SRY-negative 45,X/46,XY adult male with complete masculinization and infertility: A case report and review of literature

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Abstract

BACKGROUND
45,X/46,XY mosaicism is a rare chromosomal abnormality with a wide range of phenotypes in both males and females, from normal individuals with different degrees of genital ambiguity to those who show signs of Turner’s syndrome. More rarely, cases of 45,X/46,XY mosaicism with a normal-appearing male phenotype are not found until a chromosome test is performed to investigate the cause of male infertility.

CASE SUMMARY
In this study, a 29-year-old male patient with complete azoospermia is reported. Chromosomal analyses of his lymphocytes revealed the karyotype 45,X[93%]/46,X,+mar(Y)[7%]. In addition, Y chromosome-specific markers, such as SRY, ZFY, AZFa, AZFb and AZFc, were not observed in his blood DNA according to multiplex polymerase chain reaction test. A literature review identified several 45,X/46,XY cases with a normal-appearing male phenotype, most of whom were diagnosed during infertility investigation. However, the present case is the first SRY-negative 45,X/46,XY male case diagnosed during a premarital medical examination.

CONCLUSION
This finding further suggests that sex determination is a complex process regulated by multiple genetic and environmental factors.

Key Words: Azoospermia; Sex chromosome; Mosaicism; Y chromosomal microdeletions; SRY-negative; Case report

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Core Tip: A rare chromosomal abnormality is 45,X/46,XY mosaicism. Here, we describe the diagnosis of a rare case of a 45,X/46,XY SRY-negative man with complete virilization and infertility as the main anomaly.

INTRODUCTION

As a rare complement, the chromosomal abnormality of 45,X/46,XY mosaicism is found in 1.7 cases among 10000 newborns[1]. The spectrum of observed phenotypes ranges continuously from normal individuals with varying degrees of genital ambiguity to Turner’s syndrome[2]. Most normal-appearing male phenotype cases are diagnosed during the prenatal period, and cases with genital/gonadal anomalies are usually diagnosed after birth[3]. More rarely, cases of 45,X/46,XY mosaicism with a normal-appearing male phenotype are not found until a chromosome test is performed to investigate the cause of male infertility.

Because the Y chromosome carries testis-determining factor, which is a genetically predominant locus, under normal circumstances, the bipotent gonadal primordium can be triggered and testes formation can be processed, which makes the Y chromosome a key factor in human sex determination. The SRY gene located in Yp11.2 was found to be cytogenetic and confirmed to play a critical role in the complex and tightly regulated processes of testis development[4] and sex differentiation[5]. However, more and more SRY-negative male cases with various karyotypes have been reported. In addition, increasing studies have shown that other factors, including both genetic and environmental factors, may regulate gender determination and differentiation through a multi-target approach.

Key genetic factors are known to regulate spermatogenesis on Yq, namely azoospermia factors (AZFs), including AZFa, AZFb and AZFc. Spermatogenetic failure caused by AZF microdeletions is a common cause of male infertility. Studies have shown that AZF microdeletions can be detected in approximately 10%-15% of azoospermia patients in China[6].

In the present report, we describe the diagnosis of a rare SRY-negative male case with 45,X/46,XY mosaicism. In addition, we review the 45,X/46,XY male phenotype cases reported in the literature to date to provide a more comprehensive description of the genetic and pathological features of this subgroup.

CASE PRESENTATION

Chief complaints
A 29-year-old man visited our urology clinic for a premarital medical examination, with complaints of occasional scrotal pain.

History of present illness
For the previous month, the patient had experienced occasional minor pain in the testicles.

History of past illness
The patient had no notable previous medical history.

Personal and family history
He denied any family history and had no specific past history.
Physical examination
His height was 167 cm, and his weight was 57.9 kg. After physical examination, we
found that he had no dysmorphisms and had a normal distribution of pubic hair and
body hair. His external urethral meatus was in a normal position, and his penis had a
normal appearance and size (5.7 cm, non-erectile).

