Genetic Variants and Polygenic Risk Score for Predicting Prostate Cancer Aggressiveness

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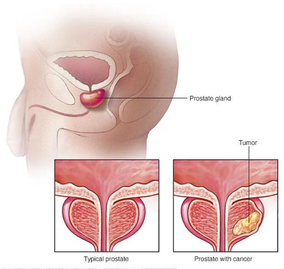
Background

- Prostate cancer (PCa) is the most common malignancy among men, accounting for ~30% of cancer cases and ranking second in cancer-related deaths in the United States.
- While individual SNPs associated with PCa aggressiveness have been identified, their effects are often weak.
- Polygenic risk scores (PRS), which aggregate multiple SNPs, have been developed to improve prediction.
- The PRS with 290 SNPs, of which 270 are biallelic SNPs (PRS-m270) is a published score, which can predict age at diagnosis of aggressive PCa (Huynh-Le et al., 2022)



- **Objective:** This study investigates the impact of this polygenic risk score (PRS-m270) in predicting PCa aggressiveness among White patients.

Method

- This study used the SNP data from 309 PCa patients with self-reported white race from the archived blood samples in LSUHSC and Moffitt Cancer Center.
- After applying quality control procedures, which include SNPs and samples with call rates ≥80%, minor allele frequency (MAF) ≥0.01, 305 patients and 495,318 SNPs remained.
- PRS was calculated using the 270 biallelic (PRS-m270) SNPs, but only 41 were available in our data.
- Logistic regression models were used to assess SNPs (treated as an additive inheritance mode as 0, 1, and 2), PRS for predicting PCa aggressiveness (~12% prevalence).

Results

- Among the 41 SNPs in PRS-m270 identified in 305 self-reported white patients, 3 SNPs rs5919393 (AR), beta-microseminoprotein gene (MSMB) rs10993994 & rs34540271 (ADAMTSL1)) were promising ($p<0.05$) for predicting PCa aggressiveness (*Figure 1*).
- The patients with the G allele in each SNP had a significantly higher risk of developing aggressive Pca (*Figure 2*).
- However, the combined PRS with 41 SNPs did not significantly predict aggressive Pca. (*Table 1*)

Results

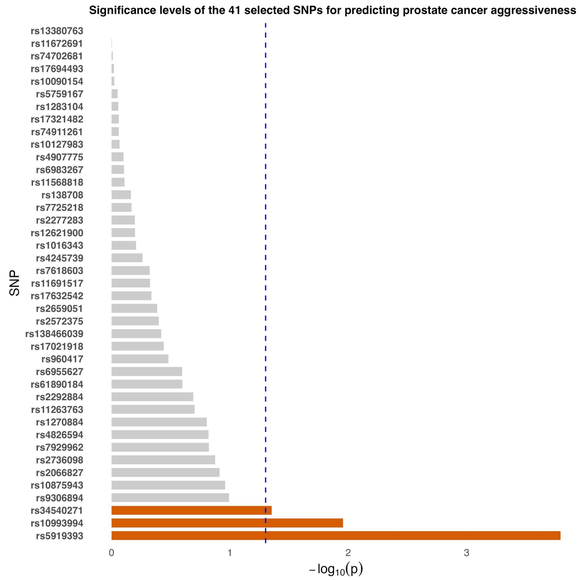


Figure 1: bar plot showing the $-\log_{10}(p)$ values for 41 SNPs

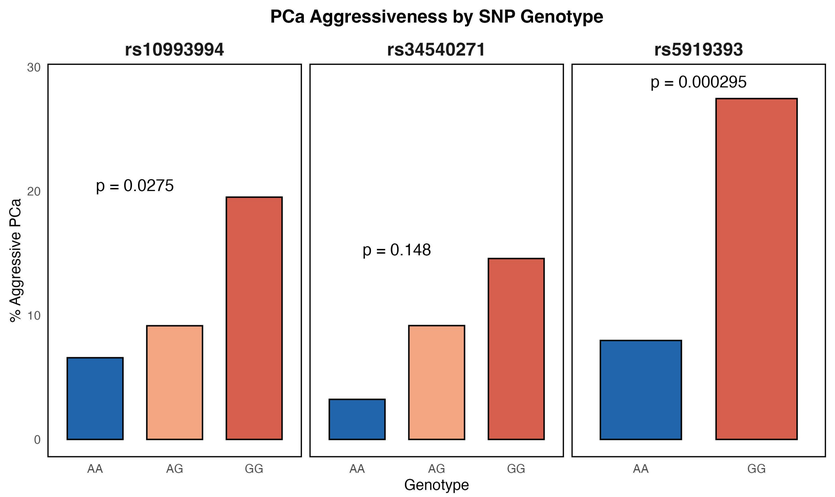


Figure 2: Bar plots for the percentage of aggressive PCa cases by genotype for the three promising SNPs

Table 1: Odds ratio estimate for PRS predicting aggressive prostate cancer; wide CI indicates uncertainty due to sample size.

	OR	p
PGS331_s43	0.509 [0.017, 15.441]	0.698

N=112 (with complete data for all 41 SNPs)

Discussion

- **Literature Evidence:** rs10993994 (*MSMB*) has been significantly associated with prostate cancer risk across multiple studies (Fu et al., 2019). *AR* gene may influence transcription, which causes an increase in Pca (Yoon BW et al., 2022).
- While three SNPs showed promising associations with PCa aggressiveness, the combined PRS did not significantly predict aggressive disease.
- The lack of significant association in the PRS may be due to limited availability of genotype data, with only 15% of target SNPs available, and a small sample size (n = 112) caused by missing data. Several SNPs showed some missingness (e.g., rs10090154: 58 missing; rs17021918: 17; rs7725218: 41; rs2736098: 48)
- Our significant individual SNPs predictor supports the biological relevance of these loci in PCa aggressiveness and aligns with other findings showing their potential role in PCa progression.
- The incomplete genotype data and resulting reduction in statistical power could have hindered the ability to detect a robust effect of the composite PRS.

Future Steps

- To improve robustness of PRS, future analyses will incorporate imputed SNP data to better assess the clinical utility of the PRS in predicting Pca aggressiveness.
- Genotype imputation will be conducted using Michigan Imputation Server) with the TOPMED reference panel; variants with INFO ≥ 0.3 will be retained.
- After Imputation, we will proceed to test the associations between SNPs, PRS, and PCa aggressiveness.

References

Huynh-Le, MP., Karunamuni, R., Fan, C.C. *et al.* Prostate cancer risk stratification improvement across multiple ancestries with new polygenic hazard score. *Prostate Cancer Prostatic Dis* **25**, 755–761 (2022). https://doi.org/10.1038/s41391-022-00497-7

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