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ETV5 mutations: revisiting Sertoli cell only syndrome

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Infertility, despite its high incidence and long history in human society, is still somewhat of a mysterious health condition. Naturally, semen defects like low sperm concentration, low sperm motility, and poor sperm morphology are associated with reduced fertility. However, normal semen parameters are not a guarantee for normal fertility. Among semen defects, azoospermia (absence of germ cells in the semen) and Sertoli cell only syndrome (SCOS, absence of germ cells in the semen and testis, also known as Spermatogenic Failure) are the most serious pathological conditions. Currently, genetic factors are considered to play an important role in male factor infertility (1). However, for many years the medical and general public perception was that chromosomal aberrations and Y-chromosome microdeletions were mainly responsible for azoospermia and oligozoospermia (2, 3). Although it is not disputable, respective genetic testing could only identify those defects in a small proportion of patients seen in the andrology clinic. The remaining majority of patients have descriptive or idiopathic diagnoses of male factor infertility. Despite many attempts and a wealth of animal male infertility models (4), little is known about the genetic basis of azoospermia and SCOS in patients with idiopathic male factor infertility.

One of the few successful attempts to reveal the genetic cause of SCOS is presented by Dr. O'Bryan and colleagues in the article ‘‘Genetic variants in the *ETV5* gene in fertile and infertile men with non-obstructive azoospermia associated with Sertoli cell only syndrome’’ in the *Fertility and Sterility* journal (5). In the article, Dr. O'Bryan and colleagues demonstrated a great example of an integral approach to human translational studies. They performed a thoughtful selection of patients with SCOS clinical phenotype and successfully collected a sufficient number of patients with azoospermia and SCOS. *ETV5* was carefully selected as a plausible gene-candidate based on the mouse orthologue knockout model with SCOS and male factor infertility (6). An antibody against human ETV5 protein was generated, which collectively provided valuable evidence that the protein has significant expression in human testis tissue and is important for spermatogenesis. Finally, they carried out an excellent genetic investigation screening of DNA alterations in all exons and flanking intronic regions by Sanger DNA sequencing in a fairly large population of azoospermic patients and fertile controls. Although the article reports only a small proportion of azoospermic patients with *ETV5* mutations, this outcome is not surprising, considering that there are hundreds of important genes that are expressed during various stages of human spermatogenesis or control the male reproductive function of mature spermatozoa. One

would estimate that genetic defects in each single gene would represent <1% of the total disease load (considering random distribution of genetic defects in studied population).

Last, but not least, an important note to those who study complex and heterogeneous conditions: the investigators carried out commendable research cooperation. They combined resources and efforts from two research groups in different countries and demonstrated the effectiveness. Such collaborative efforts should be applauded considering the highly competitive environment of research. It brings optimism and promising new opportunities to investigations of the genetics of azoospermia and male factor infertility in the future.

In summary, this is first study that shows an association of *ETV5* gene defects with SCOS. Yet, replication studies are needed to corroborate results of the present report. This would support initial findings and could bring importance of the gene to a new level, by its utilization in future preconception genetic testing of parents, as mutation carriers, and/or preimplantation genetic testing.

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