Laboratory examinations
The results of the patient's serum test revealed that the luteinizing hormone (LH)
concentration was elevated at 15.73 IU/L (normal range: 1.7-8.6 IU/L), and the follicle-
stimulating hormone (FSH) concentration was elevated at 14.13 IU/L (normal range:
1.5-12.4 IU/L). However, the serum testosterone hormone concentration was 3.22
μg/L, which was in the normal range for adult males of 2.49-8.36 μg/L. Azoospermia
was determined after repeated seminal analysis. Chromosomal analysis was
performed twice on samples collected at different times, and 100 metaphases were
analyzed in each analysis. Two different cell lines with the karyotype 45,X[93%]
/46,X,+mar(Y)[7%] were observed by GTG banding. Fluorescence in situ hybridization
analysis with screening of metaphase and interphase lymphocytes was carried out to
confirm the result of the karyotype analysis. Two cell lines, one with one green signal
for Xcen (182/200) and the other with one green signal and one red signal for Xcen and
Ycen (18/200), respectively, were observed according to fluorescence in situ
hybridization (Figure 1A and B). All the metaphase and interphase lymphocytes
showed one signal for Xcen but no SRY signal, except for cell lines containing SRY
(Figure 1C). Polymerase chain reaction amplification of 16 Y-STS gene loci (SRY, ZFY,
sY86, sY84, CDY2, SMCY, sY127, sY134, sY1161, sY1191, sY254, sY255, DAZ, sY157,
CDY1, ZFX, SMCX, DAZL) using a Y-chromosome microdeletion detection kit
(Microread Gene; Beijing, China) demonstrated the presence of Y chromosome-
derived sequences. The SRY and ZFY genes were not amplified in the AZF region
(Figure 1D). The negative amplification of SRY further confirmed the partial absence
of the Y-chromosome sequence.

Imaging examinations
Ultrasound scanning of the scrotum showed that both testicles were located in the
scrotum, but the volumes (6.6 mL and 6.8 mL, respectively) were significantly smaller
than the normal adult male testicle size (range: 15-23 mL). In addition, a normal-sized
prostate and seminal vesicles were observed by internal genitalia ultrasound analysis.

FINAL DIAGNOSIS
Azoospermia.

TREATMENT
The recommended treatments were hormone replacement therapy, including oral
testosterone undecanoate to maintain sexual function, and sperm donation and
assisted reproductive technology to solve fertility problems.

OUTCOME AND FOLLOW-UP
Follow-up found that the patient had a normal penile erection. He was married 1 year
later, and the couple decided to adopt a child after marriage.

DISCUSSION
Stability of the number and structure of chromosomes is the basic requirement for
maintaining the normal sex differentiation process. Two decades ago, Telvi et al[3]
found that 45,X/46,XY mosaicism can manifest as a normal male phenotype and can
also cause some abnormal clinical phenotypes, including Turner’s syndrome,
pseudohermaphroditism, and mixed gonad dysplasia. The subgroup of 45,X/46,XY
mosaicism with normal adult male phenotype is usually diagnosed during infertility
investigation. Lashkari et al\textsuperscript{[7]} reported that the occurrence rate of 45,X/46,XY mosaicism in azoospermic and oligozoospermic patients was 0.78%. Among the 49 infertile adult male patients with the 45,X/46,XY mosaicism karyotype that they evaluated, 21 showed azoospermia, 24 had sperm abnormalities, and four displayed a normal spermogram.

We reviewed additional literature regarding 45,X/46,XY adult male cases (Table 1).\textsuperscript{[8-18]} Among the 34 cases reviewed, 96.5% (28/29) showed azoospermia or oligozoospermia. The 45,X/46,XY mosaicism rates ranged from 6/93.3 to 94/6.7. There was no relationship between the mosaicism rate in peripheral blood lymphocyte and the phenotype, which was consistent with previous results.\textsuperscript{[19,20]} The mosaicism ratio in different tissues may explain the variety of phenotypes in mixed gonadal dysgenesis.\textsuperscript{[21]} Moreover, these individuals showed short or normal stature, with height ranged from 148-181 cm (data from 24 cases). Most of the patients had small testicles (92%, 23/25), elevated LH concentration (65.2%, 15/23), elevated FSH concentration (80.9%, 17/21), and normal testosterone concentration (95.2%, 20/21). All patients had the SRY gene, while 62.1% (18/29) had the AZF microdeletion. The most common AZF microdeletions were AZF(b+c) (66.7%, 12/18) followed by AZFc (22.2%, 4/12), AZFb (5.5%, 1/18), and AZF(a+b+c) (5.5%, 1/18). In our study, the man with the 45,X/46,XY mosaic karyotype also showed complete masculinization and azoospermia, with short stature, small testicles, elevated LH and FSH concentrations, and a normal T concentration. However, the SRY gene, ZFY gene, and AZF(a+b+c) regions of blood DNA were missing in this case, and this is the first male with the SRY-negative 45,X/46,XY mosaic karyotype according to our literature search results.

