Review Article on Genetic Causes and Management of Male Infertility

Y chromosome copy number variation and its effects on fertility and other health factors: a review

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Abstract: The Y chromosome is essential for testis development and spermatogenesis. It is a chromosome with the lowest gene density owing to its medium size but paucity of coding genes. The Y chromosome is unique in that the majority of its structure is highly repetitive sequences, with the majority of these limited genes occurring in 9 amplionic sequences throughout the chromosome. The repetitive nature has its benefits as it can be protective against gene loss over many generations, but it can also predispose the Y chromosome to having wide variations of the number of gene copies present in these repeated sequences. This is known as copy number variation. Copy number variation is not unique to the Y chromosome but copy number variation is a well-known cause of male infertility and having effects on spermatogenesis. This is most commonly seen as deletions of the AZF sequences on the Y chromosome. However, there are other implications for copy number variation beyond just the AZF deletions that can affect spermatogenesis and potentially have other health implications. Copy number variations of *TSPY1*, DAZ, CDY1, *RBMY1*, the DYZ1 array, along with minor deletions of gr/gr, b1/b3, and b2/b3 have all be implicated in affecting spermatogenesis. *UTY* copy number variations have been implicated in risk for cardiovascular disease, and other deletions within gr/gr and the AZF sequences have been implicated in cancer and neuropsychiatric diseases. This review sets out to describe the Y chromosome and unique susceptibility to copy number variation and then to examine how this growing body of research impacts spermatogenesis and other health factors.

Keywords: Azoospermia; copy number variation; male infertility; spermatogenesis; Y chromosome

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Introduction

Infertility is estimated to affect 10–15% of couples with male factor being the solitary cause in about 20% of those cases and playing a role in another 40% of cases (1-4). A semen analysis is the workhorse of a male factor workup and when a result returns with a concentration of <5 million sperm/mL it is recommended that the patient undergo genetic testing (5). The two most common genetic tests are a karyotype and a Y chromosome microdeletion (YCMD) analysis (5,6). It is estimated that karyotypic abnormalities will be found in 3–5% of oligospermic men and up to 19% of men with non-obstructive azoospermia (NOA) (7,8). YCMD are found in 2–5% of severely oligospermic men and 5–10% of men with NOA (9-11).

Copy number variants (CNV) are well known in the human genome as they allow for phenotypic diversity (12). CNV affect more nucleotides in the human genome than SNPs and can arise via several mechanisms including; non allelic homologous recombination, non-homologous end joining, and retroelement insertions (13,14). However, CNV can also lead to negative consequences and have been implicated in intellectual disability (15), epilepsy (16), cancer (17), and other disease processes. For reasons we will discuss further, the Y chromosome is particularly susceptible to CNV which can lead to fertility issues. The most well-known CNV on the Y chromosome are the total AZF

deletions, but also includes AZFc partial deletions, such as *gr/gr* gene alterations, and the *TSPY* gene array. The AZF deletions will be discussed in detail in another article in this journal and will only be touched on briefly here. And while most studies of CNVs have revolved around fertility, there is some growing evidence that they could lead to other health issues, such as cancer (18).

The Y chromosome

The Y chromosome is acrocentric, meaning it contains a shorter Yp and longer Yq arm, with a total of around 60 million-base (Mb) pairs, making it one of the smallest chromosomes in the human genome. It is one of the most unique and important chromosomes, as amongst other genes, as it contains the *SRY* gene region that provides the genetic data for embryonic sex determination. Yet, it is also the only chromosome that can be missing entirely without lethal consequences (19). Due to an evolutionary effect known as gene decay, where unused genes are slowly removed from the genome, the Y chromosome now contains 54 protein coding genes compared to the X chromosome that contains approximately 700 protein coding genes. The Y chromosome is generally divided into two domains, the pseudoautosomal regions (PAR1 and PAR2) and an area known as male-specific Y region (MSY) (9,20). The PAR regions contain genes that work similar to autosomal genes and defects here can cause issues such as short stature, schizophrenia, and bipolar disorder (21-23). PAR1 also serves as a region to allow for pairing with the X chromosome that is crucial for meiosis (24).

