Variants in major histocompatibility complex genes: novel factors resulting in male factor infertility?

Genetic influence on male fertility was first demonstrated in 1976 when cytogeneticists Tiepolo and Zuffardi found that a deletion in Yq11 correlated with azoospermia. This finding inspired their identification of the Azoospermia Factor (AZF) gene, which is necessary for spermatogenesis. In 1992, the cloning of the Y chromosome allowed for identification of the Y chromosomal regions that were essential for male fertility. Subregions of the AZF region—AZFa, AZFb, and AZFc—were shown to result in varying degrees of male factor infertility when deleted. Karyotype analysis described higher rates of chromosomal abnormalities in subfertile men compared with the healthy population, with a higher frequency of abnormalities as the degree of infertility worsened. The advent of fluorescence in situ hybridization pushed the bounds of genetics and infertility research further. Sperm fluorescence in situ hybridization has been used to assess defects in meiosis and gonadal mosaicism in males with normal somatic karyotypes, as well as the deleterious effects of gonadotoxins such as caffeine, alcohol, and chemotherapeutic agents. At high resolution, more recent methods, such as array comparative genomic hybridization, whole-genome sequencing, and next-generation sequencing, are able to identify new genes and gene regulatory processes involved in male fertility. The article by Huang et al. (1) contributes to the growing literature exploring the genetic basis of nonobstructive azoospermia (NOA), the most severe form of male infertility.

Monogenic disorders, such as Kallman and Klinefelter syndromes, chromosomal abnormalities including Yq microdeletions, and single nucleotide polymorphisms, have been associated with male factor infertility. Yet, half of male factor infertility cases remain classified as idiopathic (2). The use of novel techniques, such as genome-wide association studies, array comparative genomic hybridization, and next-generation sequencing, has identified >1,000 male fertility-related genes, and although a number of specific genetic abnormalities have been associated with NOA, these alterations likely make up only a small fraction of all of its genetic causes (3). Prior genome-wide association studies have identified specific loci associated with NOA risk, including rs3129878 and rs498422, both of which are located within the major histocompatibility complex (MHC) locus (3). The MHC region encodes human leukocyte antigen (HLA) immune-regulatory proteins involved in immune and autoimmune responses, which may be associated with development of antisperm antibodies in men with cryptorchidism, and may modulate male fertility (4). Other studies have attributed the MHC's role in male fertility to genes involved in spermatogenesis located within or close to the HLA class II region of the MHC locus. Significant differences in the HLA class II allele and haplotype frequencies have been identified between males with normal spermatogenesis and infertile males, further supporting a role for the MHC locus in male infertility. Tsujimura et al. (5) linked the HLA-A33, HLA-B44, and HLA-DR13 antigens and the HLA-DRB1*1302 allele to susceptibility to NOA in Japanese men.

Drawing on a previous genome-wide association study that incorporated 981 men with idiopathic NOA and 1,657 male controls, Huang et al. (1) identified single nucleotide polymorphisms located in the MHC region (29–34 Mb on chromosome 6, National Center for Biotechnology Information human genome build 37), imputed HLA variants, and performed association analyses of these HLA variants with NOA risk. Ultimately, Huang et al. (1) confirmed a previously reported single nucleotide polymorphism—rs7194—as being associated with NOA, and also associated the rs4997052 MHC class I variant, the most novel finding of this investigation. This work is interesting because it further substantiates a role for the MHC locus in male fertility, and identifies additional candidate genetic variants that may be involved in NOA pathogenesis. Huang et al. (1) attribute inconsistencies in previous HLA allele studies to the complex structure of the MHC, the limited number of HLA loci analyzed, or the relatively small sample size used for those studies. However, Huang et al. (1) fail to explain the significance of the MHC structural complexity to their findings, and provide no data causally linking these variants to NOA, which is the most significant limitation of the work, and which limits the ability to use these findings in a clinical setting at this time.

Nevertheless, the study by Huang et al. (1) adds to the growing data on specific genetic alterations that are associated with NOA, and can potentially meaningfully inform clinical practice in the near future. As clinicians working with infertile couples, one of our most significant limitations is the inability to inform them of the exact reason why the male partner has NOA. With an increasing understanding of the genetics of male factor infertility, we can look toward a future in which these conditions are precisely diagnosed and for which we can offer definitive, effective treatment. As Huang et al. (1) state, the continued discovery of these associated variants holds importance for the future, as these genetic variants possess the potential to be used as biomarkers for NOA in high-risk individuals, as well as targets for treatment.

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