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Case Report

A Rare Case of 45,X/46,X,del(Y)(q12→qter) Mosaicism in An Infertile Male with Y Chromosome Microdeletion

Sunny Kumar Jignesh Kumar Patel [1], Rahul Kabir [1], Ruchismita Nayak [1], Indira Palo [2], Birendranath Banerjee [1*]

1- inDNA Center for Research and Innovation in Molecular Diagnostics, inDNA Life Sciences Private Limited, Odisha, India
2- Department of Obstetrics and Gynecology, Amit Hospital, Odisha, India

** Corresponding Author:* Birendranath Banerjee, Director and Head of inDNA Center for Research and Innovation in Molecular Diagnostics, inDNA Life Sciences Pvt. Ltd., Odisha, India
E-mail: biren.banerjee@indnalife.com

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Abstract

Background: Males with 45,X/46,XY karyotype have two different types of cells. This condition is associated with a wide range of clinical phenotypes. In infertile males, the mosaic 45,X/46,XY karyotype is a frequent sex chromosome defect and they might be able to conceive with the help of assisted reproductive technology; nevertheless, there is a potential risk of transmission of azoospermia factor (AZF) microdeletions in addition to 45,X to all the male progeny. In this case report, the purpose was to present a rare sex chromosomal mosaicism of an infertile man.

Case Presentation: Comprehensive molecular and cytogenetic analysis of an infertile male was performed in this case study. A 27-year-old male was presented with history of azoospermia and was unable to conceive after being involved in five years of marriage. Cytogenetic investigation revealed a rare mosaic karyotype pattern of 45,X/46,X,del(Y)(q12→qter). Y chromosome microdeletion (YMD) analysis revealed notable deletions of 06 loci. Comparative genomic hybridization (CGH) microarray was performed to investigate probable functional genetic associations.

Conclusion: Deletion of Y-linked genes leads to different testicular pathological conditions contributing to male infertility. Individuals with normal male phenotype harbor YMD, although size and location of the deletion do not always correspond well with quality of sperm. Therefore, in addition to semen analysis, identification of genetic variables is important which will play a crucial role in proper diagnosis and management of infertile couples. The present case study demonstrates the significance of comprehensive molecular testing and cytogenetic screening for individuals with idiopathic infertility.

Keywords: Azoospermia factor (AZF), Chromosomal microarray analysis (CMA), Comparative genomic hybridization (CGH), Fluorescence in situ hybridization (FISH), Infertility, Y-chromosome microdeletion (YMD).
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Introduction

Infertility is described as the inability to conceive following a year of consistent unprotected sexual intercourse (1). It has become a frequent medical condition that affects approximately 15% of individuals attempting to conceive a child where male factor infertility accounts for approximately half of the cases (2, 3). Male infertility is a spectrum of conditions with multiple etiologies and diagnosis, rather than a single clinical symptom. It is most commonly caused by azoospermia, oligozoospermia, teratozoospermia, and asthenozoospermia, which account for 20% to 25% of incidents (4). Among various factors contributing to male infertility, 10–15% of cases are due to genetic factors. The foremost of these factors includes either structural or numerical chro-

mosomal anomalies (2). The most prevalent structural chromosomal abnormality observed in infertile males is significant deletions of the long arm of Y chromosome and robertsonian translocation. Y-chromosome microdeletion (YMD), occurring at a rate of 1% to 50%, is the second most common genetic cause of azoospermia which is closely linked to male infertility (2, 5). Other than structural chromosomal aberrations and YMD, numerical sex chromosome anomalies like 47, XXY and the mosaic 45,X/46,XY karyotype are frequent sex chromosome defects in infertile males (6). A case study of an azoospermic male who had been married for five years and had been unable to conceive is reported in this study. The male showed a mosaic karyotype pattern 45,X/46, X, del(Y)(q12→qter) along with microdeletions of the Y chromosome comprising portion of AZFb and AZFc. The 45,X/46,X,del(Y)(q12→ qter) mosaicism is a rare chromosomal abnormality and is frequently misdiagnosed owing to its rarity (7).

