The Y chromosome: male reproduction and beyond

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The crucial role of Y chromosome genes in male gonadal determination and reproductive fitness has been recognized for decades. Y chromosome microdeletions are the most common molecular genetic causes of azoospermia and severe spermatogenic impairment. Since the late 1990s, screening for these microdeletions has become a routine part of the diagnostic work-up of severe male factor infertility. In this article, we provide a concise overview of the Y chromosome's structure and gene content. We describe its clinically relevant alterations, detectable through karyotyping or molecular genetic tools, with a focus on their phenotypic impact and significance for genetic counseling. Finally, we discuss the broader implications of Y chromosome variations on health conditions beyond male infertility. (Fertil Steril® 2025;123:921–32. ©2025 by American Society for Reproductive Medicine.)

Key Words: Y chromosome, male infertility, genetics, AZF deletion, azoospermia

Y CHROMOSOME AND ITS ROLE IN MALE FITNESS

After a troubled evolutionary trajectory, the sex chromosomes have diverged significantly, with the Y chromosome—once equal in size to the X—ultimately becoming the smallest of the 23 chromosomes in humans. Indeed, its evolutionary history is marked by significant degradation and gene loss, retaining only a small fraction of the genes originally carried by the ancestral autosomes, from which the sex chromosomes evolved about 300 million years ago (1).

Over two decades ago, based on the rate of loss of five genes per million years and the Y chromosome vulnerability to genetic drift and hitchhiking, it was predicted that it could disappear within the next 5 to 10 million years (2). However, with the assembly of the Y chromosome sequences and the discovery of their structural organization and gene content, it became clear—quoting an editorial in *Cell*—that "rumours of its demise have been greatly exaggerated" (3, 4). Indeed, this chromosome disposes of a set of seven regions, referred to as the ampliconic regions, containing several testis-specific multicopy genes, with predicted role in male reproduction (3). Thanks to this structural peculiarity, a mechanism known as "intrachromosomal gene conversion" may occur, helping to preserve these genes from decay by allowing the correction of spontaneous mutations, thereby preventing the formation of pseudogenes. The maintenance of essential fertility genes will therefore enable the Y chromosome to persist in some form, even after millions of years. Unfortunately, the ampliconic structure is not solely a "tool" for survival; it is a "double-edged sword," because it also confers fragility, leading to the loss of genetic material through deletions, which results in the loss of genes essential for spermatogenesis.

The large majority of genes involved in spermatogenesis are located on the long arm of the Y chromosome, whereas the master gene (*SRY*) for testis determination is located on Yp, in the close proximity of the pseudoautosomal region 1 (3, 5). *SRY* is a transcription factor and the initiator of a cascade of gene activation events that culminate in Sertoli cell differentiation and the subsequent organization of the testicular tissue. The absence of this gene results in sex reversal, leading to a 46,XY female, whereas its acquisition by the X chromosome during meiosis, causes the de la Chapelle syndrome, resulting in a 46,XX male.

The Yp pericentromeric region contains a gene array, called *TSPY*. *TSPY1* copy number varies between 11–76 in the general population (6–8). Only a few studies have investigated the potential influence of *TSPY* on spermatogenesis, yielding conflicting results (7–11). Given the variability in *TSPY1* copy number across different Y haplogroups (12), it is crucial to match cases and controls for Y haplogroups to minimize bias. The first study to account for Y-haplogroup distribution between cases and controls identified a positive correlation between sperm count and *TSPY1* copy number (7), a

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finding later confirmed in an expanded study population (10). Following the Italian study, a large-scale Chinese study further validated this correlation, demonstrating a positive association between *TSPY1* copy number and sperm production (sperm concentration and total sperm count) in 898 men (11). Overall, *SRY*, Yq-linked genes, and most likely *TSPY*, play a significant role in male reproductive fitness.

CLINICALLY RELEVANT MICROSCOPICALLY DETECTABLE Y CHROMOSOME ALTERATIONS

In 1976, Tiepolo and Zuffardi (13) first provided cytogenetic evidence for the existence of a region in Yq11 essential for spermatogenesis, observing *de novo* terminal deletions (Yq) in azoospermic patients. The hypothetical region was termed the "azoospermia factor" (AZF) region, and its absence was thought to be responsible for the observed infertile phenotype.

Besides large terminal deletions, other alterations, visible at karyotype analysis, are Y isochromosome (isoY) and isodicentric Y chromosomes (idicY). Y isochromosome results from an improper centromere division which leads to an abnormal chromosome with two copies of either the short or the long arm. Y isodicentric chromosome originates from an aberrant interchromatid crossing-over resolution of double-strand breaks between palindrome sequences, followed by the duplication of the centromere. Due to the presence of most MSY (male-specific region of the Y) palindromes on the long arm (Yq), the recombination typically results in the formation of idic (Yp) chromosomes with two copies of the short arm, two centromeres and lacking different sizes of Yq sequences depending on the breakpoint (14).