The process of sexual differentiation begins in the early stages of human embryo development. After a series of complex and orderly procedures, bipotential gonads eventually develop into testes or ovaries. The SRY gene plays a critical role in the cascade of events of sexual differentiation. The histogenesis of testis is initiated by the
Table 1 Characteristics of 34 reported 45,X/46,XY adult male cases

| Ref.  | No. in yr | Karyotype [%] | Reason for examination | Semen analysis | Height in cm | Genital/gonads | LH in U/L | FSH in U/L | T in ng/mL | E2 in pg/mL | AZF | SRY |
|-------|-----------|---------------|------------------------|----------------|--------------|----------------|-----------|-----------|------------|-------------|------|------|
| Wu et al [8], 2017 | 1 | 22 | 45,X[93.3]/46,XY[6.7] | Primary sterility | Male/left and right TV: 4.4 mL, 1.6 mL. dysplasia of epididymis | 148 | 17.07 | 52.78 | 3.94 | 13.58 | No missing | + |
| | 2 | 23 | 45,X[36.7]/46,X,del(Y)(q11.223)[63.3] | Primary sterility | Male/left and right TV: 8.7 mL, 8.7 mL. | 159 | 9.98 | 16.22 | 4.32 | 37.38 | AZF(b+c) | + |
| | 3 | 23 | 45,X[65]/46,XY[35] | Primary sterility | Male/left and right TV: 4 mL, 5.4 mL. | 173 | 9.10 | 15.33 | 2.52 | <5.00 | AZF(b+c) | + |
| | 4 | 26 | 45,X[6]/46,XY[94] | Primary sterility | Male/left and right TV: 3.8 mL, 4.5 mL. | 170 | 9.32 | 17.04 | 4.06 | 47.79 | AZF(b+c) | + |
| | 5 | 26 | 45,X[83.3]/46,X,Yqh–[16.7] | Primary sterility | Male/left and right TV: 6 mL, 6 mL. | 165 | 10.44 | 28.20 | 7.12 | 33.26 | AZF(b+c) | + |
| | 6 | 29 | 45,X[45]/46,XY[55] | Primary sterility | Male/left and right TV: 5.4 mL, 6.2 mL. | 160 | 13.58 | 22.00 | 3.49 | 40.95 | AZF(b+c) | + |
| Akinsal et al [9], 2018 | 7 | 29 | 45,X[28.3]/46,XY[71.7] | Primary sterility | Male/left and right TV: 6 mL, 3.2 mL. | 165 | 14.26 | 31.31 | 3.26 | 20.64 | AZF(b+c) | + |
| | 8 | 24 | 45,X[66]/46,XY[34] | Primary sterility | Male/left and right TV: 18 mL, 12 mL. | 158 | 19.7 | 15.15 | 3.83 | AZF | + |
| | 9 | 26 | 45,X[70]/46,XY[30] | Primary sterility | Male/left and right TV: 9 mL, 9 mL. | 178 | 7.5 | 9.8 | 6.74 | AZF | + |
| | 10 | 29 | 45,X[40]/46,XY[60] | Primary sterility | Male/left and right TV: 7 mL, 7 mL. | 156 | 7.97 | 20.4 | 7.44 | 48.6 | AZF | + |
| | 11 | 40 | 45,X[30]/46,XY[70] | Primary sterility | Male/left and right TV: 14 mL, 14 mL. | 165 | 9.96 | 22.29 | 3.78 | No missing | + |
| | 12 | 26 | 45,X[55]/46,XY[45] | Primary sterility | Male/left and right TV: 12 mL, 14 mL. | 165 | 7.96 | 6.91 | 3.96 | 19.01 | No missing | + |
| | 13 | 29 | 45,X[66]/46,XY[34] | Primary sterility | Male/left and right TV: 8 mL, 10 mL. | 164 | 13.2 | 28 | 4.00 | 40.8 | AZF(b+c) | + |
| | 14 | 33 | 45,X[73]/46,XY[27] | Primary sterility | Male/left and right TV: 18 mL, 18 mL. | 160 | 3.8 | 11.12 | 2.52 | 18.63 | No missing | + |
| | 15 | 41 | 45,X[45]/46,XY[55] | Primary sterility | Male/left and right TV: 8 mL, 7 mL. | 155 | 19.25 | 25.16 | 1.68 | 72.06 | No missing | + |
| Lindhardt et al [10], 2012 | 16 | 20 | 45,X[63]/46,Xdel(Y)(q12)[37] | Delayed puberty | Male/left and right TV: 12 mL, 15 mL. | 162 | AZF(b+c) | + |
| | 17 | 28 | 45,X[20]/46,XY[80] | Infertility | Male/left and right TV: 2 mL, 0 mL. | 160 | No missing | + |
| | 18 | 33 | 45,X[55.6]/46,XY[44.4] | Infertility | Male/left and right TV: 12 mL, 6 mL. | 160 | AZF(b+c) | + |
| | 19 | 49 | 45,X[33.3]/46,Xidi(Y)(p)[66.7] | Infertility | Male/left and right TV: 4 mL, 4 mL. | 160 | AZF(a+b+c) | + |
Wu YH et al. SRY-negative 45,X/46,XY mosaicism karyotype

