Review Article on Genetic Causes and Management of Male Infertility

Y-microdeletions: a review of the genetic basis for this common cause of male infertility

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Abstract: The human Y-chromosome contains genetic material responsible for normal testis development and spermatogenesis. The long arm (Yq) of the Y-chromosome has been found to be susceptible to self-recombination during spermatogenesis predisposing this area to deletions. The incidence of these deletions is estimated to be 1/4,000 in the general population but has been found to be much higher in infertile men. Currently, Y-microdeletions are the second most commonly identified genetic cause of male infertility after Klinefelter syndrome. This has led to testing for these deletions becoming standard practice in men with azoospermia and severe oligospermia. There are three commonly identified Y-microdeletions in infertile males, termed azoospermia factor (AZF) microdeletions AZFa, AZFb and AZFc. With increased understanding and investigation of this genetic basis for infertility a more comprehensive understanding of these deletions has evolved, with several other deletion subtypes being identified. Understanding the genetic basis and pathology behind these Y-microdeletions is essential for any clinician involved in reproductive medicine. In this review we discuss the genetic basis of Y-microdeletions, the various subtypes of deletions, and current technologies available for testing. Our understanding of this issue is evolving in many areas, and in this review we highlight future testing opportunities that may allow us to stratify men with Y-microdeletion associated infertility more accurately

Keywords: Y-microdeletions; male infertility; reproductive medicine

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Introduction

Approximately 8–15% of couples are affected by infertility—the inability of a man and a woman to conceive a child or carry a pregnancy to delivery, after 12 months of unprotected intercourse (1-4). A male factor is the primary contributor among approximately 20% of the cases and contributes in another 30–40% of cases (3-11). Genetic factors are diagnosed in approximately 15–20% of severe male factor infertility (azoospermia or severe oligozoospermia) (12,13).

The mammalian Y-chromosome is an acrocentric chromosome composed of two pseudoautosomal regions (PARs) and two arms—a short arm (Yp), and a long arm (Yq), separated by a centromere (*Figure 1*) (14). The PARs

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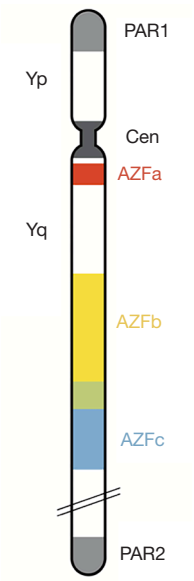

Figure 1 Structure of the human Y-chromosome.

(PAR 1 and PAR2) are short regions of homology between the X- and Y-chromosome, that behave like an autosome, recombining during meiosis (15). They are located at the termini of both chromosomes—PAR1 is 2.7 Mb region at the telomere of the short arm, whereas PAR2 is a much smaller 0.3 Mb region at the telomere of the long arm (16).

The male-specific region of the Y-chromosome (MSY), first reported in 2003 by Skaletsky *et al.*, spans 95% of the chromosome's length, and is flanked by PAR1 and PAR2 (17). The MSY is a mosaic of heterochromatic sequences and three classes of euchromatic sequences; X-transposed, X-degenerate, and ampliconic (17,18). One hundred and fifty-six transcription units are contained in the reference MSY, which include 78-protein coding genes encoding 27 proteins. Sixty of the 78 coding genes and 74 non-coding transcription units comprise ampliconic sequences (17). These ampliconic sequences are somewhat novel, as they are largely homogenous with almost identical sequence identity, yet contain rich teste specific gene regions (19). Within the MSY and on the long arm of the Y-chromosome, are regions known as the azoospermia factor (AZF) regions, which contain genes critical for spermatogenesis and male fertility (11,20). These regions contain repeated homologous sequences vulnerable to deletions or duplications through non-allelic homologous recombination (NAHR) (13).

Microdeletions on Yq are the second most common genetic cause of male infertility after Klinefelter syndrome. Molecular diagnosis of these microdeletions is now a standard clinical investigation in the workup of severe male infertility (21-24). The incidence of Yq microdeletions is estimated to be 1/4,000 in the general population, but has been found to be much higher in infertile men (21). Incidence of Yq microdeletions in azoospermic men is greater than in oligozoospermic men, and has been reported to be as high as 15–20% in some populations (21,24-26).

Most of the Yq microdeletions resulting in azoospermia or severe oligozoospermia occur in the AZF regions. Five recurrent deletions within three different regions have been reported: AZFa, AZFb, AZFbc (with two different breakpoints) and AZFc (13,27,28). A fourth region, AZFd, was first described by Kent-First *et al.* using multiplex-PCR reactions and postulated to exist between AZFb and c (29). The existence of the AZFd region remains controversial; whereas Krausz *et al.*—in their European Academy of Andrology (EAA)/European Molecular Quality Network (EMQN) best practice guidelines—argue that it does not exist, others have reported AZFd deletions independent of AZFc deletions (21,29-34). Microdeletions can also involve combined regions (i.e., AZFab, AZFabc, AZFac, AZFad, AZFbc, AZFbd and AZFbcd), leading to different degrees of oligozoospermia/azoospermia (22,35-37). This manuscript will review the genetic basis, as well as the methods for diagnosis, of this common cause of male infertility.

