Genomic Profiling of Prostate Cancers from Men with African and European Ancestry

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ABSTRACT

Purpose: African American (AFR) men have the highest mortality rate from prostate cancer (PCa) compared with men of other racial/ancestral groups. Differences in the spectrum of somatic genome alterations in tumors between AFR men and other populations have not been well-characterized due to a lack of inclusion of significant numbers in genomic studies.

Experimental Design: To identify genomic alterations associated with race, we compared the frequencies of somatic alterations in PCa obtained from four publicly available datasets comprising 250 AFR and 611 European American (EUR) men and a targeted sequencing dataset from a commercial platform of 436 AFR and 3018 EUR men.

Results: Mutations in ZFHX3 as well as focal deletions in ETV3 were more frequent in tumors from AFR men. TP53 mutations were associated with increasing Gleason score. MYC amplifications were more frequent in tumors from AFR men with metastatic PCa, whereas deletions in PTEN and rearrangements in TMPRSS2-ERG were less frequent in tumors from AFR men. KMT2D truncations and CCND1 amplifications were more frequent in primary PCa from AFR men. Genomic features that could impact clinical decision-making were not significantly different between the two groups including tumor mutation burden, MSI status, and genomic alterations in select DNA repair genes, CDK12, and in AR.

Conclusions: Although we identified some novel differences in AFR men compared with other populations, the frequencies of genomic alterations in current therapeutic targets for PCa were similar between AFR and EUR men, suggesting that existing precision medicine approaches could be equally beneficial if applied equitably.

Introduction

Despite declines in mortality related to cancer in the United States, disparities by race have persisted. African American (AFR) men have a higher incidence, present with more advanced disease at an earlier age, and have increased mortality from prostate cancer compared with European Americans (EUR; 1). Differences in outcomes persist even after correcting for socioeconomic covariates (2, 3). There is emerging evidence that across some clinical trials and equal-access health systems, outcomes between AFR men and European American men with prostate cancer are similar (4, 5). Although these data suggest that disparities can be ameliorated, there is limited knowledge of the genomic alterations that differ between groups and that could impact clinical outcomes. Certain somatic alterations in tumors differ in frequency across ancestral populations and have significant clinical implications. For instance, EGFR mutations are more common in patients with lung adenocarcinoma in patients of East Asian ancestry for which targeted therapies are the mainstay of treatment (6). In prostate cancer, TMPRSS2-ERG rearrangements and PTEN deletions are less frequent in prostate cancers from AFR men (1) and lack targeted treatments at this time. Notably, FOXA1 (7, 8) mutations are highly prevalent among Asians with prostate cancer while being less frequent in prostate tumors from men of European ancestry (9).

To date, cancer genomic studies have largely underrepresented racial/ethnic minority groups and have not been powered to detect differences in genomic alterations despite the greater burden of prostate cancer in AFR men (10, 11). Larger sample sizes from men of African ancestry are needed to detect significant associations in genes with lower mutational frequencies and to determine whether tumor genomic features associated with benefit from clinical therapies differ between men of African and European ancestry. In this study, we aggregate a large cohort of prostate cancers from AFR men to identify genomic alterations associated with race and investigate tumor genomic features in primary and metastatic disease between these two groups.

Materials and Methods

Mutational analysis and copy-number analysis of publicly available datasets

Data retrieval and preprocessing

For the meta-analysis of publicly available datasets, the selection criteria included studies that fulfilled the following requirements:
(i) performed whole exome sequencing (WES) or targeted DNA sequencing of prostate adenocarcinoma, (ii) included at least 10 patients with AFR ethnicity by self-report, and (iii) had mutation sequencing of prostate adenocarcinomas, (ii) included at least 10 exome sequencing data across 33 tumor types (12). Within the MC3 file located at https://api.gdc.cancer.gov/data/1c8ce5f-e52d-41ba-94da-f0513ea150aefc. Somatic variants that were deemed to have not passed all filters denoted within the "FILTER" column were excluded. Clinical annotation information for this cohort was retrieved from the file "nationWide.childrens.org_clinical_patient_prad.txt" available at the GDC Data Portal. Ancestry calls were obtained by running EthnoSeq as performed previously (13).

