



Genome-wide burden analysis reveals novel genetic determinants of survival in patients with metastatic prostate cancer receiving androgen-targeted therapies: Results from the Million Veterans Program

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BACKGROUND AND OBJECTIVES

Literature has suggested that various genes influence treatment response in prostate cancer (Pca). While the androgen receptor (*AR*) gene is the primary target for hormonal treatment, studies increasingly highlight the roles of genes in pharmacogenetics, including *APOE*, *BGN*, *AHSG*, *CYP2D6*, *SLC2A4*, and *HSD3B1*. Genetic variants that allow androgens to enter cells more efficiently may increase therapy resistance, worsening outcomes in recurrent or metastatic disease. A deeper understanding of biomarkers and resistance mechanisms is essential to address this process. We conducted a genome-wide search for genes that exhibit an effect on survival in patients on androgen receptor-targeted therapies.

METHODS

Study population:

Using a combination approach from the Veterans Affairs Central Cancer Registry (VACCR) categorized as having distant metastasis and a previously developed natural language processing tool to identify metastatic disease, 6,532 patients were identified as having metastatic prostate cancer (mPCa). To ensure patients identified as metastatic using the algorithm were newly diagnosed within the VA, we limited to those who had a biopsy within 90 days of PCa diagnosis and had 1. a Gleason score or 2. received a biopsy within 90 days from their metastatic diagnosis date. We developed two models for our analysis. Model 1 identified 5,107 patients with mPCa receiving androgen deprivation therapy while model 2 focused on a subgroup which included 2,240 patients on abiraterone.

Data collection and Analysis:

All analyses were conducted using the Million Veteran Program (MVP), the nation's largest biorepository of Veteran data. We performed 18,544 distinct gene-level tests across the human genome using all coding variants within each gene, analyzing rare (minor allele frequency <1%) loss-of-function variants, and both rare loss-of-function and missense variants. All analyses utilized the MVP's whole genome Release2 genomic data consisting of approximately 96,000 males. We conducted separate analyses for African and European ancestry subjects. Gene-level survival analysis was performed using the SeqMeta R package that performs burden, Skat, and Skat-O tests. A Bonferroni correction was applied for 82,567 tests, requiring $p < 6.06E-7$ to establish significance and $p < 5.00E-6$ for suggestive evidence.