Types of deletions

AZFa

The AZFa region is 1,100 kb long and contains two single-copy genes: *USP9Y* and *DDX3Y*. Studies have identified the origin of complete AZFa deletions to be the homologous recombination between two identical sequence blocks (21,38-40). Even though two major patterns of deletions are found with slightly different breakpoints, both result in the loss of approximately 792 kb which includes both *USP9Y* and *DDX3Y* (21,39-41).

AZFa region deletions comprise 0.5–4% of all Yq-microdeletions (21,42). Complete AZFa deletions lead to azoospermia and Sertoli cell-only syndrome (SCOS) (13,21,22,25,27,41,43,44). In complete AZFa deletions, the chances of finding spermatozoa upon surgical testicular exploration for intracytoplasmic sperm injection (ICSI) is nil, therefore, testicular sperm extraction (TESE) or micro-TESE should not be offered (13,21,25). Gene-specific

deletions are very rare, and have only been reported in the AZFa region (i.e., *USP9Y*), and can lead to a phenotype varying from normozoospermia to azoospermia (13,23,45).

AZFb

The AZFb region is structurally complex and partially overlaps the AZFc region. Within AZFb, there are 14 multi-copy sequence units, or amplicons. Of these 14 amplicons, seven are restricted to AZFb, while the remaining are shared with AZFc. These amplicons are further categorized based on symmetrical arrays of contiguous repeats called palindromes. AZFb contains palindromes P2–P5, as well as the proximal part of P1. The complete deletion of AZFb is caused by the homologous recombination between the palindromes P5/proximal P1 and leads to the loss of a 6.2 Mb region that comprises 32 gene copies and transcription units (21,46,47). Complete deletions of AZFb occur at a frequency of 1–5% of all Yq-microdeletions and lead to similar results as AZFa deletion, namely SCOS or spermatogenic arrest resulting in azoospermia (21,25,42-44). It is worth noting however, that three case reports found arrest of spermatid and oligozoospermia with complete deletion of AZFb (48,49). Proposed explanations for the unusual phenotypes include different Y-chromosome backgrounds and different breakpoints leading to a smaller deletion. Such a breakpoint (P4/proximal P1 deletion) could possibly spare some AZFb gene copies including *XKRY*, *CDY2* and *HSFY* leading to a less severe phenotype (21).

AZFbc

Although it was originally proposed that AZFb and AZFc were discrete regions of MSY, further molecular characterization of the deletions revealed that AZFb and AZFc were in fact overlapping (21,22). AZFb and AZFbc deletions have been suggested to be caused by at least three different deletion patterns—the P5/proximal P1 leading to the complete deletion of AZFb, and two AZFbc deletion patterns: P5/distal P1 and P4/distal P1 (46,47). AZFbc deletions cause the loss of 7.7 Mb and 42 copies removed or 7.0 Mb and 38 copies removed, respectively, and occur at a frequency of 1–3% of Yq-microdeletions (21,42,47). Similar to AZFb deletions, AZFbc deletions lead to SCOS and azoospermia, therefore, TESE is generally not recommended, as the chances of finding spermatozoa is low (13,24,25,50).

AZFc

AZFc deletions are the most frequent Y-chromosome microdeletion type (~80%) (21,42). The deletion originates from the homologous recombination of the 229 kb direct repeats b2 (in P3) and b4 (in P1), and deletes 3.5 Mb including 21 gene copies and transcription units (46). Unlike the complete deletions above, complete AZFc deletions have been associated with a variety of clinical and histological phenotypes, ranging from azoospermia to residual spermatogenesis and oligozoospermia (51-54). In complete AZFc deletions leading to azoospermia, there is a 50% chance of spermatozoa retrieval with TESE. Success rate depends on technique and ranges from 9% to as high as 80% with micro-TESE (24,26,43,53,55-64). In addition, since progressive decreases of sperm production have been reported in the literature, men found to have oligozoospermia and AZFc deletions should be offered preventive sperm cryopreservation at time of diagnosis (13,21). Male offspring from men with AZFc deletions will also host a similar or larger AZFc deletion, making genetic counseling for these families an integral part of their care (65-70).

Although partial deletions in AZFa and AZFb regions are rare, AZFc is particularly susceptible to partial deletions caused by NAHR events (46,71,72). Of the various deletions reported in the literature, *gr/gr* deletions seem to be of clinical interest (21,73). This partial deletion removes approximately half of the AZFc region affecting nine transcription units (42). The reported effects of *gr/gr* deletions are highly dependent on the ethnic and geographic origin of the studies. Carriers of *gr/gr* deletions have been reported to exhibit phenotypes ranging from azoospermia to normozoospermia (73-79). Moreover, *gr/gr* deletions have been postulated as a risk factor for testicular germ cell tumors (TGCT) (80). A 2019 European study found a predisposing effect of *gr/gr* deletion to TGCT as an independent factor and recommended regular tumor screening in infertile *gr/gr* deletion carriers and male family members of TGCT patients with *gr/gr* deletions (81).

