DECODING THE GENETIC ETIOLOGY OF FEMALE INFERTILITY: INSIGHTS FROM DE NOVO MUTATIONS

Infertility is a widespread issue affecting more than 10% of women of reproductive age. Oocyte maturation arrest and early embryonic arrest are among the leading causes of this phenotype. But, despite its prevalence, the molecular mechanisms that underlie these conditions remain poorly understood. To address this gap, the authors of this study investigated the role of de novo mutations (DNMs) in female infertility (Li e t al. 2023[1]; Genome Biology 24:68). They analyzed whole exome sequencing data from 473 infertile parent-child trios and identified 481 DNMs, with around 8.32% affecting genes presumed to be involved in female reproductive biological processes. Gene Ontology analysis revealed significant associations with meiosis, embryonic development, and reproductive development. The study focused on TUBA4A, which showed the most significant enrichment of rare DNMs in the infertile trios. Functional assays showed that TUBA4A mutations led to microtubule instability, reduced rates of oocyte maturation, and disruptions in embryo development, mimicking the infertile phenotypes observed in women. The study also identified three other genes (UBQLN1, HTR2C, and ZFPM2) that may play a role in female infertility besides TUBA4A. UBQLN1 is a granulosa cell biomarker for predicting pregnancy in ART, alterations of HTR2C have been associated with implantation failure and pregnancy loss after IVF, and ZFPM2 is necessary for proper fetal ovary development.

This study sheds light on the genetic etiology of female infertility with oocyte and embryo defects and highlights the role of DNMs in human infertility, as demonstrated in other human diseases.

1-https://genomebiology.biomedcentral.com/articles/10.1186/s13059-023-02894-0