# Next-generation Sequencing Panel Help to Find Genetic Defects of Premature Ovarian Insufficiency

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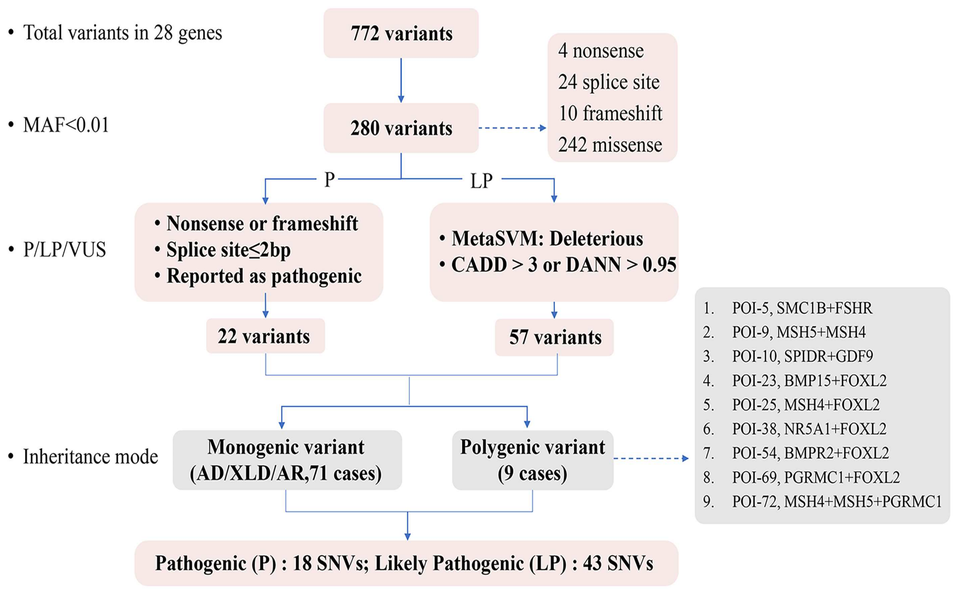
## Abstract

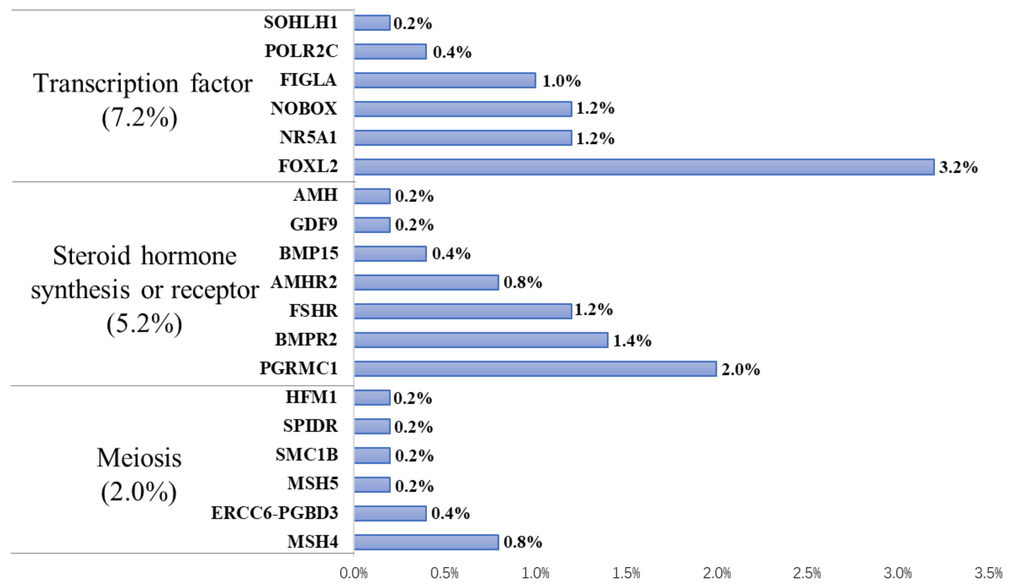
**Background:** Premature ovarian insufficiency (POI) refers to the loss of ovarian function before 40 years of age (1). The etiology of POI is heterogeneous, and genetic factors account for 20–25% of cases (2). With the development of next generation sequencing, new candidate genes and variants responsible for POI have been identified. However, how to transform these genetic findings to clinical molecular diagnose remains a challenge (3).

**Methods:** A next generation sequencing panel with 28 known causative genes of POI was designed, and a large cohort of 500 patients with POI was screened directly. The clinical characteristics were compared between patients carrying monogenic variations and those with digenic or multigenic variations.

## Result

A total of 14·4% (72/500) of the patients carried 61 pathogenic or likely pathogenic variations in 19 of the genes in the panel. Interestingly, 58 variations (95·1%, 58/61) were firstly identified in patients with POI. *FOXL2* harbored the highest mutation frequency (3·2%, 16/500), among whom presented with isolated ovarian insufficiency instead of blepharophimosis-ptosis-epicanthus inversus syndrome. The novel compound heterozygous mutations in *NOBOX* and *MSH4* were confirmed by pedigree haplotype analysis, and digenic heterozygous mutations in *MSH4* and *MSH5* were firstly identified. Furthermore, nine patients (1·8%, 9/500) with digenic or multigenic pathogenic variants presented with delayed menarche, early onset of POI and high prevalence of primary amenorrhea compared with those with monogenic variation(s).




## Conclusion

In conclusion, a self-designed targeted gene panel screened in 500 patients with POI expanded the variations spectrum and genetic architecture of POI. Specific variations in pleiotropic genes may result in isolated POI; whereas polygenic defects could exert cumulative deleterious effect on clinical severity and phenotype of POI. A fuller understanding of POI genetics would contribute to the individualized prediction, diagnosis, and intervention for women with POI or at high risk for developing POI.

## References

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