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Abstract Title:- Genome to Phenome Pathway Functional Annotation Using Whole Exome Sequencing of Prostate Cancer Specific to India

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Aims:-To explore the associations between PCa and comorbidities by utilizing whole exome sequencing (WES) potentially leading to better diagnosis and treatment strategies.

Methods:- We performed a pilot study by applying (WES) on comorbid 5 samples of prostate adenocarcinoma cancer from north-western region of India. We used Illumina NOVASEQ 6000 platform for sequencing wherein raw data was analysed using our bench marked pipeline in two phase's viz., pre-processing which involves read alignment, variant discovery and variant prioritization and then down-analysis with different databank tools. We performed the pathway enrichment studies to highlight the crosstalk with other pathways. We screened a gene set of 37 genes with significant pathogenic, clinically verified variations from which we selected 13 gene mutations for validation with help of Sanger sequencing. These variants helped to predict the risk and the polygenic effect in PCa. Later, we matched the number of variants of different aged patients to each other and their Gleason score statistics to conclude which age category has more tumor burden.

Results:- We have identified a total of 123,480 variants from our cohort genome. One sample seemed highly mutated with 43,701 mutations. The significant mutations harbored by our cohort were mostly non synonymous missense mutations and putative somatic mutations. The selected mutated genes set of 13 genes i.e., MYO15A, MPO, MYRF, BRCA2, ATM, PTEN, HNF1A, ITGB4, GJB2, PKP2, SDHB and UBR1, identified with significant mutations helped to establish the associations with diabetes. The studies through databanks, pathway enrichment analysis and literature search showed that most of the genes are enriched in the pathways of glucose metabolism, insulin resistance and other disease conditions like mitochondrial dysfunction linked type 2 diabetes, prediabetes, type 2 diabetes, alcoholic cardiomyopathies, inherited hearing loss with maternal diabetes, and other cardiovascular diseases. On correlating the variant burden we found the patient with Gleason score of 4+4 and age of 80 years has the highest variations and suggesting higher tumor burden as compared to the 3+4 (60 and 68 years) and 3+3 (65 and 70 years) which had lower variation count.

Conclusions:- The correlation of the grading score and number of mutations gave the prediction that the patients with age 80 or above and Gleason score of 8 had higher tumor burden. Also, the result of this study confirms that there is an association between PCa and comorbidities like diabetes and cardiovascular diseases. The study moreover highlights the need to consider the comorbidities at the time of both diagnosis and treatment. Further investigation is warranted to understand more about the mechanism and early prediction of PCa.

Keywords:- Diabetes, Heterozygous, adenocarcinomas, Whole Exome Sequencing, Prostate Cancer, Polygenic