Assessing Germline Variations among Black Patients with Early-Onset Prostate Cancer

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Introduction

Prostate cancer (PC) is a heritable cancer of the prostate gland, a part of the male reproductive system responsible for producing seminal fluid. Despite being the most common malignant cancer in males, PC disproportionately affects black men, who are 1.7 times more likely to be diagnosed yet often underrepresented in PC studies. Thus, this project aims to examine the underlying genetic risk factors behind this disparity of PC.

Characteristics of Black PC Cases Participating in the EPC Study (N = 744)

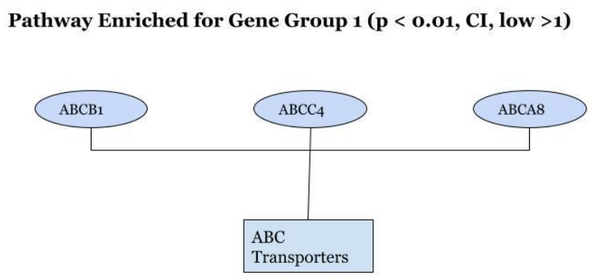
Characteristics	N (%)
Age at Diagnosis	
55-62 years	487 (65.5)
<55 years	257 (34.5)
First Degree Family History of PC	
No	528 (71.0)
Yes	214 (28.8)
Not reported	2 (0.3)
First Degree Family History of Any Cancer	
No	290 (39.0)
Yes	452 (60.8)
Not reported	2 (0.3)
First Degree Family History of DDR Associated Cancers*	
No	290 (39.0)
Yes	452 (60.8)
Not reported	2 (0.3)
Aggressive Disease**	
No	498 (66.9)
Yes	236 (31.7)
Unknown	10 (1.3)
PSA at diagnosis, ng/mL	
<10	512 (68.8)
>=10	182 (24.5)
Unknown	50 (6.7)
Gleason Score	
<= 7 (3+4)	497 (66.8)
>= 7 (4+3)	218 (29.3)
Unknown	29 (3.9)
SEER Stage	
Local	565 (75.9)
Regional	150 (20.2)
Distant	26 (3.5)
Unknown	3 (0.4)

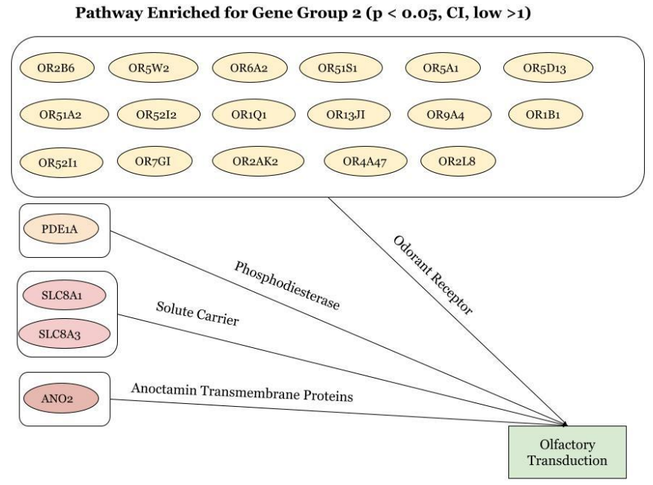
**Aggressive Disease is characterized as having a Gleason score of 8 or higher, PSA level greater than or equal to 20ng/mL, and/or a regional/distant SEER stage.

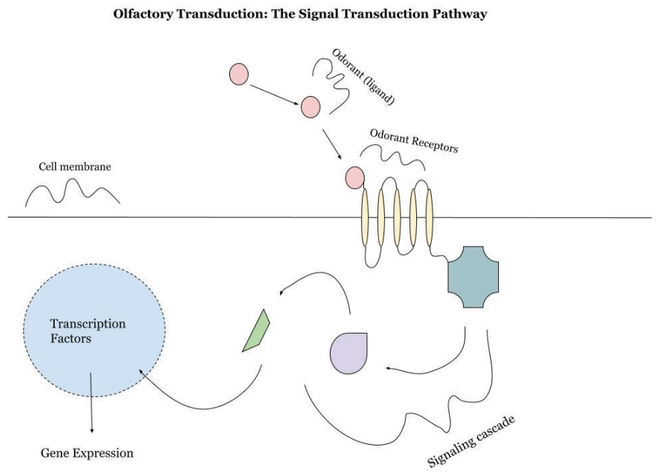
Methods

- Data source: Metropolitan Detroit Cancer Surveillance System
- Whole exome sequenced data was mapped by variant.
- The data were filtered to include a subset of only variants that impacted protein function, were most likely to be deleterious and pathogenic, had a rarer allele frequency in the global population, and were not associated with benign phenotypes.
- Following this, 2x2 contingency tables were generated that showcased frequencies of patients having variants based on characteristics that measured the severity of prostate cancer like age of diagnosis, family history, likelihood that cancer progresses, stage at diagnosis, and diagnostic screening results.
- Utilizing these tables, Fisher tests were run to calculate p-values, odds ratios, and confidence intervals–these values were used to develop a pool of the most relevant genes.
- Gene collection was done by examining genes that had p-values < 0.05 and the lower end of the confidence interval > 1. These genes that were collected were put through pathway enrichment analysis to determine which biological functions, or pathways, were highly represented.
- Genes and variants were also sorted by significance specific to family history and aggressiveness by utilizing specific severity measures' p-value divided by odds ratio value.

