Cohort of 1096 Patients Supports a Role of *ATM*, *CHEK2*, and *PALB2* in Hereditary Prostate Cancer

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Introduction

Prostate cancer is the most common cancer among men, accounting for 9.6% of all newly diagnosed cancers each year in the United States[1]. It has been well-established that pathogenic variants in *BRCA1*, *BRCA2*, and Lynch syndrome genes increase the relative risk of hereditary prostate cancer, potentially at a younger age of onset[2–4]. As such, these genes have been the primary focus of the 2017 Prostate Cancer Consensus Conference[5] as well as the 2018 National Comprehensive Cancer Network (NCCN) guidelines[6] for genetic evaluation of prostate cancer. Several recent studies have reported on the potential contribution of *ATM*, *CHEK2*, and *PALB2* to hereditary prostate cancer[7,8]. Similar to individuals with *BRCA1* and *BRCA2* pathogenic variants, individuals with pathogenic variants in *ATM*, *CHEK2*, and *PALB2* may present with a distinct molecular subtype of prostate cancer, which could be associated with lower survival rates and potentially benefit from targeted therapies such as PARP inhibitors[9]. However, the rarity of germline pathogenic variants in these genes has made it difficult to understand associated risk. To further investigate the frequency and spectrum of pathogenic variants found in hereditary prostate cancer, we studied a cohort of individuals with a personal history of prostate cancer who were referred for multi-gene next generation sequencing panel testing. Here, we describe the demographics and results obtained from these 1096 individuals who received the Color Hereditary Cancer Test, providing data on family history and age of prostate cancer diagnosis. We also present the results with respect to the current recommendations for genetic testing provided by the NCCN.

Methods

All individuals were referred by physician order for the Color Hereditary Cancer Test which analyzes 30 genes in which pathogenic variants have been associated with increased risk for hereditary breast, ovarian, uterine/endometrial, colorectal, melanoma, pancreatic, prostate, and stomach cancer (*APC*, *ATM*, *BAP1*, *BARD1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A* (p14ARF and p16INK4a), *CHEK2*, *EPCAM*, *GREM1*, *MITF*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PMS2*, *POLD1*, *POLE*, *PTEN*, *RAD51C*, *RAD51D*, *SMAD4*, *STK11*, and *TP53*). The majority of these genes were assessed for variants within all coding exons and non-canonical splice regions. Laboratory procedures were performed at the Color laboratory under CLIA and CAP compliance. Variants were classified according to the American College of Medical Genetics and Genomics 2015 guidelines for sequence variant interpretation[10], and all variant classifications were approved by an American Board of Medical Genetics and Genomics board certified medical geneticist. Ethnicity assignments and personal/family history of cancer were based on self-reported information.

Conclusions

- In this retrospective cohort of 1096 individuals with a history of prostate cancer, the pathogenic frequency for the subset of hereditary cancer genes that have been associated with prostate cancer was 12.3%.
- Approximately 50% of pathogenic variants were found in *BRCA1*, *BRCA2*, and Lynch syndromes genes, reinforcing the well-established roles of these prostate cancer susceptibility genes. The data presented here also support the contribution of the additional DNA repair genes *ATM*, *CHEK2*, and *PALB2* in hereditary prostate cancer.
- The number of affected first degree relatives was not correlated with a younger age of prostate cancer diagnosis. However, Lynch syndrome gene pathogenic variants showed a trend toward earlier age of prostate cancer diagnosis, which could be important for the surveillance strategy of individuals with Lynch syndrome.
- NCCN criteria for family history targeting to identify individuals with *BRCA2*- and Lynch syndrome gene-associated hereditary cancer syndromes missed more than 50% of individuals with pathogenic variants in these genes.

Results

Table 1. Cohort demographic details

The majority of individuals with a history of prostate cancer who received the Color Hereditary Cancer Test were over age 60 years and of Caucasian ethnic background. PV, pathogenic variant in prostate cancer susceptibility genes (Lynch syndrome genes, *BRCA1*, *BRCA2*, *ATM*, *CHEK2*, and *PALB2*).

		Individuals (n)	Population	Individuals w/ PV (n)	Pathogenic Frequency
Total		1096	100.0%	135	12.3%
Age (Years)	35-50	49	4.5%	8	16.3%
	51-60	192	17.5%	24	12.5%
	61-70	476	43.4%	62	13.0%
	71-80	319	29.1%	36	11.3%
	>80	60	5.5%	5	8.3%
Ethnicity	Caucasian	828	75.5%	129	15.6%
	Ashkenazi Jewish	132	12.0%	27	20.5%
	African	31	2.8%	5	16.1%
	Hispanic	29	2.6%	2	6.9%
	Asian	20	1.8%	5	25.0%
	Native American	4	0.4%	0	0.0%
	Multiple Ethnicities	31	2.8%	1	3.2%
	Unknown	21	1.9%	4	19.0%

Figure 1. Pathogenic variant spectrum

Similar to previous reports[4,8], 4.2% of individuals in this cohort had a pathogenic variant in *BRCA2*. While pathogenic variants were most frequently found in *BRCA2* (34.1%), *CHEK2* (22.2%), and *ATM* (17.0%), *PALB2* and Lynch syndrome gene (*MSH2*, n=5; *MSH6*, n=5; *PMS2*, n=3) pathogenic variants were also observed at a rate similar to *BRCA1* pathogenic variants (8.1-9.6%).

