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Abstract Title:- Unravelling the Genetic Basis of Prostate Cancer Phenotype in the Indian Population
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Aims:-This study aims to explore the genetic variations associated with prostate cancer (PCa) in the Indian population through Whole Exome Sequencing (WES)

Methods:- 39 Malignant PCa FFPE samples with Gleason grade between 7-9 were collected from CK/Rukmani Birla hospital, Jaipur with institutional ethics committee (IEC) clearance and informed consent from all participants was duly obtained prior to the commencement of the study as part of our Cancer Prostate consortium of India (CAPCI) efforts. WES was performed on an Novaseq 6000 Platform with the raw reads then run through our in-house benchmarked variant calling pipeline, CONsensus Variant EXome (CONVEX) which employs four different variant callers, viz. VarScan, bcftools call, vt and Freebayes to obtain consensus variants of significance, after which gene annotation was done using ANNOVAR/SnpEff. The list of common variants among all samples was then compared to the missense deleterious genes obtained after benign subtraction earlier reported by Ravindran et al., 2023 to obtain a list of common genes representative of both north and south indian population. Furthermore, the list was compared to that of the OncoArray chip project from Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) consortium which genotyped 140,000 PCa patients of European ancestry for 600,000 SNPs associated to PCa and other cancers.

Results:- Our analysis revealed a spectrum of genetic alterations with 2561 variants found to be consensus to all malignant samples of which 1669 were identified as exonic variants, 724 intronic and 28 ncRNA variants. Among the exonic variants, 754 were identified as non-synonymous using ANNOVAR/SnpEff. Key cancer-related genes that were consensus in our samples include CYP11B2, COL6A1, MYO15A, HEXB whose role in tumour invasiveness, angiogenesis and metastasis has been extensively studied. The comparison of our list of consensus variants to the missense deleterious genes' list reported by Ravindran et al., 2023 revealed six common genes, viz. ERV3-1, GPRIN2, MUC16, PHC1, UMODL1 and ERV3-1-ZNF117 readthrough. Notable among these are MUC16 which is found to be overexpressed in various cancers and promotes migration and invasiveness of cancer cells and ERV3-1, an endogenous retroviral protein which could possibly serve as a prognostic marker. The comparison of consensus variants from our data to OncoArray data from PRACTICAL consortium revealed 118 SNPs common between the datasets representing common SNPs between Indian and European populations.

Conclusions:- The WES performed on PCa samples in our study revealed a diverse genetic landscape of the Indian PCa phenotype , emphasising the need for population-specific studies to better understand the disease. The genetic variations identified in this study may open new avenues for further research into their functional significance and potential as novel diagnostic and prognostic markers.

Keywords:- Prostate cancer, systems genomics, next generation sequencing, exome sequencing, variants.