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Germline pathogenic variants in unselected Korean men with prostate cancer

Min-Kyung So[1], Hyun Kyu Ahn[2], Jungwon Huh[1], Kwang Hyun Kim[2]

Departments of [1]Laboratory Medicine and [2]Urology, Ewha Womans University College of Medicine, Seoul, Korea

Purpose: Prostate cancer is one of the most heritable cancers and prostate cancer with germline mutations is associated with aggressive features and a poor prognosis. We investigated germline variants in unselected Korean men with prostate cancer.

Materials and Methods: In this study, we prospectively collected buccal swab DNA from 120 unselected Korean men with prostate cancer, and performed massively parallel sequencing. Identified germline variants were interpreted according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology 2015 guidelines.

Results: Of the 120 patients, 30 had regional or metastatic disease and 10, 34, 25, and 21 patients were categorized as having low, intermediate, high, or very high-risk disease, respectively. Of the 88 germline variants, 6 pathologic or likely pathogenic variants were identified in 7 patients (5.8%) with *BRCA2* (1.7%), *HOXB13* (1.7%), *PALB2* (0.8%), *ATM* (0.8%), and *MSH2* (0.8%). Of 7 patients, 2 possessed intermediate risk disease that was not included in the recommendation for genetic testing. We identified the Gly132Glu variant, which was different from the Gly84Glu variant of the *HOXB13* gene in Western populations.

Conclusions: This study presents the first analysis of germline variants in unselected Korean men with prostate cancer. Our results showed comparable germline prevalence with previous studies and provides evidence for the necessity of genetic testing in Korean men with prostate cancer.

Keywords: Genetic testing; Germ-line mutation; High-throughput nucleotide sequencing; Prostatic neoplasms

INTRODUCTION

Prostate cancer is one of the most heritable cancers [1,2]. Epidemiological studies show an increased risk of prostate cancer in men with a family history [3,4]. Furthermore, a family history is associated with early onset prostate cancer and a high risk for clinically significant prostate cancer [2,5]. Prostate cancer is also implicated with other familial cancer syndromes such as hereditary breast and ovarian cancer syndrome and Lynch syndrome. Alterations in homologous DNA repair genes and DNA mismatch repair genes are recognized as a major hallmark for these syndromes [6,7]. Recent studies with regard to the genetic landscape of prostate cancer have shown a significant proportion of prostate cancers with alterations in these genes [8-10]. In particular, prostate cancer patients with germline mutations in these genes have yielded aggressive and advanced disease and are associated with a poor prognosis [10-12].

Growing evidence suggests the importance of germline variants in the early diagnosis of significant prostate cancer and the role of genetic testing for prostate cancer is increasing. Genetic testing can guide personalized treatment,

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Corresponding Author: Kwang Hyun Kim https://orcid.org/0000-0002-6264-5109
Department of Urology, Ewha Womans University Seoul Hospital, 260, Gonghang-daero, Gangseo-gu, Seoul 07084, Korea
TEL: +82-2-6986-1685, FAX: +82-2-6986-3258, E-mail: khkim.uro@gmail.com

screening for potentially lethal prostate cancer, and provide information with regard to the hereditary cancer risk for men and their relatives. Current guidelines recommend genetic testing for men with high risk or metastatic prostate cancer as well as men with a family history of hereditary prostate cancer using a multi-gene panel including at least *BRCA2*, *BRCA1*, *ATM*, *CHEK2*, *PALB2*, *MLH1*, *MSH2*, *MSH6*, and *PMS* [13]. However, the guidelines of genetic testing for prostate cancer are mainly based on data from Caucasian populations. Epidemiologic and genomic differences exist between Asian and Western men [14,15]. Currently, research on germline variants in Asian men with prostate cancer is scarce. Although few studies have investigated germline variants in Japanese and Chinese patients, there is no published data for Korean men with prostate cancer. More evidence is needed for an implementation of genetic testing for prostate cancer in Asian men.

In this study, we investigated germline variants in unselected Korean men with prostate cancer using a targeted gene panel. We evaluated the significance of germline variants according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) 2015 guidelines. To the best of our knowledge, this is the first study on germline variants in Korean men with prostate cancer.