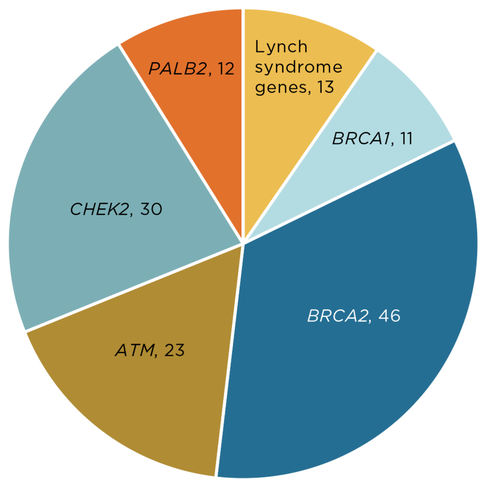


Figure 2. Gene and age of prostate cancer diagnosis associations

The age of diagnosis for individuals with a pathogenic variant in *BRCA1* or *BRCA2* (median 59.6±9.7 years) was not different compared to negatives at 60.5±8.7 years (Welch's t-test: p = 0.49). Interestingly, individuals with a PV in one of the Lynch syndrome genes were diagnosed at a relatively young age of 56.8±7.4 years (p = 0.096 vs negative). Negative reports were limited to individuals without a pathogenic variant in any of the 30 hereditary cancer genes on the panel.

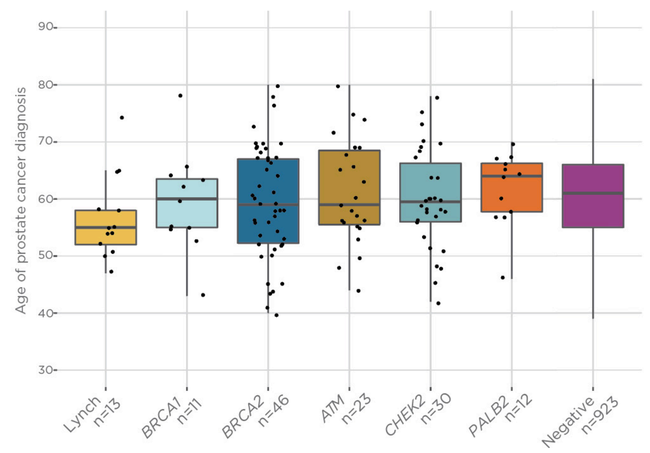


Figure 3. Number of affected family members and age of prostate cancer diagnosis associations

The number of first degree relatives affected by prostate cancer did not correlate with an earlier age of prostate cancer diagnosis (Kruskal-Wallis test: no significant differences between groups).

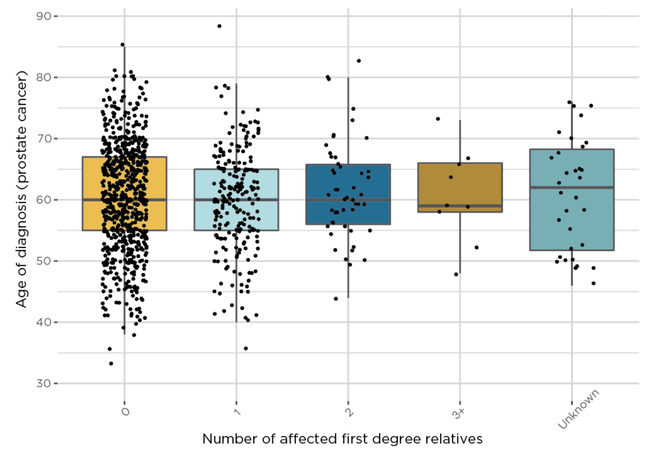
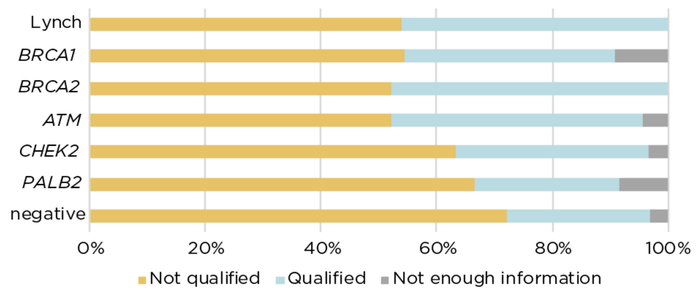


Figure 4. Eligibility by NCCN for Prostate Cancer

The recently released NCCN guidelines for prostate cancer[6] recommend consideration of germline testing for all patients who are 1) at high-risk based on clinical and/or pathological features or 2) at low/intermediate-risk with a strong family history of prostate cancer or hereditary cancers associated with *BRCA2* or Lynch syndrome. Based on family history alone, 55 (40.7%) individuals with a positive report would have met NCCN criteria, 76 (56.3%) would not, and 4 (3.0%) provided insufficient information. To note, a subset of these individuals would likely have qualified for genetic testing based on clinical and/or pathological features.



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