Verification of a Cryptic T(Y;15) Translocation in a Male With an Apparent 45,X Karyotype

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Abstract

Background

A rare disease is that an individual with a non-chimeric karyotype of 45, X develops into a male. We explored the genetic aetiology of an infertility male with an apparent 45, X karyotype, which was subsequently verified as cryptic translocation between chromosomes Y and 15.

Methods

Peripheral blood sample was collected from the patient and subjected to a range of genetic testing, including conventional chromosomal karyotyping, short tandem repeat (STR) analysis for azoospermia factor (AZF) region, fluorescence in situ hybridization (FISH) with specific probes for CSP X/CSP Y, CSP Y/D15Z1/PML and SRY/D15Z1/PML, and chromosomal microarray analysis (CMA) for genomic copy number variations (CNVs).

Results

The patient was found to have an apparent 45,X karyotype. STR analysis showed that he possessed a short arm of the Y chromosome, including the SRY gene but the absence of a long arm of the Y chromosome, including AZFa+b+c and Yqter. A FISH assay using CSP X and CSP Y probes showed a green signal at the centromere of the X chromosome and a red signal for the Y centromeric sequence on a D-group-sized chromosome. By FISH assaying with D15Z1 and CSP Y probes, chromosomes 15 and Y centromeric signals appeared closely on a single chromosome, as ascertained by the PML control probe. A further FISH assay with D15Z1 and SRY probes revealed a signal of the SRY gene at the end of one arm of chromosome 15. The result of the CMA indicated a deletion with an approximate size of 45.31 Mb spanning from Yq11 to Yter.

Conclusion

Although the 45,X male patient did not harbour an intact Y chromosome, his genome contained the SRY gene derived from the translocation of the Yp, which probably triggered the male differentiation and development. Imbalanced translocations of Yp to other chromosomes can result in short stature and infertility among patients. Delineation of the genetic aetiology can guide early intervention and assisted reproduction in adulthood.

Background

Most individuals with a 45,X karyotype will develop into females with a Turner syndrome phenotype. However, very rare 45,X individuals are sterile males with testes. So far fewer than 40 cases of 45,X males have been reported, and most of them have harbored chimeric XY cells[1, 2]. Only about 10 cases were discovered as 45,X males who do not possess the Y chromosome but translocation of the Y chromosome with an autosome[3-5]. Of note, about 70% of translocations between the Y and a telocentric chromosome involve chromosome 15, which may be attributable to the homology between heterochromatin sequences at 15p and Yq[6]. Furthermore, t(Y;15) is usually unbalanced, with a majority of breakpoints occurring on 15p (15p11-13) and the heterochromatin region of Yq12. We hereby report on a male with an apparent 45,X karyotype, which was subsequently verified as cryptic translocation between chromosomes Y and 15.

Methods

Subject

The patient, a 27-year-old male, was referred to our hospital due to primary infertility. The patient, with a height of 160 cm and a weight of 51.5 kg, had a male appearance with a few whiskers and Adam's apple. He was found to have small testis measured approximately 8 mL on both sides. Sperms were not found on three routine semen examinations. The levels of sex hormones examined at another hospital were as follows: testosterone: 15.12 nmol/L (reference value: 4.94 ~ 32.01 nmol/L), prolactin: 168.09 nmol/L (reference value: 77.75 ~ 435.92 nmol/L), estradiol: 70.4 pmol/L (reference value: 404 ~ 161.5 pmol/L), luteinizing hormone: 5.33 IU/L (reference value: 0.57 ~ 12.07 IU/L), follicle-stimulating hormone 13.24 IU/L (reference value: 0.95 ~ 11.95 IU/L). His parents had worked at a printing and typography company for more than three years and had exposure to ink and lead.
before his birth. His father and mother had a height of 174 cm and 160 cm, respectively, and denied a family history of genetic disorders and consanguinity. No infertility problems or similar patients had existed in their relatives. The karyotypes of his father and mother were 46, XY and 46, XX, respectively.

**Specimen preparation**

Peripheral venous blood samples of the patient and his parents were collected with heparin sodium and EDTA-Na$_2$ anticoagulant tubes for the analysis.

**Chromosomal karyotyping analysis**

Peripheral blood lymphocytes were cultured, harvested, and loaded onto microscope slides for Giemsa staining using conventional methods. As previously described, a Zeiss (Germany) karyotype analysis system was adopted for chromosome count and karyotype analysis.