Ren et al[11], 2015

| No | Age | Karyotype | Clinical Presentation | Testosterone | LH | FSH | EMS | AZO | AZF | AZF(b+c) |
|----|-----|-----------|----------------------|--------------|----|-----|-----|-----|-----|---------|
| 20 | 27  | 45,X[50]/46,XY[50] | Primary infertility | N            |     |     |     | Azoospermia |     |         |

Rosa et al[6], 2014

| No | Age | Karyotype | Clinical Presentation | Testosterone | LH | FSH | EMS | AZO | AZF | AZF(b+c) |
|----|-----|-----------|----------------------|--------------|----|-----|-----|-----|-----|---------|
| 21 | 24  | 45,X[33]/46,XY[67] | Primary infertility | Azoospermia |     |     | EMS 12 |     |     |         |

Ketheeswaran et al[13], 2019

| No | Age | Karyotype | Clinical Presentation | Testosterone | LH | FSH | EMS | AZO | AZF | AZF(b+c) |
|----|-----|-----------|----------------------|--------------|----|-----|-----|-----|-----|---------|
| 22 | 39  | 45,X[61]/46,XY[94], buccal mucosal cells | Primary infertility | N            |     |     |     | Azoospermia |     |         |

Reddy et al[14], 1998

| No | Age | Karyotype | Clinical Presentation | Testosterone | LH | FSH | EMS | AZO | AZF | AZF(b+c) |
|----|-----|-----------|----------------------|--------------|----|-----|-----|-----|-----|---------|
| 23 | 37  | 45,X[47]/46,XY[53], testis | Infertility | Azoospermia | Male/atrophic testis |     |     |     |         |

Gassó-Matoses et al[15], 1992

| No | Age | Karyotype | Clinical Presentation | Testosterone | LH | FSH | EMS | AZO | AZF | AZF(b+c) |
|----|-----|-----------|----------------------|--------------|----|-----|-----|-----|-----|---------|
| 24 | 33  | 45,X[85]/46,XY[15], testis | Infertility | Azoospermia | Bilateral small testis | 10 | 17.2 | 430 |         |

Li et al[16], 2013

| No | Age | Karyotype | Clinical Presentation | Testosterone | LH | FSH | EMS | AZO | AZF | AZF(b+c) |
|----|-----|-----------|----------------------|--------------|----|-----|-----|-----|-----|---------|
| 25 | 23  | 45,X[19]/46,XY[81] | Primary infertility | Azoospermia |    |     |     | Azoospermia |     |         |
| 26 | 25  | 45,X[15]/46,XY,Yq-[85] | Primary infertility | Oligozoospermia |    |     |     | Azoospermia |     |         |
| 27 | 30  | 45,X[15]/46,XY[85] | Primary infertility | Azoospermia |    |     |     | Azoospermia |     |         |
| 28 | 24  | 45,X[56]/46,X,dic(Y)[44] | Primary infertility | Azoospermia |    |     |     | Azoospermia |     |         |
| 29 | 36  | 45,X[55]/46,XY,Yp+[45] | Primary infertility | Azoospermia |    |     |     | Azoospermia |     |         |
| 30 | 26  | 45,X[22]/46,X,dic(Y)[78] | Primary infertility | Azoospermia |    |     |     | Azoospermia |     |         |

