Genetic Ancestry Associations with Somatic Mutations in a Real-World Cohort of Over 5,000 Prostate Adenocarcinoma Patients

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INTRODUCTION

Disparities in incidences and outcomes of prostate cancer among racial groups have been reported. Black men have a higher incidence of prostate cancer compared to white men and are more likely to be diagnosed at a later stage, resulting in poorer outcomes. These differences are likely due to a combination of genetic, socioeconomic, and healthcare access factors. Furthermore, evidence has revealed racial differences in molecular profiles of prostate cancer, such as a higher incidence of *ERF* mutations and increased transcriptional activation of the androgen receptor signaling and inflammatory pathways in tumors derived from black men compared to white men, opening the possibility of follow-up studies to understand whether underlying biology may contribute to these disparities. Here, we aimed to identify differences in the mutational profiles of prostate cancers by genetic ancestry in a de-identified real-world cohort of 5,775 prostate cancer patients that underwent the Tempus xT 648-gene next-generation sequencing (NGS) tumor profiling test.

METHODS

We inferred genetic ancestry from 5,775 de-identified records of prostate cancer patients who underwent tumor genomic profiling with the 648-gene Tempus xT NGS assay.

We used 654 ancestry-informative markers selected to overlap the target regions of the assay. We used a re-implementation of the ANCESTRY algorithm (Alexander et al, 2019) to infer global ancestry proportions for the following continental ancestries: Africa (AFR), Americas (AMR), Europe (EUR), East Asia (EAS), and South Asia (SAS), using public reference allele frequencies.

Analysis Inclusion Criteria:

- Prostate adenocarcinoma (n=5,273) and carcinoma (n=502) patients. Two sets of somatic mutations were tested: (1) non-silent (short protein-altering) mutations and somatic copy number alterations (SCNAs), and (2) cancer driver mutations predicted by the boostDM algorithm (Muiños *et al* 2021), when the model was available.
- Prostate cancer-related genes in our panel for which at least 1% of patients, and a minimum 10 patients, harbored a somatic mutation.
- Patient records with known gender and age. Matched normal samples were available for 3,638 (62%).

Statistical Analysis:

- Likelihood ratio (LR) tests comparing logistic regression models were used to test for associations between continental ancestry proportions and presence of somatic mutations, controlling each ancestry association for assay version, age, and the other 4 ancestries.
- LR test *P*-values were adjusted for multiple testing by the Benjamini-Hochberg method to control the false discovery rate at 5%. Individual ancestry associations with $P<0.05$ are shown.

RESULTS

Distribution of continental ancestries in the cohort

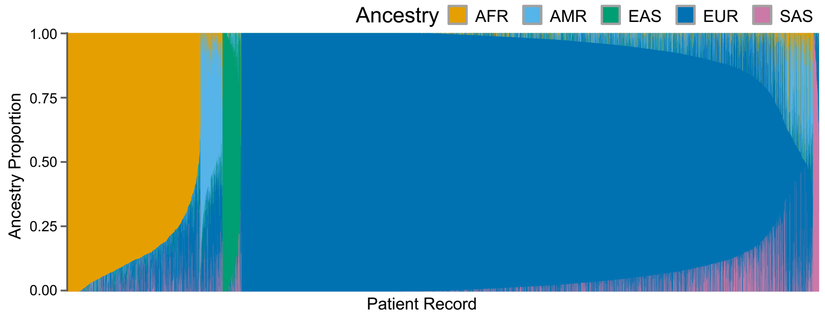

Figure 1. Continental ancestry proportions for patients in our cohort (N=5,775). Clinical stages: 91% stage IV, 6.2% stage III, and 2.9% stage I-II.

