X-CHROMOSOME GENE VARIANTS AND THEIR IMPACT ON SPERMATOGENIC FAILURE

The authors of a study that appeared in 2013 (Mueller et al. 2013, Nature Genetics[1]) showed that some ampliconic genes on the X chromosome are primarily expressed in testicular germ cells and are functionally connected to sperm production. These results suggested that the X-chromosome, like the Y-chromosome, is crucial for male fertility. Consequently, the X chromosome has become a good candidate for discovering new genetic causes of spermatogenic failure. Nevertheless, the current list of causes is not that long; even with the use of high-throughput sequencing technologies, the number of X-chromosome gene variants associated with male infertility remains low (reviewed by Houston et al. 2021, Human Reproduction Update[2]).

In a recent article published in the American Journal of Human Genetics (Riera-Escamilla et al. 2022[3]), the authors present an analysis of the whole set of X chromosome protein-coding genes in a huge population of infertile patients. Specifically, a total of 2,354 men with idiopathic non-obstructive azoospermia (absence of sperm in the ejaculate) or cryptozoospermia (fewer than 100,000 sperm per milliliter of ejaculate) have been screened using whole exome sequence analysis. The main objective of the article was to identify new monogenic anomalies associated with severe spermatogenic defects.

This article makes one realize the importance of some crucial steps in this kind of study, such as variant filtering and the application of different strategies of gene selection and prioritization. The authors identified 21 novel gene anomalies linked to severe spermatogenic failure. Importantly, the 21 candidate genes were found to be crucial for spermatogenesis-related pathways.

The results presented in this paper emphasize the importance of the X chromosome in the etiology of male infertility by doubling the number of X chromosome genes associated with severe spermatogenic defects. From a clinical perspective, these results will contribute to the development of gene panels addressed to the diagnosis of male infertility.

1 https://www.nature.com/articles/ng.2705

2 https://academic.oup.com/humupd/article/28/1/15/6366465?login=false

3 https://www.cell.com/ajhg/fulltext/S0002-9297(22)00260-9