The MSY is a far larger region of the Y chromosome and is unique in that it does not recombine with its X chromosome pair. There are three classes of sequences within the MSY region; X-transposed, X-degenerate, and amplionic (25). The majority of the genes involved in male reproduction and spermatogenesis are located in the amplionic regions (19,26). The amplionic regions are comprised of 9 separate protein-coding multi-copy gene families that total 10.2 Mb pairs. These amplionic sequences demonstrate sequence pairs that are nearly identical with other regions within the MSY. Eight of these nine regions exist as palindromic sequences, consisting of highly similar inverted sequence repeats with short spacer sequence dividers. The ninth sequence, called *TSPY*, exists as a tandem array of repeats located on the Yp arm. It is suggested these palindromic sequences exist to allow for intra-chromosomal gene transfer to preserve genes important for male fertility and prevent the accumulation of mutations that would eventually lead to the reduction of fertility. However, this also allows for deletions and or duplications of repeated sequences through non-allelic homologous recombination which can negatively impact male fertility (9,25,27-29). It is this mechanism that can lead to gene copy number variations with resultant difficulties conceiving. Interestingly, even among healthy men there are variations in the Y amplionic gene copy number (30-32). Some of this variation is related to Y haplogroups, ethnicity, and geographic region, further complicating study of this phenomenon (32). This review will focus on CNV on the Y chromosome and how they play a role in male infertility and overall health.

Initial study of copy number variation on the Y chromosome

Infertility-related copy number variations were first recognized as a clinical entity in 1976 by Tiepolo and Zuffardi (33). In their study of 1170 sub-fertile men, karyotype analyses revealed a subset of men with a deletion within the Yq11 region. These men had normal body habitus in contrast to the previously recognized Klinefelter's syndrome, the predominant cause of genetic male infertility (34-36). The deleted regions were termed 'azoospermia factor' (AZF). The AZF region was further confirmed by both cytogenetic and molecular studies (37-39). Building on this work, Vogt *et al.* sought to further define this region and determine if it were a single gene locus or multiple loci by screening 376 men with normal karyotype and azoospermia or severe oligospermia. The Y chromosome was specifically analyzed for 76 different DNA loci. Through this technique they were able to define 3 distinct regions within Yq, termed AZFa, AZFb, and AZFc (40). This was the first clinical work to demonstrate how copy number variation, in this case reduced copy number, could lead to fertility issues in men.

Clinically, it has been suggested that copy number variations can be defined in 3 ways: (I) AZF deletions (and partial AZFa and AZFb), (II) partial AZFc deletions/duplications, (III) the *TSPY* region (9). AZFc is the largest region measuring at 4.2 Mb followed by AZFb at 3.2 Mb and finally AZFa at 792 Kb. The palindromic sequence within AZFc is the largest, most uniform, and elaborate of identified inverted repeats among previously studied organisms and is about three times longer than the next largest palindrome in humans (located on chromosome 5). It measures 3 Mb in length (41). This has led to great interest and further study, however studying large palindromic

sequences makes the endeavor more complicated due to the difficulty in ordering the defined sequences since they appear similar (41). Some of this complex work is detailed in Kuroda-Kawaguchi *et al.* (41).

AZFa

The AZFa region is the shortest of the three named regions, measuring in at 792 Kb (42). It contains only four coding genes that are ubiquitously expressed within the body but that each have only a single copy within the AZFa region (20). This region is found deleted about 0.5–4% of the time when AZF deletions are found (43). Despite being the smallest of the AZF regions, complete deletion leads to the most severe phenotype, Sertoli-cell only. The 4 genes isolated to this region are *USP9Y*, *DBY*, *UTY*, and *TBY4* (26,44-46). Both *USP9Y* and *DBY* play important roles in spermatogenesis with it being believed that *DBY* is the more important of the two genes. At this time, *UTY* and *TBY4* have unclear roles (20). No men with an identified AZFa deletion have ever been found to have sperm. Since these are only single gene copies, any copy number variation in this region has extreme consequences.

AZFb

The AZFb region is in the midportion of Yq11 and spans a total of 3.2 Mb, with 1.5 Mb overlapping with the AZFc region. It is found deleted in approximately 1–3% of cases with AZF deletions (43). It contains 3 single copy regions, a 19-satellite repeat array, and 14 multi-copy amplicons organized into 6 sequence families. AZFb contains 15 coding protein genes and 17 non coding RNAs (20). The classical copy number variation within this section is a complete deletion that overlaps 1.5 Mb with AZFc and leads to a complete loss of 32 coding genes. It is generally accepted that AZFb deletions lead to azoospermia, though with elements of maturation arrest as opposed to Sertoli-cell only found in AZFa. However, there have been rare reports of men with AZFb deletions that had some residual sperm production, likely due to an aberrant deletion patterns (47,48). Another article within this journal will go into more depth with regards to AZFb.