**DNA extraction**

Genomic DNA was extracted from EDTA-Na$_2$ anticoagulated blood with a QIAamp DNA Mini Kit (QIAGEN, Germany) by following the manufacturer's instructions. DNA was qualified with a concentration over 30 ng/μL and an OD$_{260/280}$ value between 1.8 to 2.0, as determined by ultraviolet spectrophotometer Nanodrop 1C (Thermo Fisher Scientific, USA).

**Analysis of AZF sequences**

Y chromosome-specific sequences were detected with a method based on short tandem repeats (STR). The PCR conditions were as follows: 94°C for 2 min, 98°C 10 s, 60°C 30 s, 68°C 30 s, 25 cycles; 72°C for 10 min. The amplicons were subjected to capillary electrophoresis on an ABI 3500Dx gene analyzer. The results were analyzed by using GeneMapper software. The selected STR loci have included the SRY gene, the long arms and short arms of chromosomes X, Y and 3, typical regions of AZF deletions (AZFa: SY84, SY86; AZFb: SY127, SY134; AZFc: SY254, SY255), and heterochromatin region at Yqter (SY160). The numbers of chromosomes were determined according to the ratio of target fluorescence peaks to that of the reference. The number of target chromosome was determined to be equal to that of the reference chromosome when the ratio was between 0.80 and 1.40, and double the reference chromosome when the ratio was between 1.60 and 2.60.

**Fluorescence in situ hybridization (FISH) analysis**

**FISH assay with CSP X and CSP Y probes**

CSP X/CSP Y probes (China Medical Technologies, Inc. Beijing, China) were hybridized with metaphase cells derived from cultured peripheral blood lymphocytes. Glass slides were denatured at 78°C for 10 minutes and hybridized at 42°C for more than 16 hours. Thereafter, the signals were observed under a fluorescence microscope.

**FISH assay with PML, D15Z1 and CSP Y probes**

Metaphase cells from the cultured lymphocytes were loaded upon prepared glass slides and hybridized with the PML, D15Z1 and CSP Y probes. The hybridization buffer and the CSP Y probe were mixed with a proportion of 4:1, and applied to the cell-loaded glass slides. Denaturation and hybridization were carried out by following the standard procedure.

**FISH assay with PML, D15Z1 and SRY probes**

The procedure was the same as the prior step, only differed with the preparation of the hybridization mix, in which the buffer and the SRY probe were mixed at a proportion of 9:1.

**Chromosomal microarray analysis (CMA)**

500 ~ 1000 μg of genomic DNA and the same amount of reference DNA were used for the experiment. After digestion, the labelled patient sample was mixed with the reference and hybridized to a SurePrint G3 CGH+SNP (180K) chip. Fluorescence signals were
scanned with an Agilent DNA Microarray Scanner. Data were extracted from the chip image with Agilent Feature Extraction Software and converted into log-ratios. Copy number variants (CNVs) were analyzed with Agilent CytoGenomics Software (Agilent Technologies, USA). Candidate variants were queried with relevant online databases such as OMIM (https://omim.org/), DGV (http://dgv.tcgag.ca/dgv/), Decipher (https://decipher.sanger.ac.uk/), ClinGen (https://www.clinicalgenome.org/) and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/).

Comparison of the clinical phenotypes of patients with a 45,X,t(Y;15) karyotype

A literature search has been carried out to identify previously reported cases with a 45,X,t(Y;15) karyotype. Clinical phenotypes of such individuals were compared.

Results

Cytogenetic analysis

The father and mother of the patient respectively had a karyotype of 46,XY and 46,XX, while the patient had an apparent 45,X karyotype (Fig. 1).

STR analysis

STR analysis showed that the patient possessed the SRY gene mapped to Yp but was negative for the AZFa+b+c and a Yqter sequences. He had only possessed a single copy of Xp, Xq, and Yp (Fig. 2).

FISH analysis

FISH with the CSP X and CSP Y probes

FISH with X and Y centromeric probes showed a green signal for chromosome X (CSP X) and a red signal for chromosome Y (CSP Y), which, however, was located on a D-group-sized telochromosome (Fig. 3).

FISH with the PML, D15Z1 and CSP Y probes

FISH with the PML, D15Z1 and CSP Y probes has revealed an aqua blue signal for D15Z1, a green signal for PML on chromosome 15, and a red signal for CSP Y on a telocentric chromosome. The signals of D15Z1 and CSP Y were in close proximity, which indicated that chromosome 15 of the patient was dicentric and has contained materials from chromosome 15 and Y (Fig. 4).