MATERIALS AND METHODS

1. Study population, sample collection

From June 2020 to October 2020, we prospectively enrolled 120 unselected patients with prostate cancer who visited the outpatient clinic; this study was also approved by the Institutional Review Board of Ewha Womans University Seoul Hospital (IRB no. 2020-02-003). The study protocol was carried out in accordance with the Declaration of Helsinki Guidelines. Participants received detailed information and provided written informed consent for genetic testing. Clinicopathologic data, family history, and buccal cells by cotton swab for germline DNA extraction were collected from all participants.

2. Target capture sequencing and sequencing data analysis

For germline variants analysis, we designed a targeted gene panel that included *ATM*, *APC*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PMS2*, *RAD50*, and *TP53*. These genes were selected based on NCCN guidelines and previous studies [13,16-18]. DNA was extracted from buccal swabs using a QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Genomic DNA was sheared and handled for Illumina sequencing through the following steps: end-repair, A-tailing, adapter ligation, and amplification for the indexed library. Prepared DNA and capture probes were hybridized to capture target regions including all coding sequences and their intron-exon boundary regions from the selected 16 genes through the use of a Celemics target enrichment kit (Celemics, Seoul, Korea). Captured regions were then further amplified by post-polymerase chain reaction (PCR) to enrich the amount of sample. The captured libraries were then sequenced on an Illumina NextSeq500 instrument (Illumina, San Diego, CA, USA) and applying the read layout 2×150 bp. The raw FASTQ file was adapter-trimmed using Adaptor removal 2.2.2. Reads were aligned to the human reference genome sequence GRCh37 using Burrows-Wheeler aligner (version 0.7.10). Genome Analysis Toolkit (version 4.0.4.0) was used to perform a Base quality score re-calibration. Samtools mpileup was used to create an mpileup file with a minimum base-quality of 17. Variant calling was carried using Varscan (version 2.4.0). We set the minimum variant frequency to 1%, minimum coverage to 8, minimum supporting reads to 2, and applied a strand-filter.

3. Variant interpretation

The classification of each variant followed ACMG/AMP 2015 guidelines [19] and all variants were classified into five tiers: pathogenic variant, likely pathogenic variant, variants of uncertain significance, likely benign variants, and benign variants (pathogenic variant [PV], likely pathogenic variant [LPV], variant of unknown significance [VUS], likely benign variant [LBV], and benign variant [BV]). Briefly, the criteria applied to classify variants in this study included that all variants with population frequencies above 5% in the Genome Aggregation Database (gnomAD; https://gnomad.broadinstitute.org/) or the Korean Reference Genome Database (KRGDB; http://152.99.75.168:9090/KRGDB) were excluded as benign variants. The remaining variants were further classified according to their pathogenicity and the previously mentioned guidelines [19]. The gnomAD and KRGDB were large population databases that used the minor allele frequency (MAF) of maximum continental population (expect Jewish and Finish) to classify the population frequencies of candidate variants. Considering the prevalence and penetrance of prostate cancer, strong evidence for a benign classification was applied when the population frequency of the candidate variants was above MAF 0.03%. As an exception, the benign strong evidence code was applied above MAF 0.3% for *MUTYH* because its mode of inheritance is auto-

somal recessive. Regarding pathogenic evidence from the population databases, only variants that were not found in the population data of both gnomAD and KRGDB provided evidence of moderate pathogenic strength. Furthermore, the variants found in an allele in gnomAD but not in KRGDB provided pathogenic evidence of supporting strength. We used two predicting tools, REVEL and SpliceAI. The REVEL score, an amino acid meta-predictor, was publicly obtained from the open-access website of Varsome (https://varsome.com/) or from gnomAD. For splice effect prediction, a SpliceAI score was obtained from the SpliceAI website (https://spliceailookup.broadinstitute.org/). When discovering evidence regarding the effect of a null variant in a gene with a loss-of-function mechanism, we followed a specific reference for interpreting the loss of function [20]. Other possible evidential criteria including functional studies or segregation data were applied to each candidate variant based on the literature and reference papers reported in ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/) or the Human Gene Mutation Database (Professional release 2021.2).

