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## INVITED EDITORIAL

Male Infertility

# “Progressive motility” in elucidating novel genetic causes of male infertility

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Asian Journal of Andrology (2022) 24, 229–230; doi: 10.4103/aja202231; published online: 22 April 2022

**G**enetic factors play important roles in the etiology of male infertility. The routine clinical genetic testing for human spermatogenic failure is currently limited to abnormal karyotypes (e.g., 47,XXY for Klinefelter syndrome) and Y chromosomal microdeletions.<sup>1</sup> However, these chromosomal variants only account for approximately 20% of the infertile males with nonobstructive azoospermia. The vast majority of male infertile cases are genetically unexplained.<sup>1</sup> With the recent advances in genomic technologies, the genome-wide dissections at the nucleotide resolution have been achieved, and the novel genetic factors involved in human male infertility have been continuously uncovered. Furthermore, the methodological progresses in gene manipulation (e.g., clustered regularly interspaced short palindromic repeats-CRISPR-associated protein 9 [CRISPR/Cas9]) and animal modeling facilitate functional verifications for the genetic etiology of male infertility. This special issue, “Genetics of Male Infertility”, contains two reviews, five original articles, and one commentary to introduce some recent research progresses in the genetic field of male infertility.

Due to the high genetic heterogeneity, there are plenty of unknown genetic causes to be elucidated for male infertility.

Uncovering these missing genetic etiologies was previously technically challenging. Because of the natural purifying selection on human infertility, these infertility-associated genetic variants could be extremely rare in human populations. Therefore, it is difficult for the candidate gene-based sequencing strategy to identify recurrently mutated genes based on a small sample size of male infertile cases. With the advances in genomic technologies, genetic variants in the protein-coding regions of all the human genes can be efficiently analyzed in a single test via whole-exome sequencing (WES).<sup>2</sup> This technology has been widely used in the genetic studies of human male infertility, especially teratozoospermia affecting the sperm head, tail (flagellum), and the coupling apparatus between them. Wang *et al.*<sup>3</sup> systematically review the genetic pathogenesis of acephalic spermatozoa syndrome (ASS), which is caused by the defects in sperm head–tail coupling apparatus. At least seven genes have been identified as the causal genes responsible for ASS, and *SUN5* (*Sad1 and UNC84 domain containing 5*) and *PMFBP1* (*polyamine-modulated factor 1 binding protein 1*) are the most significant genes contributing to ASS.<sup>3</sup>

Sperm tail malformation, also known as multiple morphological abnormalities of the flagella (MMAF), is another hot field of male infertility. More than half of the MMAF cases can be genetically explained by the genes uncovered during the past 8 years.<sup>4</sup> Here, Zubair *et al.*<sup>5</sup> conducted WES and identified a homozygous missense variant of *CCDC103* (*coiled-coil domain containing 103*) in two infertile brothers with severe sperm mid-piece and tail abnormalities. This study also expands the phenotype spectrum of *CCDC103*. Furthermore, Man *et al.*<sup>6</sup> systematically review and introduce the molecular functions of

intraflagellar transport protein 25 (IFT25) and its interactions with other IFT particle subunits during flagellogenesis.

Genetic defects also affect sperm head. After conducting WES for a case with severe oligozoospermia and macrozoospermia, Kherraf *et al.*<sup>7</sup> identified a homozygous frameshift variant in *ZMYND15* (*zinc finger MYND-type containing 15*), a previously known gene associated with nonobstructive azoospermia. Since *AURKC* (*aurora kinase C*) defect is the major cause of macrozoospermia, Kherraf *et al.*<sup>7</sup> recommended the direct use of WES to discover genetic causes for the macrozoospermia cases with negative *AURKC* diagnosis. In a previous study by Xin *et al.*<sup>8</sup>, WES helped the identification of a homozygous missense mutation of *ACTL7A* (*actin-like protein 7A*) in two infertile brothers with acrosomal ultrastructural defects. In a recent study on *ACTL7A*, Yang *et al.*<sup>9</sup> further showed that *ACTL7A* is a promising biomarker for fertilization outcomes of assisted reproductive technology.

WES has been an efficient genetic method to identify causal genetic variants in male infertility. However, small deletions and duplications cannot be readily ascertained by WES; moreover, most of noncoding variants are beyond the coverage of WES. Therefore, further genetic analyses are needed for the WES-negative cases. Array-based comparative genomic hybridization can reliably identify deletions and duplication in coding and noncoding regions of the human genome,<sup>10</sup> but this technology is not applicable for balanced structural variants. Here, Chau *et al.*<sup>11</sup> conducted low-pass mate-pair genome sequencing for the cases with male infertility and revealed genomic structural variants with truncating breakpoints in spermatogenesis-associated genes and potential noncoding regulatory elements/domains.

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Received: 01 April 2022; Accepted: 02 April 2022

Technical advances in DNA sequencing did help the efficient discovery of novel genetic factors in male infertility. But, the human variant evidence alone is not sufficient to confirm the causal relationship between a specific gene and male infertility. Gene manipulation in animal models is a frequently used strategy for further functional and mechanistic investigations on pathogenic variants. Thanks to the technical advances in gene manipulation, such as CRISPR/Cas9,<sup>12</sup> gene knock-out and knock-in can be efficiently achieved in mouse models. Since most of the spermatogenesis-related genes are predominantly or specifically expressed in the testis, no conditional knock-out is needed when generating mouse models for male infertility; a regular gene manipulation assay is applicable when functionally verifying the identified novel genes in human infertile males.<sup>3,4,8,10</sup> Furthermore, Oyama *et al.*<sup>13</sup> have conducted CRISPR/Cas9-mediated editing in mice and showed that some testis-enriched genes are dispensable for male fertility. As for this phenomenon, Houston<sup>14</sup> has highlighted the potential contributions of environmental factors and gene-environment interactions to the phenotypic variances between human cases and animal models.

As highlighted in this special issue, rapid progresses in the genome technologies and animal models have provided a better understanding of the genetic etiology of male infertility. For some specific subtypes (*e.g.*, MMAF) of male infertility, most of the human cases can be genetically explained, which further facilitate the genetic diagnosis and personalize treatment for the monogenic male infertility. Furthermore, recent progresses in medical genetics also revealed gene-gene interactions and some multilocus variant combinations in manifesting clinical phenotypes.<sup>15</sup> When genetic diagnosis can not be achieved based on the variants at a single locus, their contributions to male infertility cannot be readily excluded. Double or triple, or more hits in different testis-enriched genes may still be involved in male infertility. Therefore, for the male infertile cases negative for any single gene diagnosis, multilocus integrated analysis may be a solution in the future studies of male infertility.

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