AZFc

AZFc is the largest of the coding regions and most complex. It measures at 4.2 Mb total and complete deletions are found in 80% of all AZF deletions (43). AZFc is arranged in 3 large palindromes that are each comprised of six distinct amplicons. The amplicons range in size from 115 to 678 kb each (41). A complete AZFc deletion, also known as a b2/b4 deletion based upon amplicon break points, is most commonly seen and tends to exhibit the least severe phenotype of the AZF deletions being the only one where patients could have either oligospermia or azoospermia but with a 50% chance of retrieving sperm on testicular extraction (49). The full AZFc deletion will be discussed in another article in this edition. This article will focus on specific partial deletions and copy number variations within AZFc.

When AZFc was first being studied it was proposed that in addition to the entire region being deleted, there were sub-sections of the region that would be susceptible to deletion given their structure (50). These specific deletions were identified and characterized as gr/gr deletion (1.6 Mb) and the b1/b3 deletion (1.6 Mb) (51). The gr/gr deletion was of concern because it removes 9 of the 32 gene coding units within AZFc and occurs within a region that is needed for normal spermatogenesis. However, for 8 of these 9 gene families, the deletions only reduce the copy number of these genes since gene copies are located elsewhere on the Y chromosome. The initial study defining these alternate deletion patterns included 689 men, of whom 473 had spermatogenic failure, and found 22 men with a gr/gr deletion and one man who had a b1/b3 deletion. The names were determined by genetic break points. After controlling for Y haplogroups, the group found that men with a gr/gr deletion had a significantly increased risk of spermatogenic failure (51). This group went on to identify another deletion within the AZFc region that affected gene copy numbers and referred to as the b2/b3 deletion based upon amplionic break points (52).

The major genes that have their copy number significantly affected by these deletions are the *DAZ* and *CDY1* genes. These genes, and their reduction in copy number, have been known to have a significant impact on spermatogenesis since the 1990s (52-54). While these early studies focused on *DAZ1* and *DAZ2* further studies went on to examine deletions of other members of the *DAZ* family and still found effects on spermatogenesis related to *DAZ* copy number (55,56). Copy number of these genes playing an important role was further suggested by German group that compared 170 men with normal spermatogenesis to 348 men with impaired spermatogenesis. The gr/gr deletion was found in 14 men with impaired spermatogenesis and

in 3 men with normal spermatogenesis, and two of them had fathered children. The b1/b3 deletion was found in 1 normal and 1 impaired man and the b2/b3 deletion was found in 5 normal men and only 2 of the abnormal spermatogenesis group. And while the gr/gr deletion was more common in the impaired group, it was not a significant difference, and therefore this group suggested that while these particular copy number variations can play a role in spermatogenesis, these deletions and the changes in copy number may not tell the entire store (57).

Another group out of India examined 822 infertile men and 225 men with proven fertility. They found gr/gr deletions in 48 of the infertile men and 2 of the fertile men, they found b1/b3 deletions in 1 infertile man and 0 fertile men, and in the b2/b3 group they found 2 and 1 deletions respectively within the infertile and fertile groups. And while the gr/gr deletion group did have a significantly increased risk of infertility, their sperm concentrations, while trending lower, were not significantly different (54.20±57.45 *vs.* 72.49±60.06 million/mL) (58).

