CLINICAL EXOME SEQUENCING AS A DYNAMIC APPROACH FOR THE GENETIC INVESTIGATION OF UNEXPLAINED INFERTILITY

CONSTANTOULAKIS, PANTELIS; ARGYRIOU, ANASTASIOS; DAFNIS, DIAMANTIS; GIAKOUMAKIS, IOANNIS; COSTARAS, CONSTANTINOS; GEORGIAKODIS, FOTIOS; OIKONOMAKI, AIKATEPINI; CHRISTOPOULOU, GEORGIA

Abstract Body

Introduction: Even though infertility is not typically a disease, it constitutes a major healthcare issue with substantial psychosocial and economical impact. The etiology is highly heterogeneous and besides all efforts, many couples remain undiagnosed. Most likely, idiopathic subfertility/infertility cases have a genetic background and may not be detected by standard investigations.
Aim: The application of clinical exome sequencing may reveal the genetic grounds of infertility, escaping traditional approaches by analyzing, in parallel, all genes known to be implicated in reproductive pathways; even those without a strong correlation yet.
Method: For the implementation of Next Generation Sequencing, DNA was extracted from blood or swab samples of men and women with fertility issues. Subsequently, exons, exon/intron boundaries and regulatory elements of 4.900 clinically significant genes were capture-enriched by >150.000 probes designed against the human genome by SOPHiA® Genetics. Following sequencing, complex bioinformatics analysis was performed and findings were classified based on their pathogenicity, according to database entries and peer reviewed literature (SOPHiA® DDM analytics).
Results: The gene spectrum analyzed was selected, mainly based on the Human Phenotype Ontology database. A total of 109 genes were included with either established correlation to both male and female infertility or a known role in reproductive pathways. Thirty two cases of men and women with unexplained infertility were investigated in 28 of which either a pathogenic or a likely pathogenic mutation was detected.
Discussion: Until recently, in order to investigate the genetic background of infertility at the gene level, single gene testing was performed. This approach is time consuming, expensive and most importantly, it fails to designate a substantial proportion of genetically undetermined infertility. Furthermore, more than one genes, as well as gene-gene interactions might be the cause of the complicated phenotypic pathology of infertility. Robust genomic methods, such as next generation sequencing of the clinically significant exome, allow for simultaneous gene investigation of well established causative genes along with others implicated in the female and male reproductive tracts. Thus, new technologies may overcome the aforementioned limitations, significantly contributing to an optimum reproduction choice and the fittest IVF strategy to be applied to each couple.