FISH with the PML, D15Z1 and SRY probes

A further FISH assay with the PML, D15Z1 and SRY probes revealed fluorescence signals for all three probes on the same telocentric chromosome, including an aqua blue signal for D15Z1, a green signal for PML on chromosome 15, and an orange signal for SRY. The SRY probe signal was seen on the end of opposite side of the PML probe at 15q24.1. These suggested that the SRY gene has translocated to 15p (Fig. 5).

Result of CMA analysis

The CMA result of the patient was arr[GRCh37] Yq11.21-q11.23 (13 988 156_59 301 502)×0, 45.31 Mb (Fig. 6). We postulated the deletion range to be from Yq11.21 to Yqter as the microarray chip contained no probe for the heterochromatin region at Yq11.23-Yqter. The above result was also in keeping with the STR analysis, which showed no peaks for the AZF sequences at Yq and the SY160 sequence at Yqter.

Comparison of the clinical phenotypes of individuals with a 45,X,t(Y;15) karyotype

Table 1 has summarized the clinical features of individuals with a t(Y;15) as shown; variation of the breakpoints has resulted in discrepancies in the deletion regions on chromosomes Y and 15. Patients 1, 2, and 3 had lost no genetic material, therefore had a normal phenotype. Patients 4 and 5 had the typical Prader-Willi syndrome (PWS) phenotype due to the 15pter→q11.2 region loss. With the presence of 15p11.2 region (SNRPN+), patient 6 showed no PWS phenotype but severe oligoasthenospermia due to partial
deletion of AZFc (sY254). Similar to our patient, patients 7, 8 and 9 had lost the entire long arm of the Y chromosome (including the AZFa+b+c regions) and showed common abnormal phenotypes, including spermatogenous and testicular dysplasia.

Table 1 Summary of chromosomal breakpoints and clinical phenotypes of individuals with a 45,X,t(Y;15) karyotype
| Case | Reference | Chromosomal karyotype | Clinical phenotype | Analytical method | Whether the derivative chromosome contains the Y centromere | Whether the derivative chromosome contains the 15 centromere |
|------|-----------|-----------------------|--------------------|------------------|-----------------------------------------------------------|-----------------------------------------------------------|
| 1    | Subrt et al. 1974[11] | 45,X,t(Y;15) (Yqter→Yp11::15q11→15qter) | Four males from four consecutive generations of a pedigree harbored 45,X,t(Y;15) translocations but with a normal phenotype | Karyotyping | Yes | No |
| 2    | Mahmut 2021[14] | 45,X,t(Y;15)(q12;q11) | The karyotypes of father and mother were 46,XY, t(15;20) (q11; 13) and 46,XX, respectively, but the fetus was a 45,X,t(Y;15) male, and no abnormal phenotype was observed up to one year after birth | Karyotyping, FISH | Yes | No |
| 3    | White et al. 1998[15] | 45,X,dic(Y;15)(q11.23;p11.1) | The karyotype of the fetus was the same as that of the father, and no abnormal phenotype was observed | Karyotyping, FISH, Microsatellite analysis | Yes | Yes |
| 4    | Qumsiyeh et al. 1992[16] | 45,X,t(Y;15) (q12;q11.2) | The male infant has typical PWS | Karyotyping, In situ hybridization | Yes | No |
| 5    | Suzuki et al. 1996[17] | 45,X,t(Y;15) (q12;q11.2) | The boy has typical PWS | Karyotype, In situ hybridization | Yes | No |
| 6    | Lin et al. 2014[18] | 45,X, der(15)(?:p11.2→qter)dn.ish psu dic(Y;15)(q12;p11.2) (D15Z1+, SNRPN+, PML+, SRY+, DYZ3+, DYZ1+) | A 33-year-old male had normal intelligence, growth and development, testicular size and sex hormones level but infertility. He had severe oligoasthenospermia due to partial AZFc (sY254) deletion | Karyotyping, FISH, Multiplex PCR | Yes | Yes |
| 7    | Antonio et al. 2008[19] | 45,X,der(15) (Ypter→q22.21::15p11.2→qter) | A 41-year-old male, 58 kg in weight and 157 cm in height, had small testis, epididymis dystrophy. Laboratory tests found low testosterone, high gonadotropin, azoospermia, and deletion of AZFa+b+c loci | Karyotyping, FISH, Y microdeletion analysis | Yes | Yes |
| 8    | Schempp, 1985[20] | 45,X,t(Y;15)(p10;p12) | A 19-year-old male had a weight of 54 kg and a height of 154 cm. He had normal mental | Different chromosome staining | Yes | Yes |
development and no deformity. He had a de novo translocation between chromosomes Y and 15. His primary anomaly is azoospermia.