In both 46,XYq- and 46,X,idic(Yp) cases, the testis phenotype can range from Sertoli cell-only phenotype to maturation arrest or hypospermatogenesis, depending on the Yq breakpoints i.e., the amount of DNA lost from the Yq (15–18). Whereas, the iso (Yp), which lacks the entire long arm, consistently results in Sertoli cell-only phenotype (19) (Table 1) (20).

Large Y chromosome rearrangements, as terminal Yq deletions, isoY and idicY chromosomes, are highly unstable and can be lost through cell divisions, leading to mosaicism, with a 45,XO cell line. Depending on the grade of mosaicism, the clinical features can range from normally virilized azoospermic men to individuals with ambiguous external genitalia or Turner's syndrome (14, 21–23). The presence of 45,XO mosaicism in an azoospermic man carrying Yq- or idicY is considered a negative predictor for testicular sperm retrieval (24).

Another cytogenetically detectable Y chromosome alteration is the 47,XYY karyotype, also called Jacobs syndrome. The 47,XYY male is a relatively frequent karyotype anomaly, occurring in 1:1000 male births, and it is observed among infertile men more frequently than in new-born males (0.26% and 0.07%, respectively) (25).

Patients with this karyotype may show a wide spectrum of semen phenotype, ranging from oligo/azoospermia to normozoospermia (26, 27). Various investigators have hypothesized that impaired spermatogenesis in these men is probably because of a high rate of germ cell degeneration induced by the persistence of the extra Y chromosome during meiosis (28–30). However, the fact that normozoospermia has also been reported in 47,XYY males suggests that the clinical impact of this aneuploidy remains unclear, as does the indication for sperm fluorescence in situ hybridization analysis before in vitro fertilization

CLINICALLY RELEVANT SUBMICROSCOPIC ALTERATIONS OF THE Y CHROMOSOME

The history of discovering the association between Y microdeletions and spermatogenic failure

The initial assumption by Tipeolo and Zuffardi (13) that AZF represented a single Y-linked gene was overturned when Vogt et al. (31), with the use of molecular genetic tools, was were able to analyze the Yq in a large group of azoospermic men.

TABLE 1

Reproductive phenotypes of the main microscopic or submicroscopic Y chromosome alterations.

Genetic test	Y chromosome alterations	Reproductive phenotypes
Karyotype	46,XYq-	SCO or MA or HS depending on the deletion breakpoint
	46,X,idic(Yp)	
	46,X,i(Yp)	SCO
	46,XYq-/45,XO	Variable phenotype depending on the grade of mosaicism
	46,X,idic(Yp)/45,XO	
	46X,i(Yp)/45XO	
	47,XYY	From oligo/azoospermia to normozoospermia
Deletion screening based on PCR +/–[a]	Y chromosome microdeletions (complete AZFa, AZFb or AZFc)	SCO (AZFa), MA (AZFb), azoo/ severe oligozoospermia (AZFc)
	Partial AZFa (not removing *DDX3Y*)	From oligo to normozoospermia
	Partial AZFb	Severe OAT or azoospermia
	gr/gr deletion	From oligo/azoospermia to normozoospermia

Note: AZF = azoospermia factor; HS = hypospermatogenesis; MA = maturation arrest; OAT = oligoasthenoteratozoospermia, SCO = Sertoli-cell-only phenotype.
[a] According to European Academy of Andrology (EAA)/European Molecular Genetics Quality Network (EMQN) guidelines (20).

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He noticed that Y chromosome deletions follow a certain pattern, with three recurrently deleted nonoverlapping subregions in proximal, middle, and distal Yq11, designated "AZFa," "AZFb," and "AZFc," respectively (31). Because these deletions cannot be observed under the microscope, they were referred to as "microdeletions". Further refining of the Y chromosome sequence revealed that the AZFb and AZFc regions partially overlap by 1.5Mb (32, 33).

Once the Y structure has been defined, the mechanism responsible for the deletions has also been identified (3, 33). These deletions occur between repeated, homologous sequences with the same orientation situated at the border of the AZF regions. This high sequence similarity can lead to nonallelic homologous recombination (NAHR).

Soon after the publication of the article by Vogt et al. (31), many laboratories started to screen for deletions in infertile and fertile cohorts. Thanks to a large survey, it became clear that these deletions were not exclusively associated with azoospermia but also with severe oligozoospermia (34).

