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Review

Y chromosome b2/b3 deletions and male infertility: A comprehensive meta-analysis, trial sequential analysis and systematic review

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ABSTRACT

The correlation of Y-chromosome b2/b3 partial deletions with spermatogenic failure remains dubious. We undertook a systematic review of the literature followed by meta-analyses and trial sequential analyses in order to compare the frequency of b2/b3 deletions between oligo/azoospermic infertile and normozoospermicmen. Out of twenty-four studies reviewed for meta-analysis, twenty reported no correlation between this deletion and male infertility and two studies each reported a direct and inverse correlation. In the collective analysis, 241 out of 8892 (2.71%) oligo/azoospermic individuals and 118 out of 5842 (2.02%) normozoospermic controls had a b2/b3 deletion, suggesting a relatively higher frequency of deletions in the cases. Eventually, meta-analysis showed a significant correlation between b2/b3 deletions and the risk of spermatogenic loss/infertility (Fixed model: OR = 1.313, 95% CI = 1.04–1.65, p = 0.02; Random model: OR = 1.315, 95% CI = 1.02–1.70, p = 0.037). Further meta-analysis on studies grouped by ethnicity and geographic regions showed that the b2/b3 deletions are significantly associated with spermatogenic loss/infertility in Mongolians, Nigro-Caucasians, East Asians and Africans, but not in Caucasians, Europeans, South Asians and Dravidians. In summary, the Y-chromosome b2/b3 deletions increase infertility risk; however, it may be significant only in the Mongolian populations and the East Asian region.

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1. Introduction

Approximately 10–15% of the couples suffer from infertility, and the male factors are thought to be responsible in roughly half of them. The indispensable role of the Y-chromosome in male fertility has been appreciated since well before its identification in the early 1990s. Tiepolo and Zuffardi, on the basis of comparison of the Y-chromosome between fertile and infertile individuals, localized factors controlling spermatogenesis on to Yq11.23 [1]. Later, another group studied Yq using 30 densely mapped fluorescent probes to further characterize and localize azoospermia factor (AZF, MIM 415000) region on the long arm of the Y-chromosome [2]. Vogt et al. [3] analyzed this region with 76 densely mapped probes to further characterize the sub-regions named as AZFa, AZFb, and AZFc. In the AZFc region, six distinct amplicon families are arranged in a complex repetitive pattern forming three palindromes that are believed to have formed as a result of the duplications and tandem inversions during evolution [4]. Thus, identification and characterization of the spermatogenic region was the next major discovery after identification of the *SRY* gene on the Y-chromosome. One or more of the three non-overlapping regions mapped to the proximal (AZFa), middle (AZFb), and distal (AZFc) portions of the Y-chromosome show propensity for deletions by non-allelic homologous recombination (NAHR), resulting in deletions, duplications, and inversions in different combinations [3]. Deletions of the AZFa and AZFb regions are less frequent and result in severe spermatogenic failure, whereas AZFc deletions are relatively more frequent and result in an array of sperm phenotypes.

The AZFc region contains several gene families, such as *DAZ*, *CDY1*, *RBMY*, *BPY2*, *PRY*, *CSPG4LY*, *GOLGA2LY*, *TTTY3*, *TTTY4*, *TTTY5*, *TTTY6,* and *TTTY17*, each with multiple copies, with a total of 32 copies [5]. Of these, at-least five are expressed only in the testes [1,6]. Complete AZFc deletions (b2/b4) have been found causative of male infertility and result almost invariably in azoospermia or severe oligozoospermia [4]. Partial deletions in AZFc result in mild to severe spermatogenic failure that may cause infertility [7–12]. These deletions occur in about 4–5% of infertile men with azoo- or oligozoo-spermia, making them the risk factors for spermatogenic failure/infertility [9,12–16]. On the basis of palindromic arrangement and propensity of recombination, three distinct AZFc sub-deletions (gr/gr, b1/b3, and b2/b3) were predicted and confirmed to exist in the populations using STS markers [10–12]. Among these, gr/gr deletions are the most prevalent, which remove about 1.6 Mb region taking away two copies of the *DAZ* gene (DAZ1/DAZ2 or DAZ3/DAZ4) and one copy each of the *BPY2* and *CDY1* genes [17]. In a recent meta-analysis on 29 case-control studies, we established a relation between the gr/gr deletions and increased risk of male infertility [18]. Another partial deletion, b1/b3, is relatively less frequent and removes about 1.6 Mb region [10,19]. A third partial deletion is preceded by an inversion event before deletion and is named as b2/b3 or g1/g3 deletion depending upon the type of inversion, which removes about 1.8 Mb and 2.2 Mb regions, respectively [12,20]. The latter two partial deletions (b2/b3 and b1/b3) have been relatively less studied [16].

B2/b3 sub-deletions (also referred to as g1/g3 or u3-gr/gr deletion) lead to the retention of two *DAZ* gene copies, one *BPY2* gene, and one *CDY1* gene. Since a single homologous recombination event cannot explain the origin of a chromosome lacking only sY1191 (b2/b3 deletion), inversion followed by deletion has been suggested to result in structural rearrangements seen in b2/b3 deleted chromosomes. A number of studies have analyzed b2/b3; however, there is a lack of consensus regarding their correlation with spermatogenic failure/infertility [20–24]. In the light of the contrasting results, the link between b2/b3 deletions and spermatogenic failure needs to be critically evaluated. Therefore, we have conducted a systematic review and meta-analyses of the published studies to understand the association between b2/b3 deletions and spermatogenic loss/infertility.

2. Materials and methods

2.1. Identification of studies

A literature search in the public databases such as Pubmed, Google Scholar, and ScienceDirect for the publication period between September 2004 and October 2015 was conducted using generic terms such as 'AZFc deletion', 'Y-chromosome partial deletions', 'b2/b3 deletion', 'Y-deletions and male infertility', 'Y-deletions and spermatogenic failure' in different combinations. The search terms were kept broad to identify all relevant articles and the last search was performed on October 5th, 2015. Initial screening was done to look for b2/b3 data and full text of the relevant articles were obtained. The corresponding author was contacted in case the full text article of a relevant study was not accessible. The references of the selected studies were screened to identify maximum number of studies.

2.2. Inclusion and exclusion criteria

For inclusion in the meta-analysis, each potential article was subjected to the following selection criteria: (a) published in English; (b) published in an international peer-reviewed journal; (c) accessible using 'b2/b3′ or '*AZFc*' as the search term; (d) used sample size of more than fifty in each group tested; (e) employed +/− sequence tagged STS method to detect deletions; (f) used association design including men with spermatogenic failure (oligozoospermia and azoospermia) as cases and those with normal spermatogenesis (verified or presumed) as controls. Studies providing inadequate information and using inadequate methods were excluded from this analysis. In the case of multiple studies from one research group, the materials and methods section was looked into carefully to find if the same subjects were included in more than one study. The best possible care was taken to exclude duplicate studies or those sharing samples with others.