Kilic et al[17], 2010

| No | Age | Karyotype | Clinical Presentation | Testosterone | LH | FSH | EMS | AZO | AZF | AZF(b+c) |
|----|-----|-----------|----------------------|--------------|----|-----|-----|-----|-----|---------|
| 31 | 28  | 45,X[5]/46,XY[95] | Infertility | Azoospermia | Testicular diameters: 3 cm × 3.5 cm | 16 | 21 | 2.21 | Azoospermia |     |
| 32 | 25  | 45,X[20]/46,XY[80] | Primary infertility | Oligozoospermia | Testicular diameters: 3.2 cm × 2.5 cm | 18 | 26 | 2.8 | Azoospermia |     |
| 33 | 32  | 45,X[45]/46,XY[55] | Primary infertility | Azoospermia | Testicular diameters: 4.0 cm × 2.8 cm | 17 | 23 | 2.77 | Azoospermia |     |

Valetto et al[18], 2004

| No | Age | Karyotype | Clinical Presentation | Testosterone | LH | FSH | EMS | AZO | AZF | AZF(b+c) |
|----|-----|-----------|----------------------|--------------|----|-----|-----|-----|-----|---------|
| 34 | 41  | 45,X[71]/46,X,dic(Yp)[26]/46,XY[3] | Infertility | Azoospermia |    |     |     | Azoospermia |     |         |

AZO: Azoospermia; E2: Estrogen; EMS: External masculinization score; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; N: Normal; Oligozoospermia; T: Testosterone; TV: Testicular volume.

SRY gene, beginning at about 6 wk post-implantation[21,22]. On the other hand, a deletion mutant of the SRY gene can affect masculinization and may cause 46,XY female sex reversal[23]. Even though the SRY gene is critical in the initiation of testis determination, some of the SRY-negative phenotype may show the typical male phenotype, as seen in the present patient. Our findings further suggest that testicular formation and development occurs via a comprehensive process jointly regulated by other key genetic factors or environmental factors in addition to the SRY gene. Several hypotheses have attempted to explain rationally the formation of testicles in SRY-negative males, such as the possible predominance of the 46,XY cell line in the gonads[23], hidden mosaicism for a Y-derivative material, or mutation of an autosomal or X-chromosomal gene downstream from SRY. In addition, studies have shown that
overexpression of the SOX9 gene can initiate testis differentiation when the SRY gene is silenced. This result indicates that the SOX9 gene, as downstream factor of SRY, plays an important role in the sex determination process\(^{26-30}\). In the present study, the patient refused to undergo genetic analysis of genital skin and gonadal fibroblasts as well as further examinations, and thus, the exact mechanism of his gender development could not be explained.

The AZF gene is located on the long arm of the Y chromosome, and its locus contains protein-coding genes essential for spermatogenesis\(^{31}\). Y chromosome microdeletion, which might result from Y-chromosome instability and lead to 45,X karyotype, is one of the key causes of severe male infertility. Clinical statistics indicate that 10%-15% of azoospermic patients and 5%-10% of severe oligospermia patients have Y chromosome microdeletion\(^{26,32}\). Studies have reported that deletion of large and submicroscopic Y chromosome may lead to an increased proportion of 45,X abnormal karyotype cells among sperm cells and lymphocytes\(^{33}\). In the present case, the patient had deletions of AZF(a+b+c) regions in addition to 45,X/46,XY mosaicism, which may explain the high percentage of 45,X cells and azoospermia.

From the perspective of oncology, gonadal germ cell tumors are detected at an elevated frequency among patients with a 45,X/46,XY karyotype and malformations of the external genitalia\(^{34}\). The risk for malignant transformation is reportedly about 10% and increases with age in patients with 45,X/46,XY gonadal dysgenesis\(^{29,35}\). It is worth noting that the prognoses of 45,X/46,XY patients with an apparently normal male phenotype until adulthood and patients who are born with severe genital anomalies show no statistical difference\(^{36}\). Therefore, adult patients with the 45,X/46,XY mosaic karyotype must be followed up for life, with particular focus on testicular function and testicular tumor screening.

**CONCLUSION**

In conclusion, we have described the clinical and genetic findings for a male with complete virilization in SRY-negative 45,X/46,XY mosaicism. We believe that a perfect karyotype analysis and Y-microdeletion analysis could not only reveal the cause of male infertility, in order to facilitate reproductive counseling, but also provide prognostic information for patients with specific karyotypes.