Some earlier studies questioned the diagnostic value of this genetic test, reporting AZFc deletions in fertile controls, although their sperm count was unknown (35). Indeed, fertility is not synonymous with normozoospermia; therefore, without information on the carriers' sperm count, the clinical implications of AZF screening remained unresolved. Finally, a multicenter double-blind study conclusively demonstrated that complete AZF deletions are incompatible with normal sperm parameters (36). Given the well-established cause-effect relationship between complete AZF deletions and impaired sperm production, Y chromosome microdeletion (YCM) screening has become a fundamental diagnostic tool in the clinical evaluation of severe male factor infertility. Indications for testing have been defined by various societies; according to the European Academy of Andrology (EAA)/European Molecular Genetics Quality Network (EMQN) guidelines, azoospermic and severe oligozoospermic men (<5 million spermatozoa/ml) should be tested (20). A similar cut-off is recommended by the European Association of Urology, according to which testing is suggested for men with sperm concentrations between 1 and 5 million sperm/mL, although it is mandatory for men with concentrations below 1 million sperm/mL (37). The American Urological Association guidelines recommend YCM analysis for men with azoospermia or with a sperm concentration $\leq$1 million sperm/mL, similar to the European Association of Urology, but specifically when accompanied by elevated follicle-stimulating hormone (FSH) and testicular atrophy (38). However, limiting testing to patients with these specific characteristics may result in overlooking individuals with a complete AZFb deletion, as well as many men with an AZFc deletion. Notably, AZFb deletion typically causes spermatocytic arrest, which is associated with normal testicular volume and normal FSH levels. Similarly, patients with an AZFc deletion often exhibit normal FSH levels and testicular hypotrophy rather than atrophy (39). The highest frequency of AZF deletions is found among azoospermic men (5%–10%) followed by a 2%–5% frequency in severe oligozoospermic patients (mostly those with <2 million spermatozoa per ml) (40).

The AZF regions and their gene content

Despite the name "microdeletion," these deletions remove millions of base pairs (Mb) and their size range from 0.8 Mb to 7.7 Mb (Fig. 1). These regions contain single and multicopy genes (most of them overexpressed or exclusively expressed in the testis) and two gene families with no or unknown protein coding potential: i) *TTTY* (testis-specific transcription Y), non-protein coding with testis-specific expression and ii) *CY-orf* family, encoding proteins with unknown functions (3).

There are seven ampliconic regions on the Y chromosome which contain eight massive palindromes, six of which contain testis genes, and five sets of more widely spaced inverted repeats (3). The smallest region, called AZFa, is situated in the proximal part of Yq11. It contains three single copy genes: *USP9Y* (formerly *DFFRY*), *DDX3Y* (formerly *DBY*), and *UTY* (41, 42). Complete AZFa deletion originates from a NAHR process between two homologous HERV15 proviruses sequences and removes ~792 kb (43–45).

AZFb locus is located at the center of Yq11 and partially overlaps with AZFc. This region contains several single copy genes as well as multicopy gene families. Single copy genes include *EIF1AY*, *RPS4Y2*, and *KDM5D* whereas multicopy gene families are *XKRY*, *HSFY*, *RBMY1*, *PRY*, *BPY*, *CDY* and *DAZ*. Among these, one copy of *CDY* and *BPY* and two copies of *DAZ* are shared with the AZFc region. Complete AZFb deletion occurs after a homologous recombination between palindrome P5 and the proximal arm of palindrome P1 and removes 6.2 Mb (33).

The AZFc locus is located at the distal end of Yq11 and contains five multicopy genes: *BPY* (2 copies), *CDY* (2 copies) *DAZ* (4 copies), *CSPG4LY* (2 copies) and *GOLGA2LY* (2 copies). Its complete deletion results from a NAHR between the b2 and b4 amplicons, in palindromes P3 and P1 respectively, removing 3.5 Mb (32).