Other studies continued to examine these different deletions and their effects on spermatogenesis, with studies often deciding to limit to certain populations to better control for Y haplogroups. A meta-analysis of the gr/gr deletion incorporated 18 case-control studies with a total of 6,388 cases and 6,011 controls and found that 6.9% of cases had the gr/gr deletion while 4.7% of controls also had the deletion. While there was a significantly increased risk of infertility in the cases group, these alterations in copy number clearly cannot tell the entire story. There was also a correlation of gr/gr deletion based upon Y haplogroups and geographic region. This studied stated that at this time they would not recommend routine screening for the gr/gr mutation as it may lead to more questions than answers (59). While some of the early studies looking at b2/b3 deletions did not demonstrate significant effects, a meta-analysis that incorporated 24 studies and had 8,892 oligo/azoospermic men compared to 5,842 normozoospermic men was performed to better examine the data. The b2/b3 deletion was found in 241 oligo/azoospermic men (2.7%) and 118 normozoospermic men (2%). In the meta-analysis, the fixed model demonstrated an OR of 1.3 that having the b2/b3 deletion would have a significant negative impact on spermatogenesis. Much like the analysis looking at gr/gr, these findings tied heavily to different haplogroups and geographic regions.

TSPY1 gene array

The testis-specific protein Y encoded 1 (*TSPY1*) gene array is located on the Yp arm. The *TSPY1* gene copies exist as 20.4 kb sequences that occur in tandem repeats. These repeated sequences range in number from 11–76 and are highly variable across haplogroups (60,61). It is suspected that copy numbers outside this range are incompatible with life and thus are not found in current populations (62). Given this belief and the large copy number variability of the *TSPY1* gene it has been examined for relation to sperm counts and fertility. A 2006 study from the Czech Republic noted copy numbers varying from 30–60 and that increased number of copies of *TSPY1* led to a significant increase in infertility (63). In direct contradiction to this finding was a study in 2009 of Italian men, where copy numbers ranged from 21–35, and found that having fewer copies of *TSPY1* led to a significant decrease in sperm counts and fertility (64). However, there was a third study examining *TSPY1* copy number in 2010 performed on Dutch men that found no effect on *TSPY1* copy number and fertility when comparing fertile and infertile men. In this study, the control group had a median *TSPY1* copy number of 34 (26–76 copies) while the infertile group had a median *TSPY1* copy number of 35 (20–73 copies) (65). Three studies, three different results. The group that produced the Italian study has theorized subsequently that because of the variation across the populations, controlling for Y haplogroups during these studies is important. This group expanded on their initial study, increasing their study size to 212 men having abnormal semen parameters compared to 168 men with normal semen parameters and continued to find a significantly lower *TSPY1* copy number in the infertile group (28.5±7.9 *vs.* 32.6±10.1 copies) (66). A very thorough study out of China in 2013 examined 2,272 Han Chinese men and found seven distinct Y haplogroups. These haplogroups had significantly different mean number of copies of the *TSPY1* gene. Overall the study found that men with <21 copies of *TSPY1* and men with >55 copies of *TSPY1* had a significantly lower sperm production and increased chanced of spermatogenic failure compared to men with 21–35 copies of the gene (67). The *TSPY1* gene thus far appears to be the clearest example of CNV having significant, and variable, impact on spermatogenesis.

Other genes and sequences

There have been several other genes or sequences studied in

relation to copy number variation on the Y chromosome and fertility. The DYZ1 array comprises between 20-40% of the Y chromosome and was found to contain a pentameric repeat with about 3,000–4,300 copies of the gene array on the Y chromosome (68-71). Initially the DYZ1 array was thought to be of little importance because it does not participate in recombination but later studies revealed it could help with chromatin stabilization (72,73). These DYZ1 arrays are interspersed through the previously mentioned AZFa, b, c regions. This led to a group in India examining the DYZ1 array for copy number variation and comparing 67 infertile men to 31 men with a normal semen analysis. They found a reduced DYZ1 copy number had significantly increased risk of infertility (74). Interestingly, even in monozygotic twins there has been found to be copy number variation of DYZ1 on the Y chromosome, opening further questions into the effects of copy number variation as a whole (75).

Another gene with noted copy number variation linked to fertility and spermatogenesis has been *RBMY1*. It is known in AZFb deletions, all active copies of *RBMY1* are deleted, which leads to azoospermia (76). It has also been observed that there is significant copy number variation of the *RBMY1* gene in the general population and the full implications of this are not fully understood (77). A study of Han Chinese men to compared *RBMY1* copy number between 506 men with normozoospermia and 564 men with oligo or athenozoospermia without previously identified chromosomal deletion to examine for copy number and relation to sperm motility. The study found that men with fewer than 6 copies of *RBMY1* were at an increased risk of athenozoospermia. Six copies of the gene were found to be the average number within this population. In contrast, 376 Estonian men with oligo or azoospermia without known prior chromosomal deletions were analyzed for *RBMY1* copy number and its effects on sperm motility. Unlike the Chinese study, there was no evidence of *RBMY1* gene copy number playing a role in determining sperm motility (78).