For the second and third datasets, we utilized somatic mutation calls from the African Ancestry prostate cancer (AAPC) cohort (13) which contained both WES and targeted sequencing data. Mutation calls were obtained from Supplementary Table S5 (WES) and Supplementary Table S10 (Targeted sequencing panel) from the publication. Finally, prostate cancers profiled with the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) panel were included (14). Mutation calls were taken from the tab "Somatic Mutations" and copy-number calls from the tab "Amplifications and Deletions" of the Data Supplement file. Race annotation for this cohort was provided within the tab "Clinical Annotation." Clinical and pathologic data for all cohorts are summarized in Supplementary Tables S1–S3. Twenty two patients from Abida and colleagues and eight patients from Huang and colleagues did not have annotation for self-reported race or Gleason score and were excluded from subsequent analyses. In total, 250 patients had self-reported AFR annotation in the Huang and colleagues and MSK-IMPACT datasets or had confirmed African ancestry in the TCGA dataset (AFR group). Six hundred eleven patients had self-reported European American ancestry in the Abida and colleagues, or had confirmed European ancestry in the TCGA dataset (EUR group).

Subsequently in all datasets, variants were filtered to only include nonsynonymous mutations, including as nonsense mutations, missense mutations, and indels. In addition, mutations with alternate allele less than 0.05 were removed to account for differences in sequencing depth between WES and targeted datasets. For TCGA, 30,869 variants were available in the analysis after filtering. The WES data and the targeted sequencing data from the Huang and colleagues study contained 7,353 and 491 variants after filtering, respectively. 1,470 variants remained after filtering in the MSK-IMPACT cohort (Supplementary Table S4).

Translational Relevance
African American men have the highest incidence and mortality from prostate cancer. It is not known whether currently targetable genomic alterations in prostate cancer differ between men of European ancestry and men of African ancestry. Analysing a large prostate cancer cohort, we identify certain differences and show that the frequency of alterations in AR, CDK12, DNA repair genes, tumor mutation burden, and MSI-high status are similar, suggesting that therapeutic approaches based on these features can be beneficial in both populations.

Identification of recurrently altered copy-number peaks
Genome-wide copy-number ratios were available from SNP6.0 data in the TCGA cohort and from WES data in Huang and colleagues cohort. GISTICv2.0.23 was applied separately to copy-number ratios from AFR men (n = 171) or from EUR men (n = 626) to identify recurrent deletion peaks ("two-cohort analysis," Supplementary Tables S8–S12). Tumors with a GISTIC thresholded call of -2 were considered deleted. For each gene, logistic regression was used to determine if deletion status for the target gene of 12 recurrently deleted peaks was associated with race, age, or Gleason score (Supplementary Table S13). Eight genes that were a target of a recurrent deletion peak and 15 genes that were a target of a recurrent amplification peak from the GISTIC2.0 analysis mentioned above were also measured in the Abida and colleagues dataset. In the Abida and colleagues dataset, a log2 fold change of less than -1 was considered deleted while a log2 fold change great than 1 was considered amplified. For each gene, logistic regression was used to determine whether deletion status (or amplification status) was associated with race, age, or Gleason score followed by an FDR correction for each term ("three-cohort analysis," Supplementary Tables S14–S17).