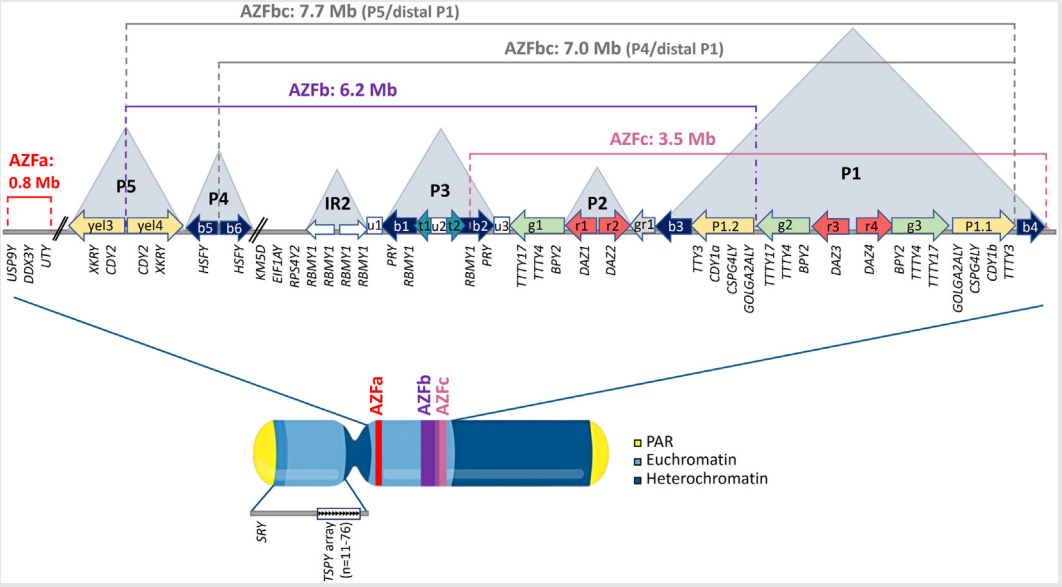
Finally, the so-called AZFbc deletion has two different potential breakpoints: between P5/distal P1; between P4/distal P1 (this is not generated through NAHR) (33). These are the largest deletions, removing 7,7 Mb with 42 gene copies in case of P5/distal P1 and 7.0 Mb with 38 gene copies in case of P4/distal P1.

Phenotypic consequences of AZF deletions and prognostic value of AZF deletion screening

The most frequent complete deletion is the AZFc deletion (70%–80%) followed by AZFa (0.5%–9%), AZFb (1%–7%), and AZFbc (1%–20%) (20). The most commonly deleted region is the AZFc region, which is associated with a variable semen phenotype, ranging from azoospermia to severe oligozoospermia (34, 40, 46). Although the deletion size is consistent across different individuals, the reasons behind the distinct semen phenotypes remain unclear. One possible explanation could be the age of the subjects. For example, in a study where AZFc deletion was transmitted from father to sons, the father was azoospermic at the time of genetic diagnosis (47). This aligns with observations of progressive depletion of the germinal epithelium over time (48).

In contrast, complete AZFa or AZFb deletions lead to azoospermia. The genotype-phenotype correlation observed

FIGURE 1



Schematic representation of the Y chromosome and the different regions/genes involved in spermatogenesis. *Triangles* represent the palindromes in AZF regions. The *arrows* with the same color represent repeated homologous sequences, which may undergo NAHR. AZF = azoospermia factor; NAHR = non-allelic homologous recombination; PAR = pseudoautosomal region.

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in deletion carriers indicates that both the AZFa and AZFb regions contain essential genes for spermatogenesis, whereas the AZFc genes mainly affect the efficiency of spermatogenesis (Table 1). As shown above, in each AZF region multiple genes are present and their removal en block does not allow us to understand their exact role in spermatogenesis and to define which gene is responsible for the AZF phenotypes. The AZFa region is the only one where a recent article has formally identified which of the three genes is responsible for the testis phenotype (49). Early studies exploring the role of AZFa genes, using the polymerase chain reaction (PCR) plus/minus method, already provided evidence that the isolated removal of *USP9Y* does not result in the AZFa phenotype (50). This gene was considered as a fine tuner rather than being essential for spermatogenesis and a major role for *DDX3Y* was already predicted many years ago (51). However, this hypothesis was only confirmed in 2023, after the identification of four distinct loss-of-function variants in four azoospermic men through whole-exome sequencing (49). Three of these patients underwent testicular sperm extraction (TESE), revealing a Sertoli-cell-only phenotype, thereby confirming that the lack of *DDX3Y* is the underlying cause of spermatogenic failure in men with AZFa deletion (49).

In addition to the varying semen phenotypes, testicular phenotypes also change depending on the type of deletion. The complete removal of the AZFa region leads to Sertoli cell-only phenotype whereas the complete removal of the AZFb region leads to spermatogenic arrest. In both cases, TESE is not recommended because the likelihood of finding spermatozoa in the testis is virtually zero both with conventional TESE or microdissection TESE (52–54).

In azoospermic men carrying an AZFc deletion (b2–b4), which is typically associated with a milder semen phenotype, the testicular phenotype also appears to be less severe, because TESE is successful in approximately 50% of cases, on the basis of an average of 32 studies (54). However, this success rate is highly variable across these studies, ranging from 15% to 71% and it can be substantially reduced in case of a mosaicism for 45,XO cell line (24). For this reason, it is advised to perform a search for mosaicism by analyzing a higher number of metaphases (possibly counting 100 metaphases) than the one performed for the standard karyotype analysis (20).