Case Presentation

A 27-year-old male was referred for cytogenetic investigation at inDNA Life Sciences, Bhubaneswar, India in December 2020. The patient was presented with history of unsuccessful pregnancy after being involved in five years of marriage. Semen analysis of the patient showed absence of sperm in the sample provided, and he was diagnosed to have azoospermia. Peripheral blood sample was collected from the patient for chromosomal analysis followed by molecular studies including fluorescence in situ hybridisation, YMD detection by PCR, and chromosomal microarray analysis.

Results

An informed consent was obtained from the patient and 2-3 *ml* of whole blood was collected in heparinized vial and was subjected to cytogenetic analysis. As per The AGT Cytogenetics Laboratory Manual (4th edition), routine 72 *hr in vitro* culture was initiated using whole blood with RPMI-1640 (Gibco-61870-036) complete media containing 10% fetal bovine serum (Gibco-10270-106), 1% antibiotics (HiMedia-A007-100ML), and Phytohemagglutinin-M (Gibco-10576-015). At 67th hour, 0.1 *μg/ml* of Colcemid (Gibco-15210-040) was added to arrest the cells in metaphase stage. Metaphase cells were harvested by hypotonic treatment with 0.075 *M* potassium chloride solution followed by fixation procedure using pre-chilled Carnoy's fixative until a clear white lymphocyte cell pellet was obtained and slides were prepared. GTG-banding was then conducted, followed by chromosomal analysis by using Olympus BX-43 microscope (Olympus Life Science, USA).

G-banded chromosome analysis revealed a mosaic karyotype pattern involving two different cell types. Upon analysis, 65% of metaphases presented with loss of Y chromosome while the remaining 35% of cells showed partial deletion of chromosome Y. As per ISCN 2016, the karyotype of the patient is represented as mos 45,X [13]/46,X, del(Y)(q12→qter) [07] (Figure 1).

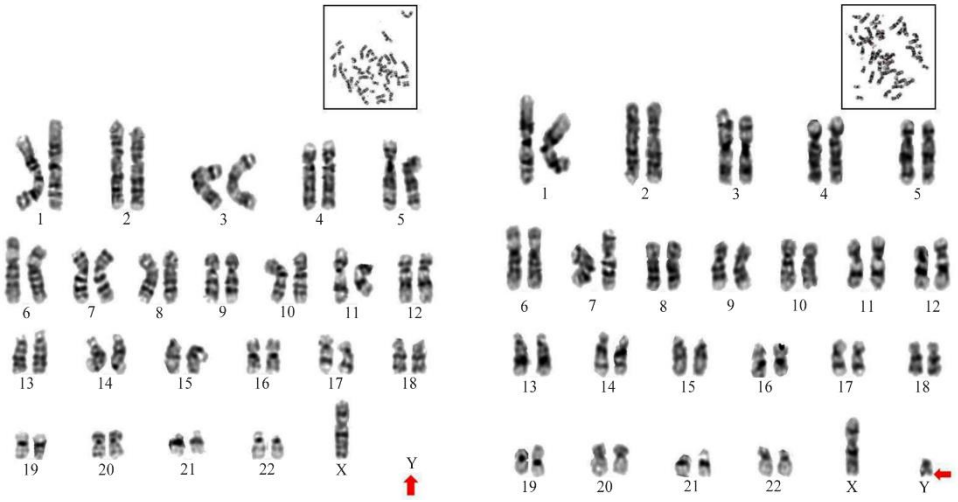

Figure 1. Image of karyotype analysis indicating loss of chromosome Y (left) along with partial deletion of Y chromosome (right)

Interphase FISH as well as metaphase FISH was performed according to The AGT Cytogenetics Laboratory Manual (4th edition) using XA/XY aneusomy probe (MetaSystems, USA) to rule out the mosaicism status more accurately. In FISH analysis, a total of 200 cells were scored and 88 cells (44%) were presented with loss of chromosome Y while the remaining 112 cells (56%) were presented with one copy of X chromosome and one copy of Y chromosome (Figure 2).