Mutational and copy-number analysis from the Foundation cohort
In total, genomic profiling data from 251 AFR and 1,940 EUR men with localized prostate cancer, as well as 185 AFR and 1,078 EUR men with metastatic prostate cancer were obtained from Foundation Medicine (Supplementary Tables S18–S20). Comprehensive genomic profiling was performed by Foundation Medicine, Inc using hybridization capture of exonic regions from either 236, 315 or 324 cancer-related genes and select introns from 19 genes commonly rearranged in cancer. Libraries were sequenced to high, uniform coverage and assessed for all classes of genomic alterations. Tumor mutational burden (TMB) was determined from 1.1 Mb of sequence and microsatellite instability (MSI) from 114 loci. Ancestries were determined for deidentified, consented-for-research samples using a supervised approach. For each platform, Phase III 1000 Genomes SNPs that overlapped with target regions in the comprehensive genomic profiling assay were projected down to five principal components, and these five features were used to train a random forest classifier that distinguishes between African, admixed American, East Asian, European, and South Asian ancestral groups. Admixture analysis was performed using ADMIXTURE 1.3.0 (ref. 15). Prior to running ADMIXTURE, imputation and phasing were performed using Beagle 5.0. Five ancestral
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Populations were predefined by running ADMIXTURE on Phase III 1000 Genomes data, and the analysis was performed using these projections to determine percent composition for each deidentified sample of these five populations. Binomial logistic regression was performed to identify associations between ancestry and biomarker alterations. Five primary categories of alterations were considered including point mutations, truncations, amplifications, deletions, and rearrangements. All of these alterations as well as any other type of variant were included in the “all” category (Supplementary Tables S17–S19). Focusing on relatively frequent gene alterations, we counted 26 genes with more than five alterations in men with localized prostate cancer and 38 genes with more than five alterations in men with metastatic prostate cancer (Supplementary Tables S18–S20). For each gene alteration class, the number of patients with this specific alteration was counted and the frequency was computed accordingly. In the Foundation cohort, a FET was applied to each type of alteration that occurred in more than five patients to identify differences between AFR and EUR populations. This test was performed including all men and then separately for men with primary or metastatic disease. Moreover, to analyze the differences between AFR and EUR men prostate cancer at a functional level, we compared the alteration frequencies in gene pathways including DNA repair, cell cycle, PI3K, RAS/MAPK, KMT, and WNT pathways (ref. 16; Supplementary Table S21). In this analysis, we included genes in each pathway that were measured in one or more alteration classes reported in the Foundation Cohort for both patients with localized and metastatic prostate cancer. Specifically, if the alteration frequency for a gene was 0, it was omitted in the dataset.

For AFR and EUR patients with localized and metastatic prostate cancer, tumor mutational burden (TMB) was computed as the percentage of patients with respect to the number of mutations (0–100). A two-sided t test was conducted then using the scipy.stats.test_ind function in the scipy package (17) to compare the means between the two ancestry groups.

All code used for the analysis is available at https://github.com/campbio/Manuscripts.

Results
Analysis of four publicly available cohorts
Four sequencing datasets had mutation calls available for analysis including WES data from TCGA, WES, and targeted sequencing data from Huang and colleagues (13), and targeted sequencing data from Abida and colleagues (ref. 14; MSK-IMPACT). Eight hundred sixty-one primary prostate cancer samples from 250 AFR men (29.0%) and 611 EUR men (71.0%) were included in the analysis across all cohorts after excluding men without sufficient clinical annotation or from Asian background (Methods; Supplementary Tables S1–S4). Gleason score was associated with race ($P < 0.001$; $\chi^2$ test) with higher proportions of lower grade (Gleason 6 and 7) in AFR men. Age was also significantly lower in AFR men ($P < 0.001$; Wilcoxon rank-sum test). Fifteen genes were present in assays from all four cohorts and were mutated in at least three patients. Logistic regression (LR) was used to identify associations with race, Gleason score, age, and mutation rate (Materials and Methods; Fig. 1A; Supplementary Table S5). The frequencies of somatic mutations in ZFHX3 were significantly higher in tumors from AFRs (6.0% vs 2.1%; FDR = 0.001; Fig. 1B; Supplementary Tables S5 and S6). The frequency of TP53 mutations was strongly associated with higher Gleason score (FDR = $3.4 \times 10^{-5}$; LR; Fig. 1C; Supplementary Tables S5 and S6). While the overall mutation rate of TP53 was not associated with race, truncating mutations were significantly higher in tumors from AFR patients (FDR < 0.05; LR; Supplementary Table S7). FOXA1 and SPOP mutations were associated with age (FDR < 0.05; LR).