Rarely, partial AZFa or AZFb deletions have also been reported in the literature with variable semen phenotypes. Partial AZFa deletions that do not affect the *DDX3Y* gene are compatible even with normozoospermia (51, 55), whereas partial AZFb deletions have been observed in men with oligozoospermia or azoospermia (56).

Analysis of the AZF deletions: technical aspects and the importance of participating in an external quality control program

Y microdeletions testing not only has a diagnostic value but also offers prognostic information, influencing pre-TESE decision making. Given its prognostic value, it is of fundamental importance to properly perform the analysis with the use of the appropriate markers and define the extension of these deletions before TESE. In the past, several papers reported "patchy" deletions, i.e., single sequence tag sites missing from more than one region. Such deletions are PCR artifacts

and are especially frequent when the laboratory uses kits based on too many markers in multiplex PCR without the possibility to confirm the deletion in simplex PCR.

Some kits refer to an AZFd region, defined on the putative absence of sY152, but this region does not exist. Similar to the sY254 and sY255 markers recommended by the guidelines, sY152 also maps to the DAZ genes (which have 4 copies in the reference sequence). Therefore, the isolated absence of sY152 is not possible when the other *DAZ* markers are present.

According to the EAA/EMQN guidelines AZF deletion screening is based on a multiplex PCR plus/minus analysis, followed by an obligatory deletion extension analysis (Table 2). In the latest edition of the guidelines, some previously considered as interchangeable extension markers became essential to provide clinically relevant information (20). For instance, for the definition of the distal part of the AZFb deletion it is essential to test for sY1192 because its presence would change the TESE prediction from virtually zero to low chance to find spermatozoa in the testis. In addition, for defining the proximal border of an AZFa deletion, it is now recommended to use only sY1064, because a complete AZFa deletion can still be compatible with the presence of the marker sY83, previously defined as interchangeable. It is highly recommended to follow the guidelines and participate in external quality programs to accurately detect and interpret AZF deletions (20). An annual external quality assessment program for laboratories performing AZF diagnostics has been established by the EMQN/EAA since more than 20 years ago in Europe and it remains the only AZF scheme in the world (www.emqn.org). Three DNA samples are distributed by the organizers and the laboratories are asked to handle them in the same way as patients' samples. The results are then evaluated by at least two independent reviewers and both genotyping and interpretation of the results are scored (20).

Despite the simplicity of the test, still about 1%–2% of laboratories fail to define the correct genotype. Therefore, clinicians should pay attention to whether the laboratory participates in the external quality control program.

The partial AZFc deletions: the gr/gr deletion is a genetic risk factor for impaired spermatogenesis

Within the AZFc locus, because of the presence of many NAHR substrates, many partial deletions (gr/gr, b2/b3, b1/b3) can be generated, each removing approximately half of the gene content (57–59). Among AZFc partial deletions, the gr/gr is the most clinically relevant (57). This partial deletion does not completely eliminate any testis-specific gene but rather reduces their copy number. All genes affected by this microdeletion—*CDY1*, *DAZ* and *BPY2*—are involved in male germ cell development. The gr/gr deletion has been detected in a wide spectrum of semen phenotypes (from azoospermia to normal sperm count). It appears that its impact on spermatogenesis varies among different populations, showing the highest risk for impaired sperm production among men of Caucasian ethnicity (60, 61). Results from five meta-analyses (60, 62–65) and a large multi-ethnic study (66) demonstrated that its frequency is significantly higher in infertile men, representing a risk factor for spermatogenic impairment. The estimated risk ranges from a 2-fold increase in the multi-ethnic study (66) to a 4-fold increase in a study including Italian and Spanish individuals (67).

Testing for gr/gr deletion is optional in clinical practice, because, although it is a genetic risk factor, it lacks clear cut diagnostic value. Given the evidence suggesting that the gr/gr deletion (and also b2/b3 deletion) can expand and result in a complete AZFc deletion when transmitted to offspring (68, 69), its clinical impact may be significant for future generations. It could function as a pre-mutation, potentially leading to a complete AZFc deletion and causing spermatogenic failure in male descendants.

However, Mau Kai et al. (70) reported twelve male children born to fathers carrying gr/gr deletion and all of them appear to share the same paternal deletion. Given the limited number of cases in literature, further studies are needed to better understand the extent of the associated risk. Literature reports data from 71 children born via assisted reproductive technology to fathers with a gr/gr deletion, indicating no major congenital anomalies (70–72).

The AZF deletions and genetic counseling

Complete or partial AZFc deletions and partial AZFa or AZFb deletions are compatible with the presence of spermatozoa either in the ejaculate or in the testis. In carriers of AZFc deletion sperm production may decline over time (47, 48, 73). For this reason, preventive cryopreservation can be offered to oligozoospermic carriers.