YMD analysis was performed to rule out its association with azoospermia (8). Genomic DNA was isolated using DNA extraction kit (DNA mini kit, catalogue number-51304; QIAGEN, Germany) according to the manufacturer's instructions. Purity of isolated genomic DNA was checked by using ratio of Abs 260 *nm*/Abs 280 *nm* as well as agarose gel. The isolated genomic DNA was PCR amplified using multiplex PCR for azoospermia factor loci (AZFa–sY84 and sY86, AZFb-sY127 and sY134, AZFc-sY145, sY160, sY254 and sY255) and for sex-determining region Y (SRY), zinc finger protein, and Y linked gene (ZFY) as control. The loci were selected based on their known role in Y-chromosome common microdeletions and also as per the EAA/EMQN best practice guidelines (8, 9). The PCR product was checked in 1.8% agarose gel and results were interpreted based on the presence or absence of specific PCR products in agarose gel analysis. AZF microdeletions were detected by multiplex PCR. In the test sample, microdeletions of the Y chromosome comprising portion of AZFb and portion of AZFc were detected (Figures 3 and 4).

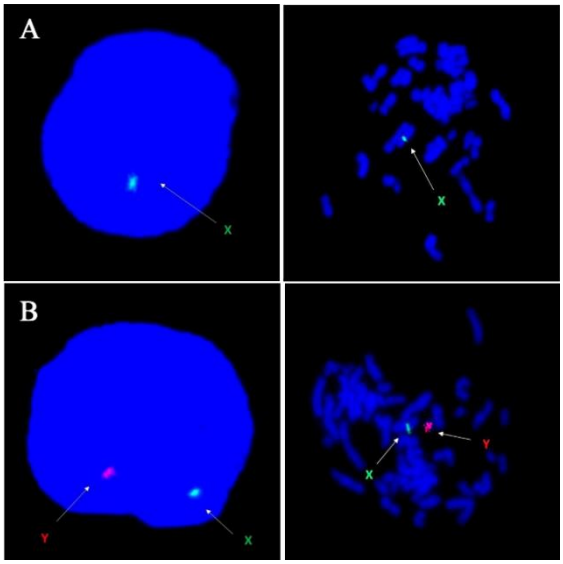

Figure 2. Fluorescence in-situ hybridization: Image A, showing loss of chromosome Y(XO) and image B is showing presence of both sex chromosomes (XY)

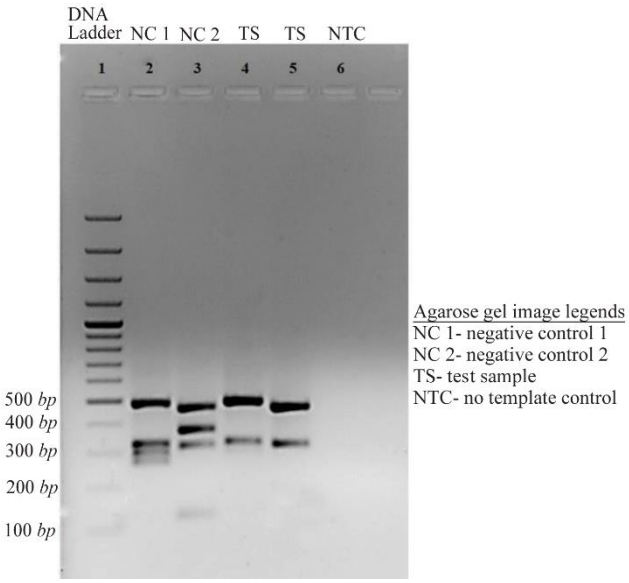

Figure 3. Agarose gel (1.8%) image of Y chromosome microdeletion analysis by multiplex PCR
Lane 1: DNA ladder (100 *bp*). Lane 2: Negative control for ZFY-495 *bp*, SY84 (326 *bp*) [AZFa locus], SY134 (301 *bp*) [AZFb locus], SY127 (274 *bp*) [AZFb locus]. Lane 3: Negative control for SRY–472 *bp*, SY254 (400 *bp*) [AZFc locus], SY86 (320 *bp*) [AZFa locus], SY255 (126 *bp*) [AZFc locus] Lane 4: Test sample; two bands indicating presence of ZFY-495 *bp*, SY84 (326 *bp*) [AZFa locus], and absence of two bands indicating deletion of SY134 (301 *bp*) [AZFb locus], SY127 (274 *bp*) [AZFb locus]. Lane 5: Test sample; two bands indicating presence of SRY–472 *bp*, SY86 (320 *bp*) [AZFa locus], and absence of two bands indicating deletion of SY254 (400 *bp*), and SY255 (126 *bp*) [AZFc locus]. Lane 6: No template control; no bands indicating absence of any kind of nucleic acid contamination