9  Gal et al. 1987[21]  45,X,-15,+der(15),t(Y;15) (Ypter→Yq11.2 F::15p12→15qter)  A 20-year-old male had a weight of 54 kg and a height of 154 cm. He had no apparent malformation and normal mental development. His penis was of average size. Testes were descended and of reduced size and increased consistency. Testosterone, luteinizing hormone and follicle-stimulating hormones were all within the normal ranges. Seminal fluid examination showed azoospermia.

Karyotyping, In situ hybridization  Yes  Yes

10  Present study  45,X,dic(Y;15)(q11;p11). ish dic(Y;15) (SRY+, CSPY+; D15Z1+, PML+)  A 27-years-old male, with a weight 51.5 kg and a height of 160 cm, had small testes. Laboratory tests found normal level of testosterone, high level of follicle-stimulating hormone. He had azoospermia due to deletion of AZFa+b+c loci, but had a normal karyotype.

Karyotyping, FISH, Multiplex PCR, CMA  Yes  Yes

Discussion

Among the previously reported t(Y;15) cases, some were initially detected with a 15p+ karyotype but later confirmed as t(Y;15) by molecular methods[8-10]. Of note, some of these translocations were inherited from parents with a normal phenotype[11-13]. Only a few non-chimeric 45,X,t(Y;15) males were reported. As summarized by Table 1, variation of the breakpoint sites in these 45,X,t(Y;15) males has resulted in their phenotypes' heterogeneity. Those only with a loss of heterochromatin had a normal phenotype[14, 15]. By contrast, individuals with loss of euchromatin had various clinical phenotypes. Deletions of 15p11.2 involving the SNRPN region have resulted in typical PWS[16, 17]. Loss of the AZFc region at Yq may explain the presence of severe oligoasthenospermia[18], while loss of the AZFa+b+c region may account for azoospermia testicular dysplasia and other phenotypes[19-21].

Chromosomal translocations are often analyzed with karyotyping, FISH and multiplex PCR. In the present study, we have adopted CMA to map the deletion region with accuracy and exclude deletion and duplication of other genomic regions. With combined karyotyping, FISH, multiplex PCR, and CMA, we have ultimately verified that the patient's azoospermia was attributable to the unbalanced translocation between chromosomes 15 and Y, which has resulted in the deletion of AZFa+b+c region on Yq.
In the present study, the patient appeared to have no Y chromosome in his karyotype but was found to carry an unbalanced Y→15 translocation by molecular genetic testing. The translocation has resulted in the SRY gene of Yp exchange onto the short arm of chromosome 15, and the two broken chromosomes containing the centromeric parts have formed a dicentric aberration. Dicentric chromosomes derived from translocations between chromosomes Y and 15 are rare[21]. As one of the centromeres was inactive or nonfunctional, the dicentric chromosome may behave and segregate as a monocentric chromosome during cell division[22, 23]. A translocation study between the Y and chromosome 21 found that the Y chromosome's centromere was preferentially inactivated in pseudodicrocentromeres[24]. The acentric fragments produced with the translocation, including the short arm of chromosome 15 and the long arm of chromosome Y, are prone to lose during subsequent cell divisions. As a result, only 45 chromosomes were left. Cytogenetically, the derivative chromosome 15 containing a small fraction of Yp could not be easily distinguished from the normal ones. Several males carrying a Y-acrocentric chromosome translocation with a breakpoint between Yq11 and Yq12 were reported previously[25, 26]. In the present study, based on the results of molecular analysis, our patient's karyotype was verified as 45,X,dic(Y;15)(q11;p11). indic(Y;15) (SRY+, CSPY+; D15Z1+, PML+). Results of the FISH assay indicated that the patient's chromosomal rearrangement had occurred de novo, as no abnormality was found with his father (data not shown). It may be postulated that the two chromosomes had broken during the first meiosis of spermatogenesis or at a very early stage of zygote formation. Human embryos will develop towards the male gender as long as the SRY gene is present in the genome, even without the Y chromosome. That may also be the primary molecular basis for 45,X males[27, 28]. Based on molecular testing, the seemingly “pure” 45,X male may not exist. The SRY gene on autosomes derived from the Y chromosome's translocations could explain the male sex determination in such cases[29].

It also appeared that, for the derivative chromosome 15, the clinical phenotype would depend on the breakpoint site and size of the deleted fragment on Yq. In our patient, the Y chromosome breakpoint was close to Yq11, resulting in the deletion of almost the entire long arm.