A potential link between AZF deletions and recurrent pregnancy loss (RPL) was first proposed in a small cohort (n = 17) using AZFc markers, which are not recommended by the EAA/EMQN Guidelines (74). The exceptionally high deletion frequency (82%) observed in this study is likely attributable to technical issues, such as amplification failure

TABLE 2

Sequence tag sites recommended by the EAA guidelines (20) for the basic and extension analysis for Y chromosome microdeletions screening.

Deletion		AZFa	AZFb	AZFc
Basic markers		sY84, sY86	sY127, sY134	sY254, sY255
Extension markers	Proximal border	sY82 (+), sY1064 (−)	sY105 (+), sY121/sY1224 (−)	
	Distal border	sY1065/sY1182 (−), sY88 (+)	sY1192 (−), sY153 (+)	sY160[a]

Note: The (+) and (−) of the extension markers show the results of PCR plus/minus in case of complete AZF deletions. AZF = azoospermia factor; PCR = polymerase chain reaction.
[a] sY160 is a heterochromatin marker which can be present (b2/b4 deletion) or absent (terminal deletion).

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because of suboptimal PCR conditions or poor DNA quality. In contrast, the two largest studies, which used canonical AZF markers for testing, did not identify any carriers of AZF deletions (75, 76). Based on the available evidence, it is clear that AZF deletions are not a cause of RPL. Intracytoplasmatic sperm injection (ICSI) represents the technique of election for the symptomatic treatment of Y microdeletion carriers allowing them to conceive their biological children.

The literature reports controversial findings regarding the effect that AZF deletions might have on ICSI outcomes. Some studies observe comparable reproductive outcomes in men with or without classic Y chromosome microdeletions (77–85) whereas others demonstrate that AZF microdeletions may adversely affect one (86–90) or more (72, 91–98) ICSI outcomes parameters (Supplemental Table 1, available online).

In the large majority of the studies, the parameter that is more frequently negatively affected is the fertilization rate with 12 studies out of 19 reporting significant lower rates among Y deleted men compared with non-deleted controls (72, 86–89, 91–95, 97, 98). All other reproductive outcomes show variable and inconsistent trends among the different studies. These conflicting observations are also evident in the results of the two most recent meta-analyses. One, including 12 studies from 2001 to 2019, showed that the only ICSI outcome significantly affected by AZF deletions was the fertilization rate, whereas all other reproductive parameters were comparable with those of patients without Y deletions (99). The other, based on 11 studies spanning from 2001 to 2022, not only observed a lower fertilization rate in men with AZFc deletions, but also a significant decrease in both pregnancy and live birth rates (100).

Overall, the fertilization rate is likely the most frequently affected parameter among men with Y chromosome microdeletions. However, whether these deletions may have any negative impact on the other ICSI outcomes remains a subject of debate. The molecular mechanism behind the reduced fertilization rate remains largely unknown and raises questions whether proteins or mRNAs encoded by the AZFc regions may have a role in the fertilization process.

In case of successful ICSI outcome, the deletion will be obligatorily transmitted to the son who will experience impaired spermatogenesis, but his semen phenotype can differ from that of his father. Therefore, it is important to ask for semen analysis in young adulthood, and if spermatozoa are present in the ejaculate, consider semen cryopreservation for preventive purposes (101). To avoid the transmission of YCM, sex selection of the embryos, i.e., selection of 46,XX embryos, can be offered to the couple. Only one article has been published on this topic, reporting 8/14 couples opting for the selection of female embryos whereas six of them refused preimplantation genetic diagnosis for sex selection (102).

Apart from the obligatory transmission of the YCM to male offspring, data on the impact of these deletions on the health of newborns is inconclusive. Concerns have been raised regarding the risk of chromosomally abnormal embryos in patients with Y chromosome microdeletions. Yq microdeletions have been associated with mitotic instability leading to the formation of 45,XO cell lines (103–105), bringing attention to the potential severe consequences of transmitting these microdeletions. A significant increase in the percentage of embryos presenting monosomy X has been observed in patients with Y microdeletions compared with oligozoospermic patients without (90). Consistent with this finding, Jiang et al. (97) observed a significantly higher rate of aneuploid embryos in AZFc patients, although they do not confirm an association with monosomy X.

Currently information is available for 509 children across a total of 34 studies (Table 3) (40, 46, 70, 72, 78–81, 85,87–90, 92–96, 106–120). Five out of 506 were born with malformations: one with pulmonary atresia and a hypoplastic right ventricle (107); three with pulmonary hypoplasia, deceased after birth (80, 114); one with a nonspecified major malformation (117).