For further investigation, chromosomal microarray analysis (CMA) was performed using Agilent CGH platform with 8×60 *K* array chip according to manufacturer's instructions (Agilent-G4410-90010, Version 8.0, December 2019) with a capacity and resolution of analyzing thousands of loci at the same time to investigate Y-linked copy number variations (CNVs). Briefly, sample preparation for microarray was done in four major steps. Genomic DNA was isolated and quantified by Qubit dsDNA BR Assay kit (Invitrogen, USA). After quantification and restriction digestion, probe labelling and purification were performed for test and control samples. Hybridization was performed at 67°*C* in hybridization chamber for 24 *hr*. Post hybridization wash was performed

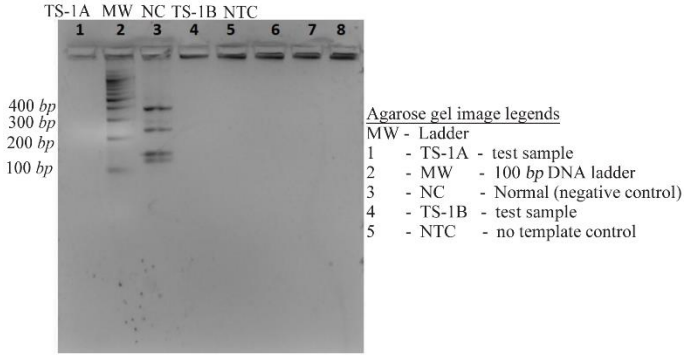

Figure 4. Agarose gel (1.8%) image of Y chromosome microdeletion (AZFc region specific) analysis by multiplex PCR Lane 1: Test sample; absence of four bands indicating deletion of SY254 (400 *bp*), SY160 (236 *bp*), SY145 (143 *bp*), and SY 255 (126 *bp*) [AZFc locus]. Lane 2: DNA ladder (100 *bp*). Lane 3: Negative control; presence of four bands indicating no deletion of SY254 (400 *bp*), SY160 (236 *bp*), SY145 (143 *bp*), and SY 255 (126 *bp*) [AZFc locus]. Lane 4: Test sample; absence of four bands indicating deletion of SY254 (400 *bp*), SY160 (236 *bp*), SY145 (143 *bp*), and SY 255 (126 *bp*) [AZFc locus]. Lane 5: No template control; no bands indicating absence of any kind of nucleic acid contamination

using Agilent Oligo aCGH/ChIP-on-Chip Wash Buffer 1 at room temperature (25°*C*) for 5 *min* and Agilent Oligo aCGH/ChIP-on-Chip Wash Buffer 2 at 37°*C* for 1 *min*. Microarray glass slide was scanned in SureScan Microarray Scanner (Agilent Technologies, USA) and analysis was performed using Agilent Cytogenomics software *vs*. 5.2 (Figure 5). Upon microarray analysis, deletion of total fifty loci on long arm of chromosome Y was observed (Table 1).

Discussion

Sex determination, which is chromosomally determined at fertilization (46,XY or 46,XX), differentiation of the gonads and differentiation of the internal and external genitalia, which will follow the male pathway in the presence of testicular hormones or the female pathway in the absence of testicular hormones are all eventual processes of normal human sex development. Disorders of sex development (DSD) is a group of congenital anomalies in which the development of chromosomal, gonadal, or anatomical sex is atypical. It can result from factors negatively impacting any step of these processes. DSD can be caused by partial gonadal dysgenesis (PGD) or mixed gonadal dysgenesis (MGD) (10). 45,X/46,XY mosaicism, also known as mixed gonadal dysgenesis, is a rare condition of sex development (7). Despite the large number of people having phenotypic abnormalities, there is a subset of 45,X/46,XY mosaicism that has a typical male phenotype. These people frequently have infertility and were identified based on the findings of a karyotype investigation during an azoospermia or severe oligospermia assessment (11). Other than male infertility phenotypes, 45,X/46,XY mosaicism could also be present in individuals with female phenotype and Turner syndrome, genital ambiguity, and ovotesticular DSD, or true hermaphroditism (10).