Genome-wide copy-number ratios were available for TCGA and Huang and colleagues WES cohorts. Using GISTIC2.0, recurrently altered copy-number peaks were identified separately in AFR ($n = 157$)

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**Figure 1.**

**A,** Gene mutation frequencies associated with race were identified with a logistic regression model containing race, Gleason score, and mutation rate. Solid purple points represent genes significantly associated with race (FDR < 0.05). **B,** The frequency of ZFHX3 mutations was associated race. **C,** The frequency of TP53 mutations was associated with Gleason score.
Gene deletion frequencies associated with race were significantly higher in AFR men (n = 436) included CCND1 amplification (6.0% vs 3.1%), HGF amplification (3.4% vs 1.4%), KMT2D truncation (10.1% vs 4.7%), MYC amplification (15.8% vs 9.4%), SPOP point mutation (10.8% vs 6.9%), and KEI1 (2.1% vs 0.5%). NOTCH2 (1.8% vs 0.5%), PTCH1 (1.8% vs 0.4%) overall alterations (FDR < 0.05; FET; Fig. 3A). In contrast, PTEN deletions (13.1% vs 22.2%) and TMPRSS2-ERG rearrangements (13.8% vs 32.9%) were significantly lower in AFR men, consistent with previous studies (FDR < 0.01; FET; Fig. 3B, refs. 1, 13). When examining localized prostate cancer, KMT2D truncation (13% vs 4.3%) and CCND1 amplification (5.2% vs 1.9%) events were significantly higher in AFR men (FDR < 0.05; FET; ref. 19), whereas no significant differences were detected in selected genes in DNA repair, RAS/MAPK, or WNT pathways (Fig. 4A). In the case of KMT2D, a significant difference in alteration frequency was detected only for truncation events but not point mutations.

Among metastatic prostate cancer, TMPRSS2-ERG rearrangement (AFR: 14.1% vs EUR: 31.6%) and PTEN deletion (AFR: 24.3% vs EUR: 37.5%) rates were significantly lower in AFR men (FDR < 0.05; FET) while MYC amplifications were more frequent (25.4% vs 16.4%; FET; FDR = 0.052). Among AFR men, RB1, MYC, AR, TP53, PTEN, APC, and CCND1 were more frequently altered in metastatic samples (FDR < 0.05; FET). Assessments of tumor mutation burden and MSI status showed no statistically significant difference between AFR and EUR prostate cancers (Fig. 4B, Supplementary Table S22). Logistic regression analysis using continuous measures of AFR and EUR ancestry percentages showed that the frequency of TMPRSS2-ERG...
rearrangements and PTEN deletions were positively correlated to EUR ancestry percentages and negatively correlated to AFR ancestry percentages (P < 0.001; LR; Fig. 5).

Examining common associations across both the meta-analysis and Foundation cohorts, a higher frequency of MYC amplifications was observed in tumors with more severe disease (higher Gleason grade or metastatic disease) and PTEN deletions were enriched in tumors from EUR patients (Fig. 6). Alterations in the AR gene were observed at higher frequencies in metastatic tumors, likely reflecting resistance mechanisms to androgen-directed therapies of metastatic prostate cancer. TP53 had the highest frequency of all nonsynonymous mutations or point mutations in all cohorts except for the low-grade tumors in the meta-analysis cohort. The next most commonly mutated gene was SPOP, which was found among the most frequently altered genes in all cohorts except metastatic tumors from EUR patients. Overall, no significant differences were observed in currently clinically-actionable genes between AFR and EUR men across all cohorts.