4. Sanger sequencing of the variant in *MSH2*

The variant (c.1160_1166delinsCATAA) in *MSH2* was a novel variant classified as LPV; we conducted Sanger sequencing to exclude the possibility of a false-positive variant. The variant in *MSH2* was investigated by PCR using primers *MSH2*-F (5′-AGA TGC AGA ATT GAG GCA GAC T-3′) and *MSH2*-F (5′-TCA TGT TTT TCC AGA GCC TGT-3′) (primer concentration 10 μM). A Go Taq polymerase (cat. no. M3001; Promega, Madison, WI, USA) was used with the following amplification conditions: heating for 2 minutes at 95°C, followed by 38 cycles at 95°C for 20 seconds, 56°C for 30 seconds, and 72°C for 30 seconds, followed by 72°C for 5 minutes. The *MSH2* PCR products (171 bp) were sequenced.

Table 1. Clinicopathological characteristics of Korean prostate cancer patients

Characteristic	Patient
Age (y)	71 (64–77)
Prostate specific antigen at diagnosis (ng/mL)	11.3 (7.2–30.6)
Gleason score	
6	10 (8.3)
7	53 (44.2)
8–10	57 (47.5)
Stage	
Localized	90 (75.0)
Reginal lymph node	18 (15.0)
Distant metastasis	12 (10.0)
Initial treatment	
Radical prostatectomy	87 (72.5)
Radiotherapy	16 (13.3)
Hormonal therapy	15 (12.5)
Active surveillance	2 (1.7)
Family history of cancer	
1st degree with prostate cancer	9 (7.5)
2nd degree with prostate cancer	2 (1.7)
Other cancer without prostate cancer	40 (33.3)
No family history	69 (57.5)

Values are presented as median (interquartile range) or number (%).

RESULTS

1. Sample information

Patient characteristics are summarized in Table 1. The median age was 71 and 9 patients were younger than 60. Thirty patients had regional or metastatic disease. Of the 90 patients with localized disease, 10, 34, 25, and 21 patients were categorized as having low, intermediate, high, or very high-risk disease according to NCCN guidelines [13]. Nine patients had a family history of prostate cancer in their first degree, but none were diagnosed with prostate cancer before age 60.

2. Germline variants

Analysis of data from the 120 samples showed a 796.5±296.4 average read depth and 99% of the targeted region covered a minimum of 100 reads. After excluding all variants with a population frequency above 5%, 88 variants remained. Each variant was assessed according to 2015 ACMG/AMP guidelines [19]. Forty-eight variants were classified as BV or LBV. Of the remaining 40 variants, 6 were classified as LPV or PV and 34 were classified as VUS, which lacked benign or pathogenic

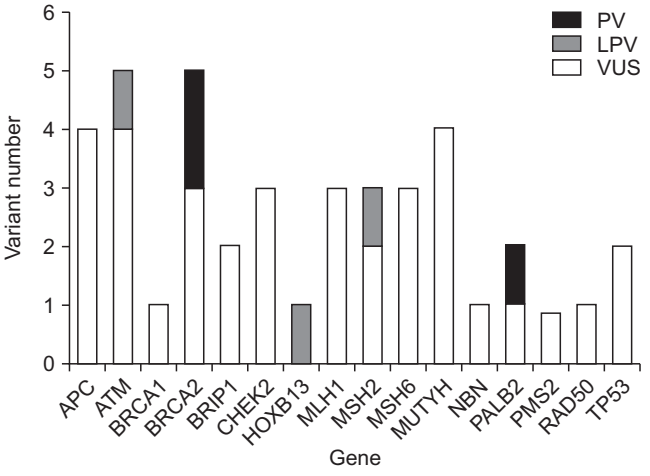

Fig. 1. Distribution of identified germline variants from sixteen genes. PV, pathogenic variant; LPV, likely pathogenic variant; VUS, variant of unknown significance.