One hypothesis for the cause of this mosaicism is that the Y chromosome was lost because of nondisjunction after normal disomic fertilization (7). Apart from chromosomal determination,

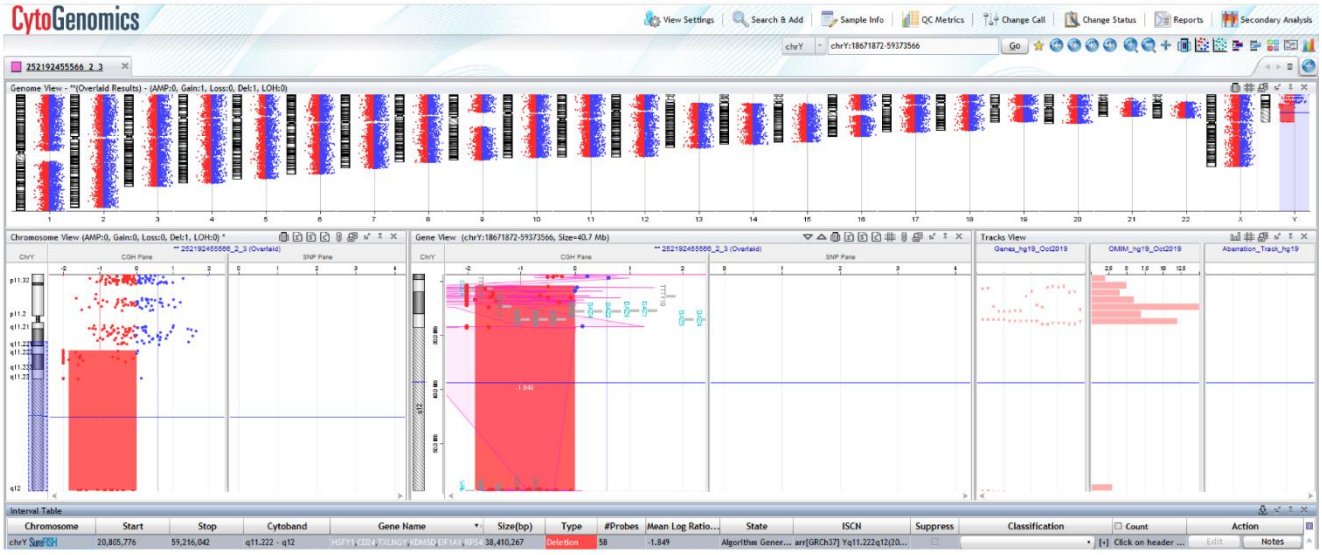

Figure 5. A representative genome view of array CGH data of the test sample

Table 1. Deletion of Y linked genes with their clinical significance as per ClinVar data