RESULTS

Figure 1. Manhattan plot for Model 1

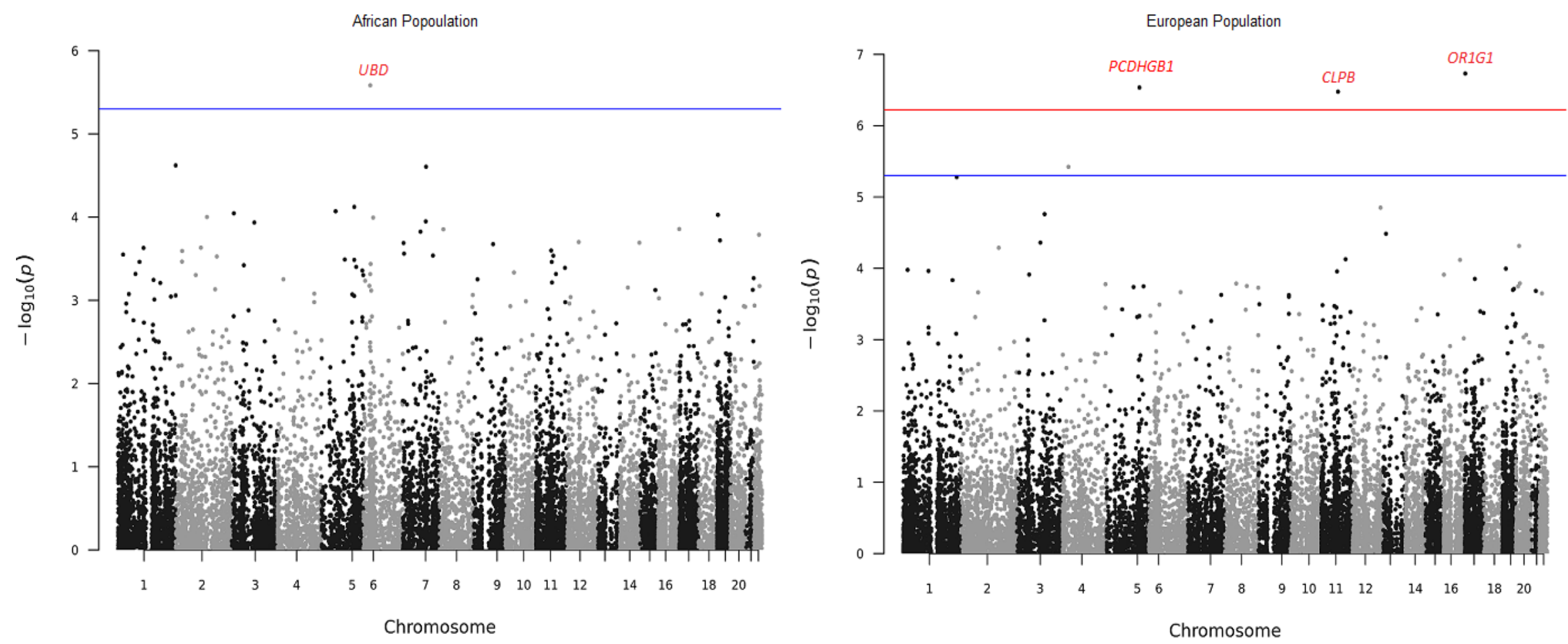


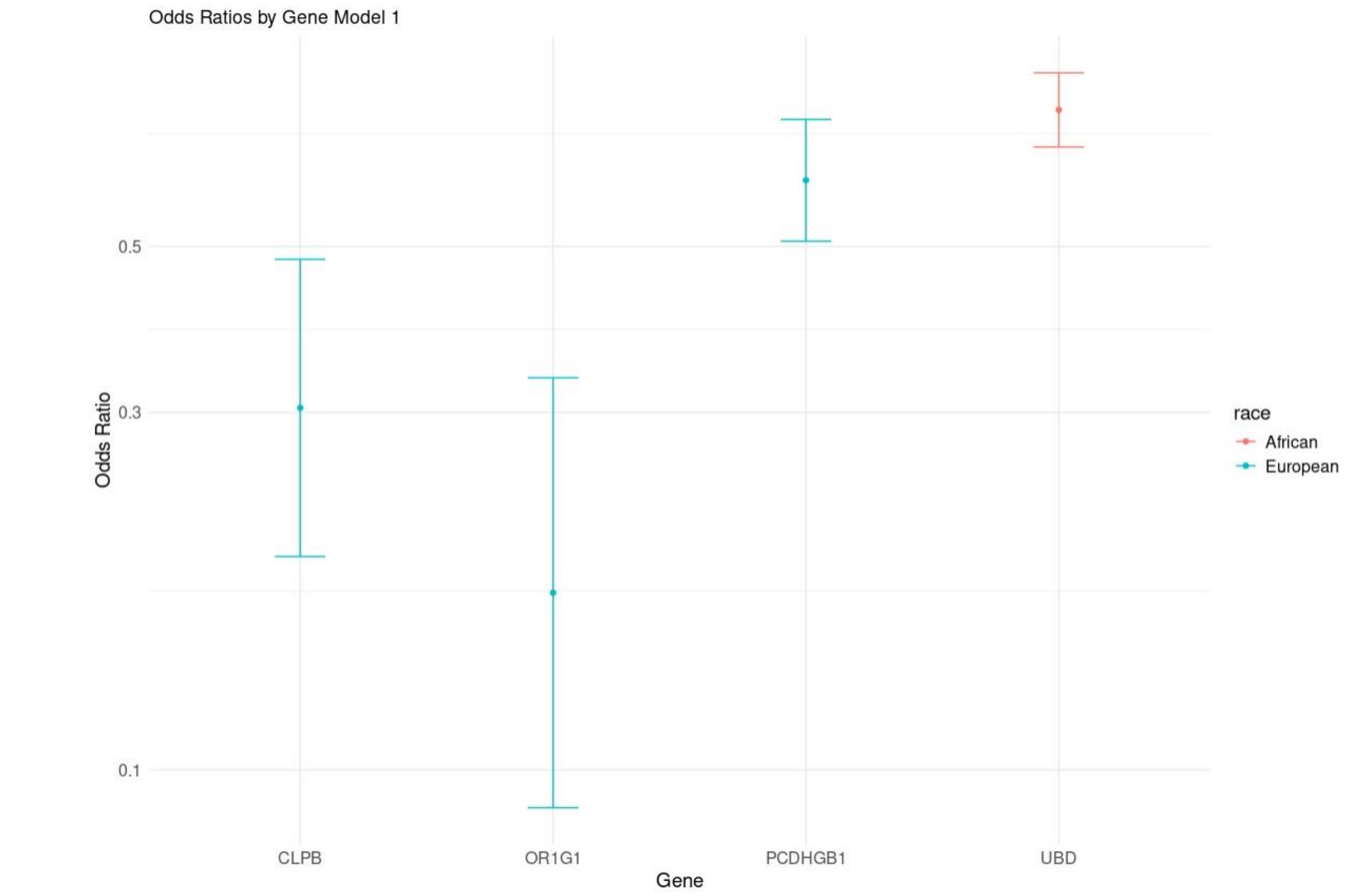
Table 1. Significant Genes and Descriptions