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evidence to confirm an effect on prostate cancer (Fig. 1, Supplementary Table). Of the 120 patients, 7 (5.8%) had LPV or PV in *BRCA2* (1.7%, 2/120), *HOXB13* (1.7%, 2/120), *PALB2* (0.8%, 1/120), *ATM* (0.8%, 1/120), and *MSH2* genes (0.8%, 1/120) (Table 2).

Except HOXB13, the other genes were currently recommended for genetic testing [13]. While 5 had high risk, very high, regional, or metastatic disease, two had localized prostate cancer with intermediate-risk. Although genetic testing is not recommended for patients with intermediate-risk prostate cancer, the percentage of positive variants in patients with the intermediate-risk disease (5.9%, 2/34) was comparable to that in patients with high, very high, regional, or metastatic disease (6.6%, 5/76). While 18.2% of patients with a family history of prostate cancer in their first or second degree had LPV or PV, only 2.9% of patients without family history had positive variants (Table 3). One patient with regional prostate cancer who had the BRCA2 variant (c.1310_1313del) was diagnosed with male breast cancer during hormonal treatment of prostate cancer.

In the *HOXB13* gene, we detected the Gly132Glu variant, which was different from the Gly84Glu variant of the *HOXB13* gene in Western populations [21]. Of 3 LPV, the variant (c.1160_1166delinsCATAA) of the *MSH2* gene was a novel variant classified as LPV based on evidence of loss of function and the absence of population data. We confirmed the novel variant by Sanger sequencing to exclude the possibility of a false-positive variant. Sanger sequencing (Supplementary Fig.) demonstrated that it was a true variant. We noticed through an integrative genome viewer that the likely pathogenic INDEL variant (c.1160_1166delinsCATAA) and a benign missense variant (c.1168C>T) were located in a trans configuration within the close sequence range of *MSH2*.

DISCUSSION

The implications of genetic testing in prostate cancer are

Table 3. Patients with germline pathogenic/likely pathogenic variants according to disease risk group and family history

Variant	No. of patient (%)
Disease risk group	
Low risk disease (n=10)	0 (0.0)
Intermediate risk disease (n=34)	2 (5.9)
High, very high, regional or metastatic disease (n=76)	5 (6.6)
Family history	
Prostate cancer (1st or 2nd degree) (n=11)	2 (18.2)
Cancer other than prostate cancer (n=40)	3 (7.5)
None (n=69)	2 (2.9)

Table 2. List of prostate cancer patients with germline pathogenic/likely pathogenic variants according to ACMG/AMP guidelines

Patient_ID	Age at diagnosis (y)	Stage, Gleason score, iPSA (ng/mL)	Family history	Gene	Coding DNA	Amino acid	ACMG/AMP guideline criteria[a]	Pathogenicity[a]	Previous reported in prostate cancer patient
S076	56	pT3aN0M0, G8(5+3), 8.5	None	*BRCA2*	c.658_659del	p.Val220Ilefs*4	PVS1, PM2, PS4	PV	Yes [12]
S089[b]	73	cT4N1M0, G8(4+4), 134.7	Father (colon cancer)	*BRCA2*	c.1310_1313del	p.Lys437Ilefs*22	PVS1, PM2_sup, PS4	PV	Yes [27]
S087	70	pT2N0M0, G7(3+4), 12.5	Brother (prostate cancer)	*PALB2*	c.695del	p.Gly232Valfs*6	PVS1, PM2, PS4	PV	None
S078	58	pT2NxM0, G7(3+4), 8.9	None	*ATM*	c.496+5G>A	p.?	PS3, PM2	LPV	None
S095	53	pT2N0M0, G7(3+4), 12.8	Father (lung cancer)	*MSH2*	c.1160_1166delinsCATAA	p.Leu387Profs*2	PVS1, PM2	LPV	None
S074	71	cT3N1M1, G10(5+5), 261.9	Brother (hematologic cancer)	*HOXB13*	c.395G>A	p.Gly132Glu	PS4, PM2_sup, PP1	LPV	Yes [16,24]
S108	77	T3aN0M0, G7(3+4), 20.4	Brother (prostate cancer)	*HOXB13*	c.395G>A	p.Gly132Glu	PS4, PM2_sup, PP1	LPV	Yes [16,24]