Loci	Gene type	Clinical significance	Variant type	Cytogenetic band
HSFY1	Protein coding genes	Pathogenic	Deletion	Yq11.222
HSFY2	Protein coding genes	Pathogenic	Deletion	Yq11.222
KDM5D	Protein coding genes	Pathogenic	Deletion	Yq11.223
EIF1AY	Protein coding genes	Pathogenic	Deletion	Yq11.223
RPS4Y2	Protein coding genes	Pathogenic	Deletion	Yq11.223
RBMY1A1	Protein coding genes	Pathogenic	Deletion	Yq11.223
RBMY1B	Protein coding genes	Pathogenic	Deletion	Yq11.223
RBMY1D	Protein coding genes	Pathogenic	Deletion	Yq11.223
RBMY1E	Protein coding genes	Pathogenic	Deletion	Yq11.223
RBMY1F	Protein coding genes	Pathogenic	Deletion	Yq11.223
RBMY1J	Protein coding genes	Pathogenic	Deletion	Yq11.223
PRY2	Protein coding genes	Pathogenic	Deletion	Yq11.223
BPY2	Protein coding genes	Pathogenic	Deletion	Yq11.223
BPY2C	Protein coding genes	Pathogenic	Deletion	Yq11.23
BPY2B	Protein coding genes	Pathogenic	Deletion	Yq11.23
DAZ4	Protein coding genes	Pathogenic	Deletion	Yq11.23
DAZ3	Protein coding genes	Pathogenic	Deletion	Yq11.23
DAZ2	Protein coding genes	Pathogenic	Deletion	Yq11.223
DAZ1	Protein coding genes	Pathogenic	Deletion	Yq11.223
CDY1	Protein coding genes	Pathogenic	Deletion	Yq11.23
CDY1B	Protein coding genes	Pathogenic	Deletion	Yq11.23
SPRY3	Protein coding genes	--	Deletion	Yq12
VAMP7	Protein coding genes	--	Deletion	Yq12
TXLNGY	Pseudogenes	--	Deletion	Yq11.222-q11.223
CSPG4P1Y	Pseudogenes	--	Deletion	Yq11.23
GOLGA2P2Y	Pseudogenes	--	Deletion	Yq11.23
GOLGA2P3Y	Pseudogenes	Pathogenic	Deletion	Yq11.23
BCORP1	Pseudogenes	---	Deletion	Yq11.222
RBMY2EP	Pseudogenes	Pathogenic	Deletion	Yq11.223
RBMY2FP	Pseudogenes	Pathogenic	Deletion	Yq11.223
LOC100652931	Pseudogenes	--	Deletion	Yq11.223
TTTY6	RNA genes	Pathogenic	Deletion	Yq11.223
TTTY5	RNA genes	Pathogenic	Deletion	Yq11.223
TTTY17A	RNA genes	Pathogenic	Deletion	Yq11.223
TTTY17C	RNA genes	Pathogenic	Deletion	Yq11.23
TTTY17B	RNA genes	Pathogenic	Deletion	Yq11.23
TTTY4	RNA genes	Pathogenic	Deletion	Yq11.223
TTTY4C	RNA genes	Pathogenic	Deletion	Yq11.23
TTTY4B	RNA genes	Pathogenic	Deletion	Yq11.23
TTTY3	RNA genes	Pathogenic	Deletion	Yq11.23
TTTY3B	RNA genes	Pathogenic	Deletion	Yq11.23
TTTY9A	RNA genes	Pathogenic	Deletion	Yq11.222
TTTY9B	RNA genes	Pathogenic	Deletion	Yq11.222
TTTY14	RNA genes	Pathogenic	Deletion	Yq11.222
TTTY10	RNA genes	Pathogenic	Deletion	Yq11.223
TTTY13	RNA genes	Pathogenic	Deletion	Yq11.223
TTTY6B	RNA genes	Pathogenic	Deletion	Yq11.223
PRORY	RNA genes	Pathogenic	Deletion	Yq11.223
LOC101929148	RNA genes	--	Deletion	Yq11.223

YMD is considered to be one of the main reasons of male infertility. In the overall population, it affects 1 in 4000 males, but infertile men are far more likely to experience it (6). Male infertility is mostly caused by the absence of Y chromosome sequences in the euchromatic region of the long arm (Yq), which is required for the formation of male germ cells. In general, 10-20% of phenotypically normal males with the history of idiopathic infertility and visibly intact Y chromosome can carry sub-microscopic deletion in the euchromatic region of the q arm, which results in the loss of genes essential for male fertility (12). It has been previously reported that the Y-chromosome microdeletion frequency was around 40% in individuals with 45,X/46,XY mosaicism who presented with mixed and incomplete gonadal dysgenesis (10). In another study, it has been found that cytogenetically visible and Yq microdeletions might be related to Y chromosome instability, which results in the development of 45,X cell lines (12). Several findings claim that genes in the AZF region are associated with spermatogenesis as well as the viability and stability of the Y chromosome. AZF gene locus, present on the long arm of Y chromosome, is micro-deleted and can cause chromosomal instability which can be responsible for chromosomal rearrangements like translocation and on few occasion complete deletion of AZF gene loci (13). In this case report, two different cell lines were observed. One with 45,X and another with 46,X,del(Y)(q12→qter). Mosaicism status was further confirmed by performing an interphase FISH as well as metaphase FISH. To rule out sub-microscopic deletions, PCR based Y-micro deletion assay was performed for selected sequence-tagged sites (STS). It was revealed that 6 STS markers, SY134, SY127 for AZFb locus and SY254, SY160, SY145, and SY255 for AZFc locus were found to be deleted. The Y-chromosome euchromatic region, along with some of its heterochromatic regions, spans 95% of its length and is known as the MSY (male-specific region on the Y chromosome). MSY contains 73 protein coding genes, 400 pseudogenes, and 122 non-coding RNA genes (NCBI Gene Database). These genes reported previously are known to play critical role in male fertility; therefore, CMA study was employed to elucidate their status in the current case. Microarray analysis revealed deletion of total 50 loci located in the region q11.222-q12 of the Y chromosome. Out of these 50 deleted loci, 23 are protein coding genes, 8 are pseudogenes and 18 are RNA genes (Table 1). The genes that have been found to be deleted in this case are directly or indirectly involved in the overall process of spermatogenesis.