Gene	P-value	Odds Ratio	Description
<i>UBD</i>	2.61E-06 ¹	0.76	<i>UBD</i> (ubiquitin D) is a protein-coding gene. Diseases associated with <i>UBD</i> include kidney disease and chronic kidney disease. Among its related pathways are metabolism of proteins and <i>BRCA1</i> pathway.
<i>OR1G1</i>	1.86E-07 ¹	0.17	<i>OR1G1</i> (olfactory receptor family 1 subfamily G member 1) encodes the G protein-coupled olfactory receptor family 1 involved in the sense of smell
<i>PCDHGB1</i>	2.92E-07 ¹	0.61	<i>PCDHGB1</i> (protocadherin gamma subfamily B, 1) encodes the protocadherin gamma subfamily B1 cell adhesion protein that maintains the microtubular cytoskeleton
<i>CLPB</i>	3.34E-07 ¹	0.30	<i>CLPB</i> (ClpB family mitochondrial disaggregase) is a protein-coding gene. Diseases associated with <i>CLPB</i> include 3-methylglutaconic aciduria, ttype Viib and neutropenia, severe congenital, 9, autosomal dominant.
<i>SNX18</i>	3.40E-06 ²	NA	<i>SNX18</i> (Sorting Nexin 18) encodes a protein that regulates endocytosis and vesicular trafficking in cells

1. Burden p value 2. Skat-O p value

Gene-level tests identified *OR1G1* (burden $p=1.87E-7$, $OR=0.17$), *PCDHGB1* (burden $p=2.92E-07$, $OR=0.61$), and *CLPB* (burden $p=3.34E-07$, $OR=0.30$) as significantly associated with PCa survival, while *SNX18* demonstrated a suggestive association (Skat-O $p=3.40E-6$) among European ancestry subjects in model 1. Among African ancestry subjects, the best performing gene was *UBD* (burden $p=2.61E-06$, $OR=0.76$). Analyses of rare loss-of-function and loss-of-function or missense variants failed to achieve significant or suggestive evidence. Model 2 did not reveal any significant findings.

Figure 2. Odds ratio for significant genes (Model 1)



CONCLUSIONS

Our results detected novel associations with genes involved in cell signaling and intracellular protein trafficking that suggest new druggable targets for prostate cancer. These findings warrant follow-up in external datasets for validation.

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