Genetic testing

The testing for AZF deletions is recommended by the American Urology Association (AUA) as part of the routine diagnostic workup of men with azoospermia and severe oligozoospermia (less than 5 million sperm per ml) (13,82). Current and possible future techniques are described below.

Multiplex-polymerase chain reaction (PCR)

Multiplex-PCR is the current gold standard testing modality for Y-microdeletions, and is used to amplify small portions of each region, with losses reported only as AZFa, AZFb and/or AZFc deletions (4,47,83,84). The 2013 EAA and EMQN guidelines standardized and reported in detail the molecular diagnosis of Y-microdeletions (21). It reported no increase in detection rate with the use of sequence-tagged site primers (STS) specific for discrete genes. STS primers that amplify anonymous MSY regions can be used to the same effect (63,83,85,86).

The use of multiplex-PCR allows for an internal control (*ZFX/ZFY* gene; present in both male and female DNA) to differentiate a negative result from technical failure. In addition, a DNA sample from a male with normal spermatogenesis should be used as a positive control (21). Although the analysis of a single non-polymorphic STS is theoretically sufficient, analysing two STS loci in each region reinforces diagnostic accuracy (21).

Array comparative genomic hybridization (aCGH)

Copy number variations (CNVs) are phenomena in which sections of the genome are deleted or duplicated, leading to different number of repeats between two compared individuals. Through combining fluorescently labelled DNA from two individuals (patient and control), aCGH can detect CNVs. aCGH involves running the hybridized DNA on custom microarrays that enable the quantification of DNA copy numbers for each probe from each individual. High-resolution aCGH (that employs multiple probes) allows detection of CNVs as small as 60 base pairs (4). When compared to PCR, high-resolution aCGH identified CNVs in 11% in a study of 104 infertile men, half of which were missed by traditional multiplex-PCR (4,87). Limitations of aCGH as it relates to Y-microdeletions are specific to CNVs, since CNVs do not necessarily equate gene expression. Partial duplications can also cause decreased expression through gene disruption (4). Moreover, the per-sample cost of aCGH is currently double that of multiplex-PCR, however that is expected to drop over time and, combined with the greater diagnostic yield, it is reasonable to expect its future use as a diagnostic tool for Y-microdeletions (87).

Next generation sequencing (NGS) technologies

NGS involves the rapid parallel sequencing of short DNA fragments and their subsequent alignment to a reference gene/genome (4). Three general categories of NGS exist: disease targeted sequencing, whole exome sequencing, and whole genome sequencing. A recently developed panel for male/female infertility genes resulted in ~100% accuracy in diagnosing single nucleotide variations, CNVs, insertion/deletions, sex chromosome aneuploidies (94% accuracy for Y-microdeletions), and *CFTR* gene thymidine tract length quantification, at the cost of $599 USD (4,88). Comparatively, karyotyping, *CFTR* sequencing and multiplex-PCR testing for Y-microdeletions could cost several thousand dollars though it is uncommon for all three tests to be ordered concurrently for the same patient. Moreover, the ability to use benchtop sequencers for disease-targeted sequencing means that NGS can be available at smaller laboratories, facilitating its adoption as a clinical diagnostic tool (4).

Compared to disease-targeted sequencing, whole exome sequencing identifies tens of thousands of variants more. In whole exome sequencing, only ~2% of the genome is sequenced, however about 85% of the known mutations causing diseases in humans are covered (4,89). A limitation of whole exome sequencing is overlooking the intergenic regions, the roles of which in human disease are more frequently becoming recognized (4). Whole genome sequencing on the other hand, identifies 3 to 4 million more variants than disease-targeted and whole exome sequencing. The costs of whole genome/exome sequencing was initially prohibitive, costing tens of thousands of dollars, however, several start-up biotechnology firms have begun to offer this testing for as little as a few hundred dollars. The accuracy of these private firm tests is difficult to assess though (90). Furthermore, given the significant repetitive sequences on the Y-chromosome, conventional short-read NGS poses challenges for the Y-chromosome. As new long-read sequencing platforms are being developed and adopted, novel diagnostics may become available for Y-chromosome abnormalities.

Conclusions

Y-microdeletions are the second most common genetic

cause of male infertility after Klinefelter syndrome. Most of the Yq microdeletions resulting in azoospermia or severe oligozoospermia occur in the AZF regions, which contain genes critical for spermatogenesis. As such, genetic testing for AZF deletions has become part of the routine diagnostic workup of men with azoospermia or severe oligozoospermia. Testing for Y-microdeletions has proven important not only for the counselling of our patients about potential treatment options but also for discussion regarding potential effects on future generations.

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Footnote

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