Genetic Ancestry Associations with Prostate Adenocarcinoma Mutational Profiles: New Insights from a Diverse 5,959-Patient Real-World Cohort

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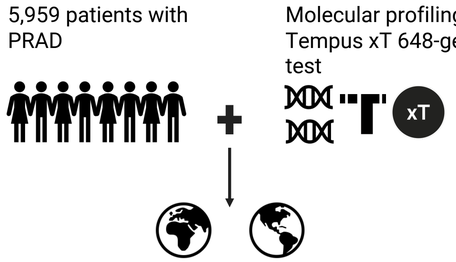
INTRODUCTION

In prostate cancer, Black men face higher incidence rates, more advanced diagnoses and worse outcomes than White men. These disparities partially stem from environmental, socioeconomic, and healthcare access factors. Recent data highlight racial differences in prostate cancer molecular profiles, with tumors from Black men showing increased *SPOP* mutations, decreased *PIK3CA* mutations, amplified androgen receptor signaling, and increased inflammatory pathway activations. Thus, somatic mutation patterns may also contribute to these disparities.

We sought to identify associations of mutational profiles in prostate adenocarcinoma (PRAD) with genetic ancestry instead of race and ethnicity categories.

METHODS



654 ancestry-informative markers used to estimate genetic ancestry by calculating similarity to reference populations for five regions: Africa (AFR), Americas (AMR), East Asia (EAS), Europe (EUR), and South Asia (SAS).

Associations between genetic ancestry proportions and somatic variants were assessed for 67 PRAD-related genes using logistic regression models. Likelihood ratio tests were employed to compare models with and without genetic ancestry terms. The Benjamini-Hochberg method was utilized to correct p-values and control the false discovery rate at 5% for each mutation type.

Separate analyses were performed for copy number alterations (CNAs), oncogenic gene fusions, small splice and non-synonymous mutations (NS), OncoKB therapeutic level L1, L2, or resistance level R1 mutations, and small missense driver somatic mutations predicted with boostDM.[1] Tests of small variants used patients with available matched normal tissue only to avoid artifacts from misclassification of germline variants.

References
1. Muiños, F., Martínez-Jiménez, F., Pich, O., Gonzalez-Perez, A. & Lopez-Bigas, N. In silico saturation mutagenesis of cancer genes. Nature 596, 428–432 (2021)..

SUMMARY

• By analyzing a large, diverse real-world cohort and leveraging NGS-inferred genetic ancestry, this study confirms known associations between somatic alterations in PRAD cancer genes and race and ethnicity.

• The study also unveiled novel associations between genetic ancestry and somatic mutations of potential significance for understanding disparities in disease outcomes.

RESULTS

Mutation types and genes tested

Mutation type	Samples included	N tests	Genes tested
Small, nonsynonymous	Tumor normal matched (N=3,692)	42	*APC, AR, ARID1A, ARID2, ATM, ATR, AXIN2, BRAF, BRCA2, CDK12, CDKN1B, CTNNB1, FANCA, FOXA1, FOXP1, HRAS, KAT6A, KDM6A, KMT2A, KMT2C, KMT2D, LRP1B, MED12, MTOR, NCOR1, NCOR2, NF1, PIK3CA, PIK3CB, PIK3R1, PTEN, RB1, RNF43, SETD2, SF3B1, SMARCA1, SPOP, TBX3, TMPRSS2, TP53, TSC2, ZFHX3*
Copy number alterations	All samples (N=5,959)	10	*APC, AR, BRCA2, FOXA1, LRP1B, MAP3K1, PTEN, RB1, TP53, ZFHX3*
Oncogenic gene fusions	All samples (N=5,959)	1	*TMPRSS2-ERG*
OncoKB therapeutic level L1, L2, or resistance level R1	All samples (N=5,959)	1	*PIK3CA*
Predicted driver somatic mutations using boostDM	Tumor normal matched (N=3,692)	12	*APC, AR, ATM, CDK12, CTNNB1, FOXA1, KMT2C, KMT2D, PIK3CA, PTEN, SPOP, TP53*

Table 1. Mutation types, sample types, number of tests, and genes tested. Only genes and gene sets with mutations present in at least 1% of patients were tested.

Additionally, genes in the PI3K/AKT/mTOR pathway (*AKT1, AKT2, AKT3, INPP4B, MTOR, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PPP2R1A, PTEN, RICTOR, RPTOR, STK11, TSC1, TSC2*) were grouped together to increase statistical power, since genes in this pathway may be mutually exclusive, requiring only a single hit to the pathway to drive cancer development. Mutation types in the pathway were also combined.