Transcript ID: *BRCA2*, NM_000059.3; *PALB2*, NM_024675.3; *ATM*, NM_000051.3; *MSH2*, NM_000251.2; *HOXB13*, NM_006361.5.
ACMG/AMP, American College of Medical Genetics and Genomics/Association for Molecular Pathology; iPSA, initial prostate specific antigen; PV, pathogenic variant; LPV, likely pathogenic variant.
[a]: Each variant was classified according to the ACMG/AMP 2015 standards and guidelines.
[b]: The patient had breast cancer diagnosed with prostate cancer.

critical for disease risk assessment, guidance for personalized treatment, and familial genetic counseling [13,22,23]. Currently, germline genetic testing is not being conducted in men with prostate cancer in Korea and there is no available data with regard to germline pathogenic variants in Korean men with prostate cancer. Thus, we evaluated germline profiles of prostate cancer in unselected patient populations using a targeted gene panel. In this study, we found PV/LPV in 5 genes including *BRCA2*, *HOXB13*, *PALB2*, *ATM*, and *MSH2* and the pathogenic variants found in these genes have been frequently reported in other studies [11,17]. In our results, the variant (c.1160_1166delinsCATAA) in *MSH2* was a novel variant classified as LPV and was confirmed as a true variant by Sanger sequencing. *HOXB13* is a susceptibility gene for prostate cancer and several germline variants in *HOXB13* have been studied for association with prostate cancer [16,18,21,24]. The Gly84Glu variant in *HOXB13* was first reported in 2012 and several studies have confirmed the association of the Gly84Glu variant with a risk for prostate cancer [21,25]. However, the Gly84Glu variant was exclusively observed in European populations and it was likely that the main pathogenic variants of Asian populations were different from those of European populations. In a Chinese study, the Gly84Glu variant was not found in 671 men with prostate cancer but the Gly135Glu variant was observed as a novel variant in the *HOXB13* gene [18]. Two Japanese studies including 140 and 7,646 men with prostate cancer also failed to find the Gly84Glu variant and a new variant Gly132Glu was found to be associated with prostate cancer [16,24]. In our study, of 7 patients with PV/LPV, 2 had the Gly132Glu variant in the *HOXB13* gene, which was the same as with the Japanese cohort. While Gly84Glu was observed in Western, African, Ashkenazi Jewish, and Latino populations, the Gly132Glu and Gly135Glu variants were found only in East Asian populations, indicating an ethnic difference of pathogenic variants in the *HOXB13* gene [26]. Although two patients with the Gly132Glu variant were diagnosed with prostate cancer at an old age, both had aggressive disease and a family history of prostate cancer or hematologic cancer. We speculate that the *HOXB13* gene should be considered for genetic testing in men with prostate cancer, specifically for the Gly132Glu and Gly135Glu variants in Asian men.

Germline alterations in DNA repair genes are potential driver of prostate cancer. BRCA2 and BRCA1 genes are well characterized. In particular, BRCA2 mutation is associated with a 2- to 6-fold increased risk of prostate cancer [27,28]. In our results, two of seven patients with PV had PV in BRCA and germline BRCA2 mutation is also most frequent in Japanese and Chinese studies [16,18]. BRCA2 and BRCA1 are involved in homologous recombination repair and ATM is critical for initiation of double-strand break repair by homologous recombination [29]. Alteration in genes involved in homologous recombination repair are associated with more aggressive disease and poor clinical outcomes in prostate cancer [28]. In addition, information on these genes can guide personalized treatment. Prostate cancer with alteration in these genes is sensitive to poly (adenosine diphosphate-ribose) polymerase (PARP) inhibition. A recent study has demonstrated a survival benefit of niraparib, a potent inhibitor of PARP1 and PAR2 in patients with homologous recombination repair gene alterations in metastatic castration resistant prostate cancer [30].