Therefore, the incidence of congenital malformation among infants born to fathers with AZF deletions is 1% which is not increased compared with 2%–3% rate in the general population (121). However, it is interesting to note that three out of five infants born with malformations, had a severe pulmonary development disorder. Overall, the birth of 504 healthy infants to carriers of AZF deletions is encouraging and suggests that these deletions are unlikely to impact the general health of the offspring.

Y CHROMOSOME DELETIONS AND GENERAL HEALTH

The Y chromosome is essential for sex determination and male fertility. However, it is now recognized that its role in human health extends to various other conditions as well. For instance, germline gr/gr deletion and the *TSPY* gene array are involved in testicular germ cell tumor (TGCT) and gonadoblastoma, respectively. In addition, somatic Y chromosome loss seems to be associated with several diseases.

First, the gr/gr deletion is a low-penetrance genetic risk factor for TGCT, as first demonstrated by Nathanson et al. (122) in 2005. They observed a two-fold increased risk of TGCT for gr/gr deletion carriers and a three-fold risk in cases of family history. This observation was confirmed in a large multicenter Mediterranean cohort (497 TGCT patients and 2030 controls), with a three-fold increased risk for TGCT among gr/gr carriers (odds ratio, 3.1; 95% confidence interval, 1.4–7.0) (123). Other than gr/gr deletion, there is no evidence to suggest Y chromosome deletions might contribute to TGCT risk (123, 124).

Concerning the classic Y chromosome deletions, the first study in 2011 reported a higher risk of *SHOX* haploinsufficiency in men with AZF microdeletions and normal karyotype, suggesting that the mechanism underlying Y microdeletions could also be responsible for pseudoautosomal region rearrangements and related diseases (125). This association was not confirmed in a large multicenter study including data from 224 patients (126).

In addition, an article from *Human Reproduction* suggested an association between AZFbc deletion and behavioral/psychiatric disorders, reporting abnormal growth and neuropsychiatric function in five out of seven patients with terminal AZFbc deletion and abnormal karyotype (127).

TABLE 3

Health status of infants born to father with AZF microdeletions.

No. of infants born to fathers carrying AZF deletions	No. of healthy infants	No. of infants born with malformations	Type of deletion	Reference
2	2	0	AZFc	(106)
5	4	1 (pulmonary atresia + hypoplastic right ventricle)	AZFc	(107)
3	3	0	AZFc	(108)
5	5	0	AZFc	(94)
11	11	0	AZFc	(46)
2	2	0	AZFc	(109)
7	4 + 3[a]	0	AZFc	(79)
3	3[a]		AZFc	(102)
6	6[a]		AZFc[b]	(110)
1	1	0	AZFc	(70)
3	3	0	AZFc	(111)
14	14	0	AZFc	(112)
3	3[a]		AZFc	(90)
15	15[a]		AZFc	(113)
4	2	2 (pulmonary hypoplasia)	Partial AZFb[c]	(114)
13	13[a]		AZFc	(88)
35	35	0	AZFc	(93)
20	20[a]		2 AZFbc + 18 AZFc	(115)
2	2	0	AZFc	(40)
33	33[a]		Deletion type not specified	(95)
39	39[a]		AZFc	(89)
1	1	0	AZFc	(116)
27	26	1 (major not specified malformation)	1 Partial AZFa[d] + 26 AZFc	(117)
1	1	0	AZFb[e]	(118)
6	6	0	1 AZFb,[e] + 5 AZFc	(81)
16	16[a]		AZFc	(119)
15	14	1 (pulmonary hypoplasia)	13 AZFc, 1 AZFb	(80)
1	1	0	AZFc	(120)
2	2[a]		AZFc	(87)
118	118	0	AZFc	(92)
8	8	0	AZFc	(96)
20	20[a]		AZFc	(78)
22	22	0	AZFc	(72)
46	46[a]		AZFc	(85)
509	**504**	**5**		**Total number**

Note: AZF = azoospermia factor; STS = sequence tag site.
[a] Assumed to be healthy (not specified in the article).
[b] Genotype cannot be verified (no data on STS markers were reported).
[c] 5.2-Mb Partial deletion in AZFb (sY127 − and sY134 +) (not removing *RBMY* and *PRY* genes).
[d] Isolated deletion of *DDX3Y*
[e] Only sY143 was tested at the distal border (possible partial AZFb deletion).

Krausz. Y chromosome and male health. Fertil Steril 2025.

However, no further confirmation for this association has been published so far.

Since a long time ago, the involvement of the *TSPY* gene array in oncogenic processes has been proposed, first of all as the putative gene for the gonadoblastoma locus on the Y chromosome (128). According to Page et al. (128) it predisposes to gonadoblastoma only in the context of a dysgenetic gonad in XY sex-reversed patients and intersex individuals (129). *TSPY* is considered a proto-oncogene because of its role in accelerating cell proliferation, binding to cyclin B and enhancing B1–CDK1 phosphorylation activity (130).

