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Abstract Topic:- Molecular and cytogenetic diagnostics

Abstract Title:- Deciphering role of de novo variants in genetic etiology of male infertility in India

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Aims:-To detect de novo variants and novel genes involved in the genetic architecture of male infertility (MI) through whole exome sequencing in patient-parent trio cohort.

Methods:- A cohort of 16 patient-parent trios were subjected to whole exome sequencing (WES) at a mean coverage of 100x and reads aligned against hg38 human genome build. Only patients with clinical history of idiopathic MI, sperm concentration <10 mil/ml and normal level of endocrine hormone levels were recruited on the study. Furthermore, these patients had prior genetic report of a normal karyotype and Yq microdeletion test. De novo variants (DNM) in WES dataset were called using a convoluted neural network based DeNovoCNN variant caller. Candidate DMN were shortlisted by posterior probability score >0.5, proportion of reads containing the DNM between 30-70% in patient and <10% in parents. All DNM were validated by Sanger sequencing.

Results:- In cohort of 16 patients, 43.8% had azoospermia, 31.3% had severe oligoasthenoteratozoospermia, 12.5% had oligospermia and 6.3% had oligoasthenozoospermia and normozoospermia each. In total, 27 DNM across 16 patients were detected with each MI patient having 1.7±1.5 DNM (min=0 and max=5); 4 patients were not detected with any DNMs. Interestingly, a de novo probable loss of function variant c.886C>T (p.Gln296Ter) was detected in the CCDC183 gene. The gene is predicted to be intolerant to loss of function variants (pLOUEF=0.98), has enriched expression in testis during spermatogenesis specifically early and late spermatids stage, and is essential for cilia construction in Drosophila. Of note, no significant correlation between the number of DNM in the patient and the age of parents was observed.

Conclusions:- We present India's first patient-parent trio approach to studying the genetic architecture of MI in India and provide evidence for CCDC183 gene as a potential candidate for causing MI.

Keywords:- Male infertility, de novo variants, whole exome sequencing, sanger sequencing, diagnostic yield