

FEMALE INFERTILITY - TWO NEW AUTOSOMAL GENES

Two papers in the July 2, 2020 issue of the American Journal of Human Genetics provide evidence for two novel, autosomal recessive causes for female infertility in humans. Both were identified in patients with normal menstrual cycles and multiple unsuccessful IVF attempts. Both papers originate from the same collective of fertility clinics and reproductive research institutes in Shanghai and other cities in China, and both demonstrate the power of Whole Exome Sequencing (WES) in the identification of genes underlying monogenic disorders of human reproduction.

First, [Zheng et al.](#) identified homozygous inactivating variants in the B cell translocation gene 4 (*BTG4*) in females from different consanguineous families. Oocytes from the affected females could be fertilized but failed to cleave. Studies of gene expression in the zygotes from these patients showed that hundreds of distinct maternal mRNA species failed to become degraded, thereby providing an explanation for the zygotic cleavage failure (ZCF) phenotype.

Second, [Zhang et al.](#) detected compound heterozygous and homozygous pathogenic missense variants in the Thyroid hormone receptor interactor 13 (*TRIP13*) gene in infertile female patients who had oocyte meiotic maturation arrest. In the mouse, *TRIP13* serves to complete meiotic recombination by removing *HORMAD2* from synapsed chromosome axes. In lymphoblastoid cell lines of the patients an abnormal accumulation of *HORMAD2* was observed. Injection of wild type, but not of mutant *TRIP13* cRNA into HeLa cells could prevent *HORMAD2* accumulation. Injection of wild type *TRIP13* cRNA into oocytes of one affected female resulted in completion of oocyte maturation as demonstrated by first polar body extrusion, successful fertilization and development up to the blastocyst stage. These observations may indicate novel therapeutic treatment options for oocyte maturation arrest.