Prevalence and Implications of Germline Genetic Variants in Prostate Cancer

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BACKGROUND

- Inherited genetic variants have considerable implications for prostate cancer staging, treatment, screening and genetic counseling of affected individuals and family members.
- Prior publications have focused on specific patient populations and there are limited data on the prevalence of germline variants in individuals with prostate cancer across stage and ethnic groups.
- The clinical impact of germline genetic testing on management of individuals with prostate cancer is not well defined.

OBJECTIVE

We report on a series of 3607 men with prostate cancer undergoing hereditary cancer testing at various stages of disease. We sought to define clinical factors associated with the presence of positive (Pathogenic, Likely Pathogenic or Increased Risk Allele) germline variants (PV) and their clinical significance.

METHODS

- De-identified personal and family history information was reviewed for 3607 consecutive men with prostate cancer undergoing germline genetic testing between 2013 and 2018.
- Genes analyzed were chosen at the discretion of the ordering clinician and varied from 2-80 genes. The 14 genes (Figure 1) included on a curated hereditary prostate cancer panel were requisitioned in 62% of orders.
- Extracted DNA was processed and subjected to paired-end sequencing on a next-generation sequencing platform. Variants were subjected to clinical interpretation using Sherloc, a schema refined from the American College of Medical Genetics and Genomics criteria.
- This study was performed under IRB approved protocol (Western IRB-1167406) allowing for evaluation of de-identified data.

ATM	BRCA1	BRCA2	CHEK2	EPCAM	HOXB13	MLH1
MSH2	MSH6	NBN	PMS2	TP53	RAD51D	PALB2

Figure 1: Genes included on the Invitae Hereditary Prostate Cancer Panel

RESULTS

- 17.2% (620/3607) of men had a positive result including 674 PV.
- Among men with the gene requisitioned, variants occurred in: *BRCA2,* 4.74%; *CHEK2*, 2.88%; *ATM*, 2.03%; *MUTYH,* 2.37%; *APC*, 1.28%; *BRCA1*, 1.25%; *HOXB13*, 1.12%; *MSH2*, 0.69%; *TP53*, 0.66%; and *PALB2,* 0.56%.
- Notably, in men having testing of mismatch repair genes, 1.74% had PV in *PMS2*, *MLH1*, *MSH2* or *MSH6.*

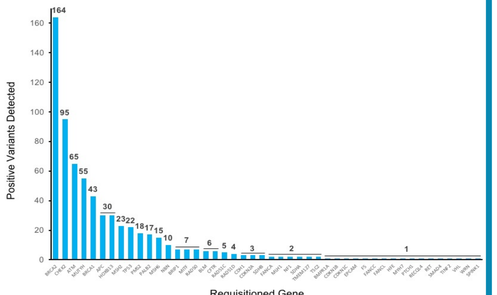

Figure 2: Distribution of unique variants detected by gene

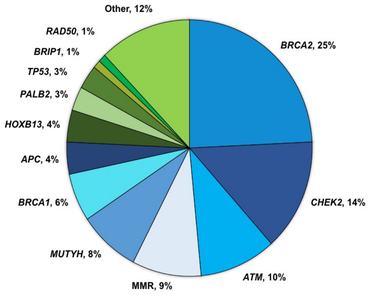

Figure 3: Distribution of genes with positive variants in men with prostate cancer

- Among men with PV, the 10 most common genes were: BRCA2, CHEK2, ATM, MUTYH, BRCA1, HOXB13, APC, MSH2, TP53 and PMS2.
- 69% of PV occurred in genes other than BRCA 1/2.
- 66% of PV occurred in genes not included in the 2018 Prostate Cancer Genetic Testing Guidelines.

Family history information was available for 90% of men with a positive variant.

- A family history of cancer did not correlate with detection of a PV.

Gleason scores were available in 1,538 men including 246 with a PV.

- Germline variants were detected in 15.1% of patients with Gleason Score of 6 or lower and 16.3% of those with Gleason score of 7 or higher.

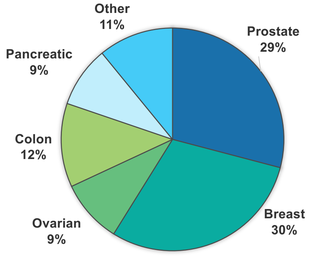

Figure 4: Cancers reported in family members

RESULTS

- Age at diagnosis (avg 60y) was distinct from age at testing (avg 67y), but did not correlate with the chance of a PV.
- The frequency of variants varied by ethnicity. Compared to other ethnic groups African Americans (OR=0.527, p=.006) and Hispanics (OR=0.325, p=.02) had a lower rate of PV.

	Total Series (n=3607)	Patients with P/LP variants (n=620)	% of Patients with a P/LP variant
<50	134	20	13.4
50-59	629	111	15.7
60-69	1308	237	16.9
70-79	1214	189	14.5
80-89	297	58	18.2
>90	24	5	20.8

Table 1: Frequency of P/LP variants by age at testing

	Total Series (n=3607)	Patients with P/LP variants (n=620)	% of Patients with a P/LP variant
White/Caucasian	2594	462	17.8
Ashkenazi Jewish	234	52	22.2
Black/African American	227	23	10.1
Hispanic	78	5	6.4
Asian	73	11	15.1
Other	401	67	16.7

Table 2: Frequency of P/LP variants by ethnicity

Results frequently had implications for medical management:

- 8.8% (59/674) occurred in genes with FDA-approved therapy for prostate cancer (PDL-1 Inhibitors).
- 63% (422/674) occurred in genes implying eligibility for open clinical trials for therapeutic agents for prostate cancer or advanced solid tumors.
- 81% (547/674) occurred in genes with consensus management guidelines for surveillance and risk reduction for prostate and other cancers.

CONCLUSIONS

- The rate of pathogenic germline variants in men with prostate cancer appears to be similar to other cancer types, such as breast and colorectal cancer, where germline testing is an established part of medical management.
- Individuals were identified from a clinical laboratory cohort implying a selection bias to this study. Other limitations include variability in the genes analyzed, limited availability of clinical and family history information, as well as the underrepresentation of men from non-White ethnic groups.
- Our data did not show significant associations between the presence of a positive germline variant and Gleason score, family history or age at testing. Further study on clinical indicators of hereditary risk is warranted.
- Germline genetic testing provides information that can significantly impact medical management including therapy, surveillance, counseling and identification of at risk family members.

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