HSFY gene plays crucial role in sperm maturation, and it has been found to be under expressed in testicular tissue from males with maturation arrest (14). It is believed that KDM5D plays a vital role in chromosome condensation during meiosis, which explains the maturation arrest seen at the spermatocyte stage associated with AZFb deletion. EIF1AY gene participates in translation initiation during spermatogenesis process (15). During spermatogenesis, expression of RPS4Y1 gene is up-regulated in the testis and might be significant for the development of germ cells (16). One of the most significant genes in the AZFb area is RBMY, which has six copies spread throughout the Y chromosome and is essential in controlling various aspects of meiotic and pre-meiotic development through formation of several protein-protein and protein-RNA complexes (15). In the nuclei of all germ cell types, RBMY1 encodes an RNA binding protein that is unique to the testis (17). Expression of this protein is decreased in the testes of males with AZFb deletions (18). Heterogeneous expression of PRY gene was observed in germ cells. These genes are believed to have a role in controlling apoptosis, which is assumed to be responsible for the elimination of defective sperm (19). Meiotic arrest has also been linked with the deletions of PRY1 and PRY2 genes. According to previous studies, spermatogenesis is entirely stopped if both RBMY and PRY are eliminated which shows that these two genes are majorly involved in male fertility (20). The expression of BPY2 is specific to testis and its protein product is important for the development of male germ cells (20). It is reported that infertile males in Indian population has a notably high incidence of BPY2 copy number variations (15). DAZ gene was identified as a frequently deleted gene from AZFc region on the Y chromosome in infertile males. Males who are infertile and have lost some of their DAZ gene copies are far more likely to develop azoospermia or severe oligozoospermia (15). Role of CDY1 in male fertility is controversial because in several studies, simultaneous loss of both DAZ and CDY1 copies in men puts them at risk for azoospermia or severe oligozoospermia. Oligozoospermia and azoospermia have also been linked to CDY1b copy deletion (21). However, some individuals with

CDY1 deletions, either alone or in association with DAZ, are fertile or normozoopermic, suggesting that these genes are not absolutely necessary for spermatogenesis (22). Some of the deleted RNA genes, TTTY17A, TTTY4, TTTY3, and TTTY9A, have been reported to be associated with spermatogenic failure (23). Therefore, CGH micro array technique would be useful to explore and correlate the clinical characteristics of male infertility which can change the dynamics of clinical investigation in the field of reproductive science.

Conclusion

Y chromosome harbors Y-linked genes expressed in the testis and is crucial for the control of spermatogenesis. It is evident that deletion of Y-linked genes leads to different testicular pathological conditions that might contribute to male infertility. Individuals with sex chromosome mosaicism and Y microdeletions having a normal male phenotype choose to undergo testicular sperm extraction (TESE) followed by in vitro fertilization with intracytoplasmic sperm injection (ICSI); the next step would be comprehensive molecular testing on testicular biopsy sample for obtaining better outcomes. On the other hand, these individuals are exposed to potential risk of transmitting AZF microdeletions in addition to 45,X to all the male progeny. The present case study demonstrates the significance of comprehensive molecular testing and cytogenetic screening for individuals with idiopathic infertility which will provide a better and improved clinical outcome.

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Conflict of Interest

The authors declare no conflicts of interest.

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