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Abstract Title:- Delineating genetic architecture of male infertility in India

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Aims:-Approximately 7% of the male population worldwide is affected by male infertility (MI). Genetic factors play a significant role in the etiology of MI. The latest WHO guidelines recommend only karyotype and Yq microdeletion analysis which has a combined diagnostic yield of 10-25%, therefore, a large proportion of patients don't receive genetic diagnosis. Recent studies suggest monogenic forms of MI phenotypes but these are not tested in clinical practice and no systematic genetic analysis of MI has been carried out in India to date. Our aim was to decipher the genetic architecture of 7 common forms of MI phenotypes in India- azoospermia, oligospermia, asthenospermia, teratozoospermia, acephalic sperm, globozoospermia, and cryptozoospermia.

Methods:- 244 patients with a clinical history of idiopathic MI, sperm concentration <10 mil/ml, and normal level of endocrine hormone levels were recruited for the study. Karyotype and Yq microdeletion analysis was carried out in all patients. Patients with normal karyotype and Yq microdeletion report and their parents were invited for whole exome sequencing (WES) study. A total of 41 patient-parent trios were subjected to WES at an average of 100x and read alignment against the hg38 genome build. Candidate SNVs were validated with Sanger sequencing.

Results:- Of 244 patients- 115 (47%), 76 (31%), 24 (9.9%), 12 (5%), 4 (1.6%), 4 (1.6%) and 2 (0.9%) have Oligoasthenoteratozoospermia, azoospermia, oligospermia, asthenospermia, teratozoospermia, cryptozoospermia and globozoospermia, respectively. Karyotype analysis diagnosed Klinefelter syndrome in 1 patient with azoospermia whereas Yq microdeletion analysis showed partial AZF deletions in 19 cases (13 with gr/gr, 4 with AZFb+gr/gr, 1 with AZFc, and 1 with AZFc+gr/gr deletion); the combined diagnostic yield was 8.2%. In patient-parent trios, no causative CNVs were detected, however, SNVs in 13 genes previously known to cause MI were identified in 14 patients (diagnostic yield= 34%). Of interest, a quarter of the variants were detected in genes involved in sperm tail morphology, specifically dynein genes- DNAH1, DNAH10, DNAH1, and ODF1. Furthermore, we detected maternally inherited heterozygous SNV in the RBM5 gene which has previously been implicated in MI. Lastly, de novo SNV was detected in a candidate gene- CCDC183 whose expression is enriched in the testis.

Conclusions:- We describe the genetic architecture of MI in India through a systematic analysis of infertile males and demonstrate a significant proportion of monogenic forms of infertility as the cause of MI

phenotype which has implications on ART outcome and reproductive fitness for future progeny. We also provide evidence for CCDC183 as a potential MI candidate gene.

Keywords:- Male infertility, Yq microdeletion, phenotypes, WES, ART