Genetics of premature ovarian failure (POF)

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Abstract

Premature ovarian failure (POF), as an increasing common disorder in reproductive aged women, its nomenclature becomes controversial and consequently its prevalence remains obscure. POF presents with a high heterogeneity in causes and a genetic contribution is considered paramount; yet identifying its genetic basis has been challenging, with most discoveries failing to be replicated. Here, we focus on the common genetic factors associated with POF reported in the past decades to facilitate to refine the complex genetic architecture that underlies POF spectrum.

Considerable progress has been made in identifying chromosomal regions and genes of interest with karyotyping and fluorescent in situ hybridization (FISH), particularly on chromosome X. Causative
mutations with deleterious effect identified by candidate gene research have been found in more than a dozen of genes, with most idiopathic and in a low frequency. Recent genomic studies (GWAS, CGH) revealed multiple susceptible loci or copy number variations (CNVs) potentially associated with POF in different populations, but in each it was difficult to map specific causative genes and results were seldom replicated. Furthermore, it is still a long way to elucidate the causative mechanism of these identified variants in POF. Whole-exome sequencing (WES) in POF pedigrees has been conducted and causative genes related with meiosis and DNA damage repair were found, which has provided new clues for pathogenesis of POF. Therefore, the studies in POF genetics are underway, although with tentative findings and slow progress, and the aetiology in most cases remains poorly characterized.

It is timely to take stock of the field, to outline the progress that has been made, and to candidly review the controversies and prospects for the future of POF genetics. With the development of high throughput sequencing technique, more genome variants will be revealed, but the results and further mechanism exploration still need to be addressed. Future advances will require strategies that target on precisely phenotyped, larger cohorts of patients, distinct approaches for sporadic
and familial cases, and incorporating environment, bioinformatics and integral signaling pathways into genetic analysis. Additional inputs, plausibly including epigenetic mechanism, non-coding RNA, transcriptional modifiers should be also considered.