to loss of hemizygous, deleted, or reduplicated chromosomes.

The polymorphism of the nonrecombinant region of the chromosome is paternally inherited and has racial and regional specificity, and the human Y chromosome is a male-specific sex chromosome. Notably, although all individuals with a high risk of hereditary tumors in a family carry the same germ cell mutation, the randomness of somatic mutations predicts the age change of primary tumor in the family (Shurong et al., 1999). In the present study, all probands of the three pedigrees had semen abnormalities, and both the probands and their immediate relatives had mosaicism, so it was suggested that reproductive genetic counseling should be

directed to the chimeric karyotype, and IVF preimplantation genetic diagnosis is beneficial for the reproductive health of the offspring.

Only a small part of the Y chromosome is paired with the X chromosome, that is, it does not exchange or rarely exchanges with the X chromosome. In evolution, mutations that occur on the Y chromosome are preserved and passed on to the male offspring. Alternatively, it can be deduced that the remaining 27 adult males out of 35 people of four generations of three pedigrees have the same 46,X,inv(Y)(p11.2q11.2)pat/45,X karyotype, and continuous chromosome examination is another means of follow-up (Zhike, 1990). It is necessary to further follow up with the remaining 27 adult males to confirm the results of chromosome examination.

In the present study, the probands and the immediate family members of the three pedigrees have 46,X,inv(Y)(p11.2q11.2)pat/45,X karyotype, which shows the recurrence of this phenomenon, and suggests that such karyotype may be an independent and unstable type of the inverted Y chromosome in somatic cells. It also shows that this is a normal phenomenon in the population, but its incidence rate is markedly low (only 0.07%, 3/4,200), and it has been reported for the first time in the present study. This suggests that the diversity of chromosome abnormalities in the Chinese population is very rich (Jiahui & Wei, 1993). The present findings may facilitate clinical research on the risk of complex diseases caused by rare genetic variations and may provide data to support, as well as guidance for, clinical genetic counseling and assisted reproductive technologies.

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Data collection was completed when the authors worked in the Second Affiliated Hospital of Hainan Medical University, Hainan Haikou, China, before July 2018.

AUTHOR CONTRIBUTIONS

Y.C. and J.H. designed study and performed study; Y.C., Y.X., X.C., C.Z., L.L., and Z.Z. participated in acquisition, analysis, or interpretation of data; Y.C. and J.H. wrote the paper. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

All authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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