Similar to those reported by Hsu et al., the main features of our patient have included azoospermia and infertility[29]. Several genes mapped to the azoospermia factor (AZF) region of Yq, including USP9Y, DBY, PRY, RBMY, DAZ and BPY2, are involved in the formation, development, and maturation of sperms, and deletions of the AZF region have proven to be the most common risk factor for male infertility[30-32], which account for 10%-15% of azoospermia and 5%-10% of severe oligozoospermia[33]. The type and location of the AZF gene deletions are correlated with the severity of fertility disorders. AZFa deletion usually results in SCOS-only type I syndrome (SCOS type I) and azoospermia, while AZFB deletion is associated with azoospermia caused by the cessation of meiosis AZFc deletion has considerable clinical heterogeneity[30]. In the present study, the patient has lost Yq (including AZFa+b+c), and no sperm was found upon routine semen tests. The patient has also failed microscopic testicular sperm extraction. The result was in keeping with previous reports[34].

Another remarkable feature of these patients(including our patient) is their short stature. The cause may be attributed to the loss of growth control genes (GCY) on Yq12[35, 36], which is different from the absence of the SHOX gene, which has a haploinsufficiency effect of the PAR1 region and is the common cause of short stature in Turner syndrome (45,X female)[37, 38]. The GCY gene can affect the height of males by approximately 8-10 cm[39]. In the present study, the patient's height (160 cm) was below the average of local males of similar age (170.86 cm).

As the most critical sex-determining gene, the SRY gene probably accounts for the male phenotype in our patient. The unbalanced translocation of Yp including the SRY gene to chromosome 15 may have resulted in his short stature and infertility. Early diagnosis of the patient can guide clinical intervention, necessary correction of external genitalia and assisted reproduction, removal gonad dysplasia in order to prevent deterioration, and hormone therapy to promote the development of secondary sexual characteristics. To avoid birth of further affected child, preimplantation genetic diagnosis and prenatal diagnosis should be provided for his parents.

As the most critical sex-determining gene, the SRY gene probably accounts for the male phenotype in our patient. Yp's unbalanced translocation, including the SRY gene to chromosome 15, may have resulted in his short stature and infertility. Early diagnosis of the patient can guide clinical intervention, necessary correction of the external genitalia and assisted reproduction, removal of gonad dysplasia to prevent deterioration, and hormone therapy to promote the development of secondary sexual characteristics. Moreover, to avoid the birth of another affected child, preimplantation genetic diagnosis and prenatal diagnosis should be provided for the parents of this kind of patient.
Declarations

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Authors’ contributions

Clinical data collection, genetic counselling and follow-up were performed by Jesse Li-Ling. Shengfang Qin contributed to the study conception and design, analyzed and interpreted the patient data. Zhuo Zhang, Ximin Chen, Yan Yin, and Mengling Ye proceeded with the molecular genetics experiments. All authors read and approved the final manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate

This study is retrospective and did not require the ethical approval.

Consent for publication

The patient had provided his consent for publication.

Competing interests

The authors declare that they have no competing interests.

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Figures
Figure 1

Karyogram of the t(Y;15) male patient. The der(15) and X chromosomes are indicated by arrows. 1b: Ideograms of chromosomes Y, 15, and der(15). The Y centromere, 15 centromere and breakpoint site of the derivative chromosome are indicated by arrows.
Figure 2

Capillary electrophoresis diagram for the detection of AZF sequences. a: Normal male; b: Normal female; c: 45,X male. A fluorescence peak representing the SRY sequence was seen, but those for the AZFa, AZFb, AZFc, and SY160 were absent, suggesting loss of the whole long arm of the Y chromosome.
Figure 3

FISH image of metaphase cells of the patient detected with the X and Y centromeric probes. The green signal indicated the centromere of the X chromosome, while the red signal indicated the Y chromosome material on a D-group-telocentromeric chromosome.
**Figure 4**

FISH image of metaphase cells of the patient detected with centromeric probes for chromosomes 15 and Y. The green signal is from the PML probe mapped to 15q24.1, the red signal is from the CSP Y probe mapped to the centromere of Y, and the aqua blue signal is from the D15Z1 probe (15q10) closely located on the same chromosome.
Figure 5

FISH image of metaphase cells of the patient detected with probes for chromosome 15 and the SRY region. The green signal is from the PML probe mapped to 15q24.1, the orange signal from the SRY probe (Yp11.31) and the aqua blue signal from the D15Z1 probe (15q10) are located on the same chromosome.

Figure 6

CMA result of the patient. The Yq region was absent in the patient. The red bar indicates the area of deletion.