Accordingly, overexpression of this gene has been observed in carcinoma in situ (129, 131), testicular germ cell tumors (132, 133) and intracranial germ cell brain tumors (134). In addition, increased ectopic expression in hepatocellular carcinoma was also reported and proposed as responsible for sexual dimorphism in the occurrence of this cancer type (135, 136). Indeed, it is known that hepatocellular carcinoma is more prevalent in men than in women (137, 138) and it is conceivable that the *TSPY* gene array could contribute to this sex difference. Concerning a typical male cancer, prostate cancer, data are controversial. Some reporting an increased (139–141) whereas others a decreased (142) *TSPY* expression.

Hence, somatic gene expression studies suggest a potential involvement of this gene in tumorigenesis. However, it remains unknown whether variations in constitutive *TSPY* gene copy number may influence susceptibility to these cancers. Only one study analyzed the *TSPY* copy number in blood and the tumor tissue in relationship with prostate cancer. The investigators observed a significant negative association between gene copies in the genomic DNA and the incidence of prostate cancer. Regarding the tumor tissue, they observed a marked loss of *TSPY* copies and a reduced gene expression (142).

The mosaic loss of Y (mLOY) has been considered only a physiological aging-related phenomenon for decades (143, 144). However, recently more and more evidence suggests a potential association between mLOY and the onset and progression of various diseases, including cardiovascular events (145–148), cancer (149–153), Alzheimer syndrome (154, 155) and diabetes (145). The mechanism by which mLOY may influence male health remains a topic of ongoing debate. Forsberg (156) in 2017 speculated that the loss of Y chromosome could be responsible for a defective immunosurveillance in blood immune cells. Others argue that there is a genetic susceptibility to LOY, that might also predispose to other diseases (151, 157). The question of whether large Y chromosomal rearrangements, leading to 45,XO mosaicism, contribute to a higher risk of mLOY was addressed by Ogiwara et al. (158) in 2021. The investigators found no statistically significant association between AZF-linked copy number variations and mLOY.

CONCLUSION

The Y chromosome harbors genes which are essential for testis development and male reproduction. Its highly repetitive structure not only protects from gene decay but also predisposes to Yq deletions which can have significant clinical consequences for spermatogenesis. The identification of Y chromosome deletions holds diagnostic, prognostic, and preventive value. From a diagnostic perspective, it identifies a clear genetic cause of spermatogenic failure, helping to avoid unnecessary medical (hormonal and non-hormonal) and surgical interventions (e.g., varicocele repair). In azoospermic men, the presence of a complete AZFa or AZFb deletion has a negative prognostic value for testicular sperm retrieval (20). For patients with oligozoospermia, who are at risk of a progressive decline in sperm concentration over time, sperm cryopreservation can serve as a preventive measure, potentially avoiding the need for more invasive procedures such as TESE/ICSI in the future. The same preventive strategy may be considered for affected sons (101). Beyond the classical AZF deletions, a partial deletion in the AZFc region, known as the "gr/gr" deletion, has been linked to male infertility, with varying degrees of spermatogenic impairment, with the highest frequency in oligozoospermic men.

Nearly 50 years after the proposal of the AZF region, some clinical questions still remain unanswered. For instance, it should be relevant to determine whether partial AZFc deletions can expand into a complete AZFc deletion across generations, given the significant implications for the future offspring of gr/gr deletion carriers. Additionally, considering the current data on ICSI outcomes, further research is needed to elucidate the biological mechanisms underlying the negative impact of AZF deletions on fertilization rates (and potentially some other parameters) in the context of ICSI.

Finally, with the widespread adoption of next-generation sequencing, large-scale screenings for Y chromosome-linked gene mutations are now possible. These studies hold the potential to identify the specific gene(s) responsible for the respective deletion phenotype in each AZF region, as well as to clarify their functional roles.

Since the publication of the first Y chromosome sequence of a single individual in 2003 (3), recent advances in next-generation sequencing technology (especially long-read sequencing) have enabled the complete sequencing of 43 diverse Y chromosomes (159). This represents a major breakthrough, as the study has identified the full extent of variation of this chromosome during human evolution. The assembly of the complete Y chromosome sequence is a crucial milestone which paves the way for a deeper understanding of the role of Y-linked genes/sequences in specific human traits and pathological conditions, including male infertility.

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CRediT Authorship Contribution Statement

Csilla Krausz: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Chiara Abrardo:** Writing – original draft, Data curation.

Declaration of Interests

All authors have nothing to disclose.

SUPPLEMENTAL MATERIAL

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