The diagnostic potential of whole exome sequencing in infertile men due to sperm production defect

Male factor infertility is an important clinical problem whose most severe phenotype, severe oligospermia or azoospermia, has a variety of genetic causes. Some, like Klinefelter syndrome or cystic fibrosis, are well understood, but most are still unknown, and Y chromosome microdeletions only explain a fraction of the remaining cases. In consanguineous and nonconsanguineous families, whole exome sequencing (WES) has been successfully used to identify likely causal mutations in severe oligospermia (1, 2).

In this issue, Tu et al. (3) use WES in a set of Han Chinese brothers with idiopathic severe oligospermia and identify a rare recessive mutation in RPL10L that may account for the phenotype. They then demonstrated decreased protein levels compared with the wild type in an in vitro model, examined a cohort of fertile and infertile men for the incidence of RPL10L mutations, and demonstrated a higher frequency in infertile men with oligospermia. Previous studies have not directly examined the incidence of identified variants in other infertile men, therefore this study sheds light on how generalizable the WES studies can be. Identifying this variant at higher frequencies in infertile men should make researchers hopeful that even rare mutations can be validated.

Because differentiating between causes of male factor infertility has clinical utility, WES may eventually become a part of the workup for men with idiopathic severe oligospermia or azoospermia in whom the usual tests, such as Y chromosome microdeletion and karyotype, have not yielded any abnormalities. Future directions of this work may include [1] pooling large cohorts of men with azoospermia for WES, [2] the use of WES and analysis of genomic structural variation in cases where WES fails to yield a result, [3] more in vitro confirmatory work when possibly causal variants are identified, and [4] identifying a future male factor infertility diagnostic gene panel that has sound evidence to support the gene-disease relationship.

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