Results

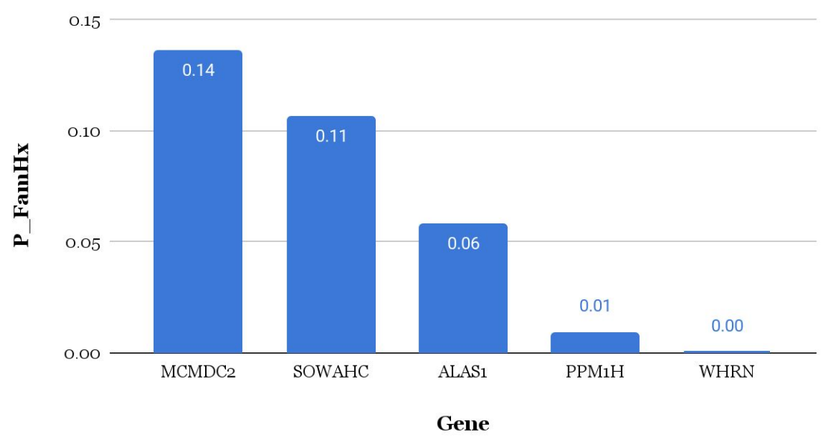




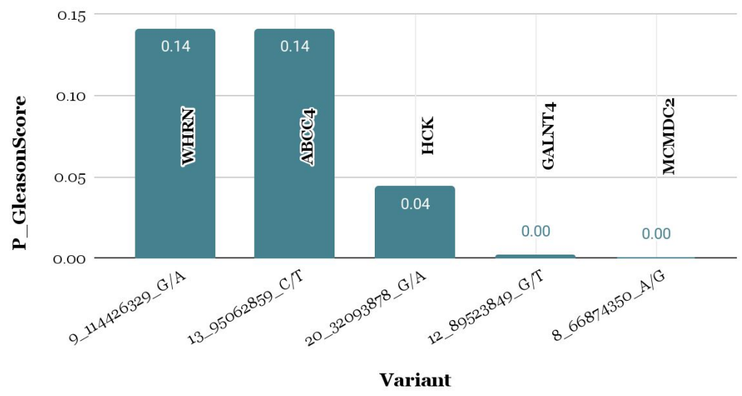


Most Significant Variants by Family History

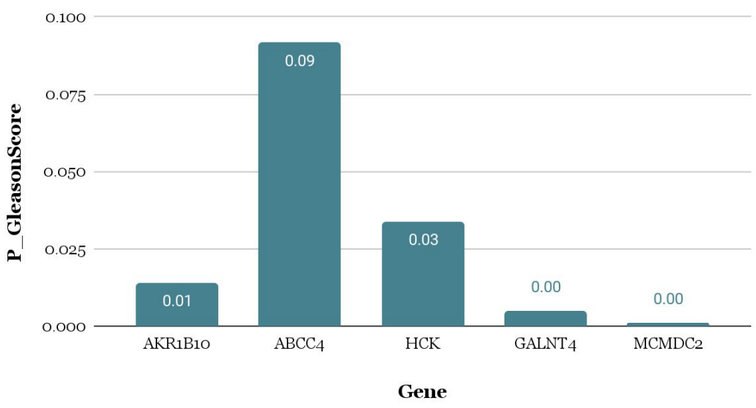
Most Significant Genes by Family History



Most Significant Variants by Gleason Score



Most Significant Genes by Gleason Score



Conclusion

- Based on family history–a measure of heritability of cancer–four of the five most significant variants lie in the WHRN gene. Overexpression of this WHRN gene is related to colorectal cancer disease progression. Colorectal cancer is also a hereditary cancer that is linked to prostate, breast, and ovarian cancer.
- In terms of the Gleason score–a measure of the likelihood of a cancer to progress–the most significant genes are related to various forms of cancer or immune responses. For instance, mutations in MCMDC2, GALNT4, and AKR1B10 contribute to other forms of cancer, and ABCC4 is known to contribute to prostate cancer by mediating a signal cascade. Additionally, the HCK gene is responsible for immune responses.
- In the cohort, 21 genes contribute to the function of the olfactory transduction pathway and seven genes contribute to the ABC transporter pathway. The olfactory transduction pathway is responsible for generating a signals that are expressed all over the body, and the ABC transporter pathway is responsible for ATP-driven transport of molecules across cellular membranes.
- Further analysis of how the most significant variants and genes of this cohort impact the function or product of known pathways related to prostate cancer can contribute to advancements in the study of prostate cancer.

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