**REFERENCES**

1. Chang HJ, Clark RD, Bachman H. The phenotype of 45,X/46,XY mosaicism: an analysis of 92 prenatally diagnosed cases. *Am J Hum Genet* 1990; 46: 156-167 [PMID: 2294747]

2. Layman LC, Tho SP, Clark AD, Kulharya A, McDonough PG. Phenotypic spectrum of 45,X/46,XY males with a ring Y chromosome and bilaterally descended testes. *Fertil Steril* 2009; 91: 791-797 [PMID: 18555994 DOi: 10.1016/j.fertnstert.2007.12.078]

3. Telvi L, Lebar A, Del Pino O, Barbet JP, Chaussain J. 45,X/46,XY mosaicism: report of 27 cases. *Pediatrics* 1999; 104: 304-308 [PMID: 10429013 DOi: 10.1542/peds.104.2.304]

4. Zeng YT, Ren ZR, Zhang ML, Huang Y, Zeng FY, Huang SZ. A new de novo mutation (A113T) in the HMG box of the SRY gene leads to XY gonadal dysgenesis. *J Med Genet* 1993; 30: 655-657 [PMID: 8105086 DOi: 10.1136/jmg.30.8.655]

5. Goodfellow PN, Lovell-Badge R. SRY and sex determination in mammals. *Annu Rev Genet* 1993; 27: 71-92 [PMID: 8122913 DOi: 10.1146/annurev.ge.27.120193.000443]

6. Zhang YS, Dai RL, Wang RX, Zhang HG, Chen S, Liu RZ. Analysis of Y chromosome microdeletion in 1738 infertile men from northeastern China. *Urology* 2013; 82: 584-588 [PMID: 23769119 DOi: 10.1016/j.urology.2013.04.017]

7. Mohammadpour Lashkari F, Sadighi Gilani MA, Ghaheri A, Zamanian MR, Borjian Boroujeni P, Mohseni Meybodi A, Sabbaghian M. Clinical aspects of 49 infertile males with 45,X/46,XY mosaicism karyotype: A case series. *Andrologia* 2018; 50: e13009 [PMID: 29527714 DOi: 10.1111/and.13009]

8. Wu Q, Wang C, Shi H, Kong X, Ren S, Jiang M. The Clinical Manifestation and Genetic Evaluation in Patients with 45,X/46,XY Mosaicism. *Sex Dev* 2017; 11: 64-69 [PMID: 28214852 DOi: 10.1159/000455260]

9. Akinsal EC, Baydilli N, Bayramov R, Ekmeckioglu O. A Rare Cause of Male Infertility: 45,X/46,XY Mosaicism. *Urol Int* 2018; 101: 481-485 [PMID: 29161714 DOi: 10.1159/000484615]

10. Lindhardt Johansen M, Hagen CP, Rajpert-De Meyts E, Kjærgaard S, Petersen BL, Skakkebæk NE, Main KM, Juul A. 45,X/46,XY mosaicism: phenotypic characteristics, growth, and reproductive function--a retrospective longitudinal study. *J Clin Endocrinol Metab* 2012; 97: E1540-E1549 [PMID: 22605431 DOi: 10.1210/jc.2012-1388]
Zenaty D, Nicolino M, Baron S, Metz-Blond C, Naud-Saudreau C, Dupuis C, Léger J, Siffroi JP, Dumeige L

Huang H

Liu AX

Müller J

Suganthi R

Vogt PH

Kilic S

Valetto A, Bertini V, Rapalini E, Baldiottini F, Di Martino D, Simi P. Molecular and cytogenetic characterization of a rearrangement of the Y chromosome in an azospermic man. *Fertil Steril* 2004; 81: 1388-1390 [PMID: 15136108 DOI: 10.1016/j.fertnstert.2003.09.069]

Martinerie L, Morey Y, Gay CL, Pienkowski C, de Kerdanet M, Cabrol S, Lecointre C, Coutant R, Baron S, Collé M, Braunier R, Thibaud E, Leger J, Nihilou-Fekte C, Bouvattier C. Impaired puberty, fertility, and final stature in 45,X/46,XY mixed gonadal dysgenetic patients raised as boys. *Eur J Endocrinol* 2012; 166: 687-694 [PMID: 22236473 DOI: 10.1530/EJE-11-0756]

Tosson H, Rose SR, Gartner LA. Description of children with 45,X/46,XY karyotype. *Eur J Pediatr* 2012; 171: 521-529 [PMID: 21978000 DOI: 10.1007/s00431-011-1600-9]