Y chromosome copy number variation—beyond infertility

While fertility consequences remain the largest concern for CNV of the Y chromosome, recent studies have demonstrated there could be health issues beyond male factor infertility. Once genes were identified on the Y chromosome, groups began to look for this gene expression in other tissues of the body. Interestingly the genes most commonly found in other tissues of the body were usually within the AZFa and AZFb regions with relatively few in the AZFc region, despite it being the largest (79). Colaco and Modi then examined the putative functions of these genes and as expected most of the functions were related to spermatogenesis, but they also found 14% of genes involved in regulation of gene expression, chromatin organization, and regulation of protein synthesis. In addition, 24% of the genes code for products involved in protein-protein interactions, 18% in nucleic acid binding, and 12% in RNA binding (80). With the wide expression of these genes throughout the body and the alternative functions besides spermatogenesis, it can be understood how these genes may play a role in other health issues.

Given the importance of the Y chromosome to testicular function; it has long been suspected that genes on the Y chromosome can play a role in testicular cancer development. This has been seen in the development of gonadoblastoma in Turner's syndrome patients (81) as well in other germ cell tumors in patients with disorders of sexual development (82). The previously discussed *gr/gr* deletion has been implicated in the development of testicular germ cell tumors (83,84). Beyond the testicle, loss of the Y chromosome in peripheral blood has been found to be a risk factor for the development of colorectal and prostate cancer (85). Additionally, certain deletions of genes from the Y chromosome can lead to more aggressive types of prostate cancer (86-88). Interestingly, the *RBMY1* gene previously discussed is only expressed within the testicle, but changes in copy number have been implicated as a risk factor for hepatocellular carcinoma in men (89) and could also contribute to a poorer prognosis in men with hepatocellular carcinoma (90).

In addition to cancer risks associated with changes in Y chromosome gene copy numbers, these genes can play a role in neuropsychiatric disorders. Three of the AZFa genes and four of the AZFb genes are expressed in the cerebral cortex (80). There is evidence that changes to these genes copy numbers can be risk factors for ischemic stroke (91) and the development of Parkinson's disease (92). Colaco and Modi were able to utilize the Decipher database, which collects clinical data on patients with CNVs, to identify 84 men with copy number variations within the AZF regions. There was clinical information in the database on 71 of these men, with 21 of these men with AZF CNVs also having neuropsychiatric concerns. Examples included delayed development, intellectual disorders, and anxiety or mood disorders (80). There is even evidence in mice that Y chromosome CNV can be linked to central nervous system

autoimmune diseases in female offspring (93).

Other studies suggest, at least in a European population, certain Y haplogroups can play a role in the risk of developing cardiovascular disease (94). Another study noted that changes in UTY expression, previously as mentioned as being within the AZFa region, could affect cardiovascular risk by playing a late role in development of atherosclerosis (95). Some of these Y chromosome effects are beyond the scope of this review as they do not strictly deal with CNV, but Maan *et al*. have an excellent review of the topic (96).

Conclusions

The Y chromosome is unique among human chromosomes in both its small size and uniquely repetitive structure. It is this unusual structure that not only provides protection from genomic degradation over time but can also lead to changes in gene copy number expression that can have dramatic effects on both fertility and in some cases overall health. While the effects of AZF whole deletions appear to be fairly well understood, specific gene copy number variations and their effects are still being isolated and understood within the context of fertility and general health. The study of this phenomenon is further complicated because it appears that Y haplogroups can play a significant role in how much copy number variation affects overall fertility. This can make comparing data and studies across populations more complicated. As it stands now, given the limited knowledge, testing specifically for these CNVs likely will not have an impact on clinical care for a man with male factor infertility. For CNV testing to play a critical role in male infertility evaluation, further research needs to be completed to look more in depth at specific areas for CNV on the Y chromosome and better defining the number of CNV that become are clinically important. Additionally, utilization in male factor evaluation would require clinically accurate and accessible testing as opposed to research testing. As research and understanding of the topic continues to grow, CNVs will likely become more frequently tested to allow for improved clinical care in the future.

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Footnote

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