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INVITED COMMENTARY

Male Infertility

The role of *CFTR* p.G970D missense mutation in male infertility

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Over the years, accumulating evidence has confirmed the crucial role of cystic fibrosis transmembrane conductance regulator (*CFTR*) mutations in male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), the most common cause of obstructive azoospermia (OA).[1,2] The distribution and frequency of *CFTR* mutations in CBAVD patients vary considerably across countries and ethnic groups, and this suggests the need to develop regional variant panels to significantly improve diagnosis and management of infertile males. Anyway, it is surprising that alterations in the *CFTR* gene may also influence spermatogenesis and sperm quality, suggesting the crucial role of a correct genotype–phenotype correlation in CFTR-related disorders (CFTR-RD). Based on this evidence, genetic counseling is particularly important to estimate the risks of having an affected child with chronic or severe diseases and to discuss the impact of novel CFTR variants on reproductive health.

In the recent issue of *Asian Journal of Andrology*, Hou *et al.*[3] investigated the relationship between loss-of-function *CFTR* p.G970D missense variant and male infertility. First, the authors identified the presence of the homozygous p.G970D variant in a patient with CBAVD and nonobstructive azoospermia (NOA). Several studies have reported an increased frequency of the *CFTR* mutation in NOA and severe oligozoospermia. There are some concrete evidence to support the hypothesis that CFTR proteins can affect spermatogenic function and sperm quality.[4] The impairment in CFTR protein quantity or quality varies widely based on genetic mutation class and type.[5] However, further investigation is needed to confirm this aspect. Second, the authors conducted a retrospective analysis of Chinese patients with CBAVD and showed that p.G970D is a common pathogenic variant in infertile male patients. Taken together, these findings provide evidence that ethnicity/geography affects the frequency and spectrum of *CFTR* mutations in CBAVD patients. In this context, a population-specific panel should be designed to provide precise molecular diagnosis to couples before undergoing assisted reproductive technologies (ART). To this regard, the identification of novel CFTR variants in these couples has important implications for genetic counseling. In fact, the estimate of the risk of having children with *CFTR* mutations is crucial for the reproductive choice of future parents. The data are interesting regarding functional genomics studies to verify the effects of *CFTR* p.G970D mutations on spermatogenesis. In particular, the authors have generated *CFTR* p.G970D-mutated cell models using the clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9) technology. *In vitro* data obtained are interesting, and p.G970D mutation may affect the proliferation of spermatocytes and Sertoli cells. In addition, this novel variant might influence CFTR expression and alter *CFTR* RNA splicing in spermatocytes. These important results demonstrate for the first time that *CFTR* p.G970D mutation is associated with disrupted spermatogenesis, especially during the early stage. From a practical clinical point of view, these data suggest usefulness of extending CFTR testing to other categories of infertile men, in particular patients with severe oligozoospermia or with reduced ejaculate volume. Although the role of this mutation in azoospermia requires confirmation in a larger patient cohort, it would be appropriate to include this variant in the routine CFTR screening not only in Chinese men with CBAVD but also in populations outside of China. In this scenario, molecular diagnostic based on sequencing of the entire *CFTR* gene followed by MPLA analysis could be considered for genetic analysis in Chinese patients.[6] Finally, the authors highlighted some limitations in their article: (i) the insufficient sample size; and (ii) more evidence needed to clarify the function of p.G970D variant. In view of these considerations, further studies should be conducted to confirm these interesting data in the future.

Based on this new insight, the identification of novel pathogenic variants emphasizes the importance of regional diagnostic protocols to improve medical and genetic care of infertile men.

COMPETING INTERESTS

All authors declare no competing interests.

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