Sinclair AH, Berta P, Palmer MS, Hawkins JR, Griffiths BL, Smith MJ, Foster JW, Frischauf AM, Lovell-Badge R, Goodfellow PN. A gene from the human sex-determining region encodes a protein capable of homology to a conserved DNA-binding motif. *Nature* 1990; 346: 240-244 [PMID: 1695712 DOi: 10.1038/346240a0]

Koopman P, Gubbay J, Vivian N, Goodfellow P, Lovell-Badge R. Male development of chromosomally female mice transgenic for Sry. *Nature* 1991; 351: 117-121 [PMID: 2030730 DOI: 10.1038/35117a0]

Akinsal EC, Baydilli N, Demirtas A, Saatci C, Ekmeckioğlu O. Ten cases with 46,XX testicular disorder of sex development: single center experience. *Int Braz J Urol* 2017; 43: 770-775 [PMID: 28379671 DOI: 10.1590/S1677-5338.IBJU.2016.0505]

Kent J, Wheatley SC, Andrews JE, Sinclair AH, Koopman P. A male-specific role for SOX9 in vertebrate sex determination. *Development* 1996; 122: 2813-2822 [PMID: 8778575]

Huang B, Wang S, Ning Y, Lamb AN, Bartley J. Autosomal XX sex reversal caused by duplication of SOX9. *Am J Med Genet* 1999; 87: 349-353 [PMID: 10588843 DOI: 10.1002/(sici)1096-8628(19991203)87:4<349::aid-ajmg13>3.0.co;2-n]

Vidal VP, Chaboisier MC, de Rooij DG, Scheidl A. Sox9 induces testis development in XX transgenic mice. *Nat Genet* 2001; 28: 216-217 [PMID: 11431689 DOI: 10.1038/90046]

Vogt PH. AZF deletions and Y chromosomal haplogroups: history and update based on sequence. *Hum Reprod Update* 2005; 11: 319-336 [PMID: 15890785 DOI: 10.1093/humupd/dmi017]

Suganthi R, Vijesh VV, Vandana N, Fathima Ali Benazir J. Y chromosomal microdeletion screening in the workup of male infertility and its current status in India. *Int J Fertil Steril* 2014; 7: 253-266 [PMID: 24520494]

Siffroi JP, Le Bourhis C, Krausz C, Barbaxus S, Quintana-Murci L, Kanafani S, Roubia H, Bujan L, Bourouiltou G, Seifer I, Boucher D, Fellous M, M reelection K, Dadoune JP. Sex chromosome mosaicism in males carrying Y chromosome long arm deletions. *Hum Reprod* 2000; 15: 2559-2562 [PMID: 11098026 DOI: 10.1093/humrep/15.12.2559]

Müller J, Ritzén EM, IVarsson SA, Raitjé-De Meets E, Norjavaara E, Skakkebaek NE. Management of males with 45,X/46,XY gonadal dysgenesis. *Horm Res* 1999; 52: 11-14 [PMID: 10640893 DOI: 10.1159/000015064]

Liu AX, Shi HY, Cai ZJ, Liu A, Zhang D, Huang HF, Jin HM. Increased risk of gonadal malignancy and prophylactic gonadectomy: a study of 102 phenotypic female patients with Y chromosome or Y-derived sequences. *Hum Reprod* 2014; 29: 1413-1419 [PMID: 24826988 DOI: 10.1093/humrep/deu109]

Huang H, Wang C, Tian Q. Gonadal tumour risk in 292 phenotypic female patients with disorders of sex development containing Y chromosome or Y-derived sequence. *Clin Endocrinol* 2016; 86: 621-627 [PMID: 27862157 DOI: 10.1111/cen.13255]

Dumeige L, Chatelais L, Bouvattier C, De Kerdanet M, Huyen C, Estela B, Samara-Boustani D, Zenaty D, Nicolino M, Baron S, Metz-Blond C, Naud-Sauldraux C, Dupuis C, Léger J, Siffroi JP, Donadille B, Christin-Maire S, Carel JC, Coutant R, Martinerie L. Should 45,X/46,XY boys with no WJCC | https://www.wjw.net 6387 December 26, 2020 | Volume 8 | Issue 24
or mild anomaly of external genitalia be investigated and followed up? Eur J Endocrinol 2018; 179: 181-190 [PMID: 29975376 DOI: 10.1530/EJE-18-0309]