**Discussion**

Given the paucity of AFR men in sequencing cohorts, the goal of this study was to identify mutational events associated with race or ancestry in prostate cancer. We first performed a meta-analysis across four different publicly available datasets and identified two putative prostate cancer tumor suppressors, ETV3 and ZFHX3, that were more frequently altered in AFR men. Loss of ZFHX3 has been shown to cause neoplastic lesions in the prostate in mice (20). ETV3, an ETS transcription factor, was recurrently deleted in AFR men and has not previously been implicated in prostate cancer. We have previously identified loss-of-function mutations in another ETS repressor, ERF, that were enriched in a cohort of prostate cancers from AFR men (13).
Together, these results suggest that while ERG rearrangements are less common in AFR men, additional mechanisms may still converge upon dysregulation of ETS factors (13, 21). We also observed that mutations in TP53 were associated with an increase in Gleason score across all racial groups. Associations between TP53 mutations or TP53 expression and metastatic disease have been previously reported (22, 23). These results suggest that if TP53 mutations are found in low-grade disease, they may potentially indicate a more aggressive clinical
trajectory. PTEN alterations were less frequent in AFR patients and have also been reported to have a lower mutation frequency in AFR patients with endometrial cancer (24). A major limitation of the meta-analysis is that some cohorts lacked matched tumors from EUR men, limiting our ability to control for cohort-specific effects that could arise due to differences in region, clinical setting, or sequencing assay. Another limitation was that the meta-analysis was limited to 15 genes because two of the four cohorts relied on smaller targeted sequencing panels for profiling. Studies examining larger numbers of tumors from AFR men profiled with whole-exome or whole-genome platforms may reveal additional genomic alterations associated with ancestry.

In our large cohort analysis of prostate cancer profiled with the Foundation Medicine assay, we found higher rates of CCND1 amplifications and KMT2D truncations in African-ancestry tumors but fewer PTEN deletions and TMPRSS2-ERG rearrangements. Significantly more frequent CCND1 amplifications and KMT2D truncation events were identified within patients with AFR localized prostate cancer. Higher expression of CCND1 has been implicated with perineural invasion in prostate cancer (25), an aggressive histologic feature in prostate cancer. Truncating mutations in KMT2D have been reported in both patients with localized and metastatic prostate cancer with unclear clinical significance (26). As a tumor suppressor, KMT2D alterations are more frequently detected in metastatic than primary tumors (27), which is consistent with the higher truncation and overall alteration frequencies in EUR metastatic tumors. MYC amplifications were more frequent in AFR metastatic samples. Germline susceptibility variants at 8q24 have been found more frequently in AFR men and may exert their effect via an impact on MYC expression (28). Our data raise the possibility that MYC amplifications may also contribute to high-risk disease in this population. The major limitation of this cohort was that clinical covariates such as age, tumor stage, and Gleason grade were not available and thus could not be included in statistical analyses.

Between the Foundation Medicine and the meta-analysis cohorts, the mutation frequencies of a subset of genes were tested in both assays including AR, BRAF, BRCA2, BRIPI, CDKN1B, CDK6, CTNNB1, FGFR1, FLCN, JAK1, KDM6A, MCL1, MED12, PIK3CA, PTEN, SPOP, TMPRSS2, and TP53. Of these genes, PTEN deletion was lower in the AFR population in both analyses of localized prostate cancer. All other genes were not significantly associated with race, suggesting an overall concordance between the two analyses. We note that MYC amplifications were found to be associated with Gleason score and not race in the meta-analysis while these amplifications were associated with race in the Foundation Medicine cohort. The lower alteration frequency observed in the meta-analysis cohorts may be partially explained by the focus on primary localized samples for the analysis. Alternatively, the lack of ability to control for clinical covariates in the Foundation Medicine cohort could produce an association if the underlying Gleason score was confounded with race.

Figure 5. Association of ERG and PTEN alteration frequencies to ancestry percentage. Logistic regression was used to identify associations of ERG and PTEN alteration status with percentage of AFR or EUR ancestry within each patient (N = 5,624). Solid lines represent the logistic regression curves between alteration status and ancestry percentage. The semitransparent band around the solid lines represent the 95% confidence interval of the logistic regression curves.

