ENRICHMENT OF GENETIC VARIANTS RELATED TO INFERTILITY IN FEMALES SEEKING FERTILITY TREATMENT

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Background: Infertility is a public health problem that affects 12% of women in their lifetime [1]. Genetic factors have previously associated with molecular pathways related to infertility: ovarian hyperstimulation syndrome (OHSS)[2], polycystic ovarian syndrome (PCOS) [3], recurrent pregnancy loss (RPL) [4] and premature ovarian insufficiency (POI) [5].

Objective: This study aimed to evaluate the rate of genetic mutations in candidate genes impacting OHSS, PCOS, RPL and POI, in females who underwent carrier screening as a part of their fertility treatment. The ultimate goal was to create a genetic diagnostic panel that assessed those four conditions related to infertility.

Materials & Methods: Through examining the literature on each of the conditions, we obtained a comprehensive list of genes that caused (tier 1) or associated with (tier 2) one or more of the infertility conditions (OHSS, PCOS, RPL and POI). Genes were evaluated to determine the frequency of curated pathogenic mutations in our database and compared to the allele frequency in the 1000 Genomes Database which represents the general population. Chi-square with Yates' correction was used to determine statistical significance in the comparison of the allele frequencies.

Results: Our cohort, which is biased towards people who have experienced infertility, is enriched for genetic mutations that might account for infertility. For example, frequency of *F5* 1601G>A mutation is 2.0% in our population compared to 0.6% observed in the 1000G cohort ($p<0.0001$). Frequency in our population of *F2* *97G>A mutation is 1.3% compared to 0.36% in the 1000G cohort. Furthermore, several genes such as *GALT*, *CYP19A1*, *FMR1*, and *LHCGR* have higher mutant allele frequency in our population compared to the 1000G cohort, although the differences are not statistically significant.

Conclusions: Genetic mutations in genes contributing to ovarian hyperstimulation syndrome, polycystic ovarian syndrome, recurrent pregnancy loss and premature ovarian insufficiency are enriched in females seeking fertility treatment. Our results indicate a role of genetics in the development of infertility, and underscore the need of genetic tests to help guide medical decisions.

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