Ancestry associations with protein-altering somatic mutations in cancer genes

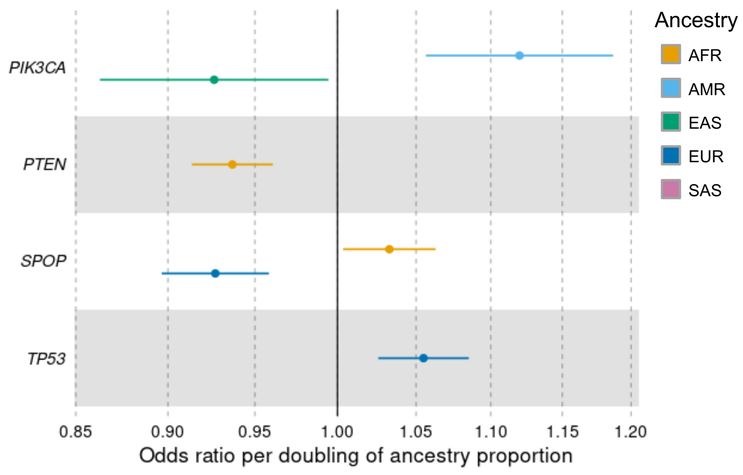

Figure 2. Odds ratios and 95% confidence intervals (CIs) of having a somatic short protein-altering mutation or SCNA in a gene for every doubling of ancestry proportion. Forty-eight prostate cancer-related genes were initially tested. Tests were restricted to matched tumor-normal cases (n=3,638).

Ancestry associations with predicted driver somatic mutations in cancer genes

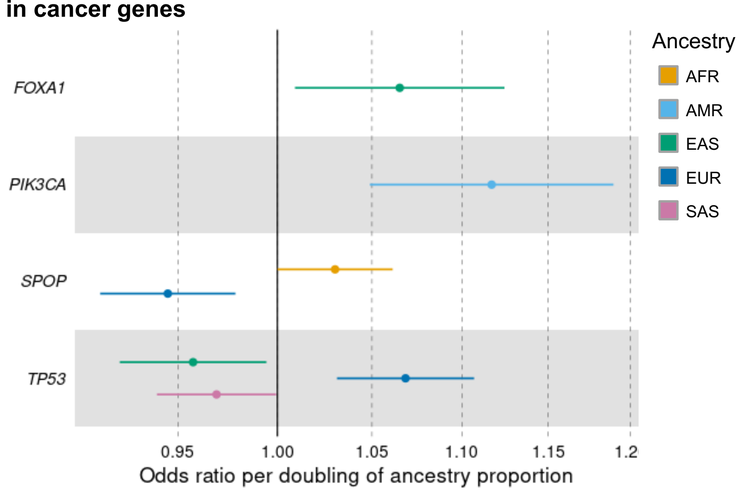

Figure 3. Odds ratios and 95% CIs of having a somatic predicted driver mutation in a gene for every doubling of ancestry proportion. Twelve prostate-related cancer genes with boostDM models where initially tested (Muiños *et al* 2021). Analyses were restricted to matched tumor-normal cases (n=3,638).

DISCUSSION

In a large, mostly metastatic cohort, we observed associations between somatic mutation patterns and ancestries consistent with prior reports based on stated race and ethnicity categories, including increased odds of non-silent or predicted driver somatic mutations in *SPOP* associated with African ancestry, in *TP53* associated with European ancestry, and in *FOXA1* with East Asian ancestry. We also confirm reduced odds of mutations in *PTEN* associated with African ancestry. Moreover, we did not identify associations of mutations in *ZFHX3* or *CCDN1* with African ancestry as previously reported.

Several previously undescribed associations were also identified, such as reduced odds of non-silent or predicted driver somatic mutations in *TP53* associated with East Asian and South Asian ancestries. In the case of *PIK3CA*, we found increased odds of mutations associated with Amerindian and lower odds with East Asian ancestries.

CONCLUSIONS

- Our analysis of a large real-world sequencing dataset is consistent with certain previously known associations between the presence of somatic alterations in prostate cancer genes and race/ethnicity.
- We also identified several novel associations between the presence of somatic mutations in the *TP53* and *PIK3CA* genes in ancestries often underrepresented in genomic studies.

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