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Figure 6. Top 10 most frequently altered genes in AFR and EUR men. A, The 10 most frequent alterations are shown from AFR and EUR patients in the meta-analysis cohort for tumors with low- and intermediate-grade disease (top; Gleason scores 6, 7) and high-grade disease (bottom; Gleason scores 8, 9, and 10). Gene alteration classes considered include nonsynonymous mutations, amplifications, and deletions. B, The 10 most frequent alterations in AFR and EUR patients in the Foundation Medicine cohort for tumors with localized prostate cancer (top) and metastatic prostate cancer (bottom). Gene alteration classes considered include amplifications, deletions, rearrangements, point (missense) mutations, and truncations.
On the basis of our analysis of the largest number of prostate cancers from AFR men to our knowledge, a single gene alteration is unlikely to account for the observed prostate cancer disparities. Furthermore, no significant differences were seen in clinically actionable DNA repair genes, MSI-high status, and tumor mutation burden, suggesting that current therapeutic strategies may be equally beneficial in both populations (29). While recent studies by Dess and colleagues and Halabi and colleagues may be interpreted to mean that biological differences driving disparities do not exist, we believe that it is important to understand that significant differences exist in tumor biology, genomics, and proteomics that underlie the molecular etiology of prostate cancer in AFRs (7, 8). These differences occur in the context of structural social and economic determinants that can drive and amplify disparities.

Additional studies that profile large numbers of well-matched tumors from AFR and non-AFR men from the same clinical setting will be needed to confirm the novel associations reported in this study and to understand the clinical significance. The genomic differences seen in genes such as MYC, ZFHX3, PTEN, and TMPRSS2-ERG suggest that different pathways of carcinogenesis may be active in AFR men, which could lead to further disparities if targeted therapies for some of these alterations become available. Understanding how outcomes are influenced by the genomic and biological features of prostate cancers in AFR men with the interaction of social and environmental factors remains an understudied area of cancer disparities research. Determining a comprehensive understanding of the genomic features of AFR prostate cancers and how they relate to adverse features or contribute to poorer outcomes overall for AFR men could inform our strategies to improve precision medicine for these patients. These studies will remain important to understand when certain therapies may preferentially benefit AFR patients, who remain underrepresented in clinical trials (30). Examining additional features such as the noncoding genome, epigenome, and tumor microenvironment will be needed to fully understand the biological contribution to the observed disparities in incidence and mortality for AFR men.

Disclosure of Potential Conflicts of Interest

Y. Newberg is an employee of Foundation Medicine and holds ownership interest (including patents) in F. Hoffmann-La Roche AG. M. Meyerson is a paid advisory board member for OrigMed and reports receiving commercial research grants from Bayer, Ono, Janssen, and Novo. G.M. Frampton is an employee of Foundation Medicine and holds ownership interest (including patents) in Roche AG. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Y. Koga: Data curation, formal analysis, investigation, visualization, writing—original draft, writing—review and editing. H. Song: Data curation, formal analysis, investigation, visualization, writing—original draft, writing—review and editing. Z.R. Chalmers: Data curation, formal analysis, investigation, visualization, writing—original draft, writing—review and editing. J. Newberg: Writing—review and editing. E. Kim: Writing—review and editing. J. Carrot-Zhang: Writing—review and editing. D. Piou: Writing—review and editing. P. Polak: Writing—review and editing. S.A. Abdulkadir: Writing—review and editing. E. Ziv: Writing—review and editing. M. Meyerson: Writing—review and editing. G.M. Frampton: Writing—review and editing. J.D. Campbell: Conceptualization, resources, data curation, software, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing—original draft, project administration, writing—review and editing. F.W. Huang: Conceptualization, resources, data curation, software, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing—original draft, project administration, writing—review and editing.

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