Genetic ancestry and small, nonsynonymous mutations

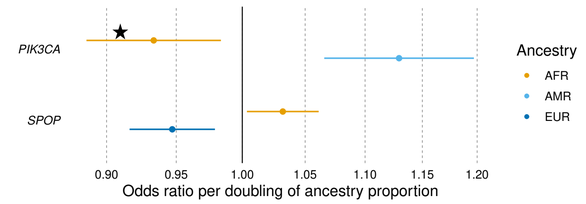


Figure 1. We confirmed reported associations between AFR ancestry and *SPOP* (OR=1.03, p=0.03) and *PIK3CA* (OR=0.93, p=0.01) mutations. There was a novel association between AMR ancestry and *PIK3CA* mutations (OR=1.13, p<0.0001) and EUR and *SPOP* (OR=0.95, p=0.001).

Genetic ancestry and copy number alterations

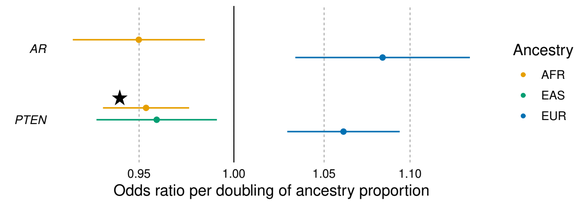


Figure 2. We confirmed decreased AFR ancestry with *PTEN* CNAs (OR=0.95, p=0.0001). We also observed negative associations between AFR and *AR* CNAs (OR=0.95, p=0.005), and EAS and *PTEN* CNAs (OR=0.96, p=0.01). EUR ancestry was positively associated with CNAs in both genes.

Genetic ancestry and gene fusions

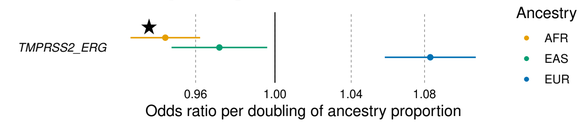


Figure 3. We confirmed a negative association between AFR ancestry and *TMPRSS2-ERG* fusions (OR=0.95, p<0.0001). We also observed a negative association with EAS and *TMPRSS2-ERG* fusions (OR=0.97, p=0.02) and a positive association for EUR ancestry (OR=1.08, p <0.0001).

Genetic ancestry and actionable (OncoKB) mutations

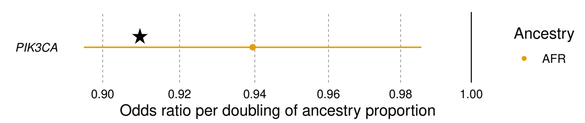


Figure 4. We confirmed a negative association between AFR ancestry and actionable *PIK3CA* mutations (OR=0.94, p=0.01).

Genetic ancestry and driver (boostDM) mutations

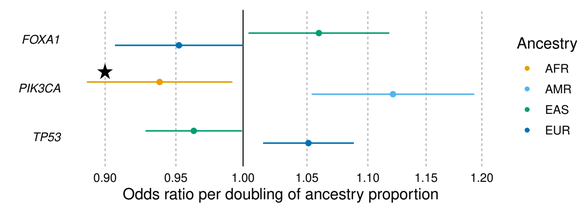


Figure 5. EAS was negatively associated with *TP53* (OR=0.96, p=0.04) and positively with *FOXA1* (OR=1.06, p=0.03) driver mutations. We also identified a novel positive association between AMR ancestry and driver mutations in *PIK3C3A* (OR=1.12, p=0.0003).

Genetic ancestry and PI3K/AKT/mTOR pathway mutations

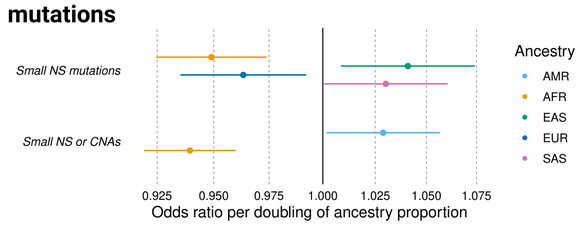


Figure 6. EAS and SAS ancestry were associated with the presence of NS mutations in the PI3K/AKT/mTOR pathway genes, while AFR and EUR ancestries had lower odds of mutations in these genes. We also identified a novel association between AMR ancestry and small NS mutations or CNAs in these PI3K/AKT/mTOR genes (OR=1.03, p=0.04).

★Indicates a previously known association.

Interpretation of ORs: the increase or decrease in odds of a patient having a somatic mutation per doubling of a specific ancestry proportion, adjusted for xT assay version and the other four ancestry proportions.

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