Previous studies have reported a wide range of prevalence with 2.9% to 17.2% of germline variants depending on the clinical characteristics of study cohorts such as ethnicity, family history, or tumor characteristics [11,16-18,25]. A multicenter study by Nicolosi et al. [17] that included 3,607 men with prostate cancer who underwent germline testing showed a wide range of germline mutation frequencies depending on ethnicity with the highest rates of 22.7% in Ashkenazi Jews and the lowest rates of 6.4% in Hispanics. In addition, the germline mutation frequency could vary by the definition of a positive variant. In our study, the interpretation and classification of the data using the ACMG/AMP 2015 guidelines showed a 5.8% overall frequency of PV or LPV. With this guideline, only the variants that influenced the development of prostate cancer and met the criteria with sufficient evidence were defined as PV or LPV. In the study by Nicolosi et al. [17], the definition for a positive variant included PV, LPV, and the increased-risk allele. This increased-risk allele was not a classification category in the ACMG/AMP 2015 guidelines. The increased-risk allele could have remained as VUS in our study due to a lack of evidence to meet the criteria for PV or LPV when applying the ACMG/AMP 2015 guidelines.

It has been reported that approximately 10% of patients with metastatic prostate cancer harbored germline mutations [11,25]. While the NCCN guidelines recommended that genetic testing be performed in patients with high risk or higher clinical features, our study included 44 patients (36.6%) with low to intermediate risk disease as this study included unselected patients who visited the outpatient clinic in our institute. A previous study that also included unselected Japanese patients showed a 2.9% prevalence of the positive germline variant [16]. However, of the 34 patients with intermediate risk disease, 2 had a positive variant in our study. Both patients were diagnosed with prostate cancer at an age younger than 60, indicating the necessity for

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different genetic testing recommendations depending on age.

Our study had several limitations. First, we did not compare clinical characteristics between PV/LPV variant carriers and non-carriers. The number of patients with a positive variant was small, making it difficult to make comparisons with statistical significance. Secondly, although we performed sequencing of 16 genes that were recommended for genetic testing, critical disease related variants or Korean specific variants could be missed. Thirdly, this was a single center study, thus the patients included in the study may not be representative of Korean patients with prostate cancer. Nevertheless, this was the first study that analyzed germline pathogenic variants with a targeted gene panel for prostate cancer in Korean men. Although the number of patients was small, we classified variants using strict criteria and provided evidence to infer the overall aspect of germline variants by analyzing unselected Korean men with prostate cancer. A further study with a large number of patients with a pan cancer gene panel, whole exome, or whole genome sequencing is required to provide comprehensive germline profiling of Korean men with prostate cancer.

CONCLUSIONS

We successfully sequenced and analyzed germline variants from 120 Korean men with prostate cancer. To the best of our knowledge, this study presents the first analysis of germline genetic profiling in Korean men with prostate cancer. Although the prevalence of germline pathogenic variants could differ depending on the study, our results showed that Korean patients had comparable germline prevalence to other studies. The study provides evidence for the necessity of genetic testing in Korean men with prostate cancer.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Kwang Hyun Kim. Data acquisition: Kwang Hyun Kim. Statistical analysis: Min-Kyung So and Kwang Hyun Kim. Data analysis and interpretation: Min-Kyung So. Drafting of the manuscript: Min-Kyung So, Hyun Kyu Ahn, and Kwang Hyun Kim. Critical revision of the manuscript: Jungwon Huh and Kwang Hyun Kim. Obtaining funding: Kwang Hyun Kim. Supervision: Jungwon Huh. Approval of the final manuscript: Jungwon Huh and Kwang Hyun Kim.

SUPPLEMENTARY MATERIAL

Supplementary material can be found via https://doi.org/10.4111/icu.20220044.

REFERENCES

1. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000;343:78-85.
2. Beebe-Dimmer JL, Kapron AL, Fraser AM, Smith KR, Cooney KA. Risk of prostate cancer associated with familial and hereditary cancer syndromes. J Clin Oncol 2020;38:1807-13.
3. Kiciński M, Vangronsveld J, Nawrot TS. An epidemiological reappraisal of the familial aggregation of prostate cancer: a meta-analysis. PLoS One 2011;6:e27130.
4. Albright F, Stephenson RA, Agarwal N, Teerlink CC, Lowrance WT, Farnham JM, et al. Prostate cancer risk prediction based on complete prostate cancer family history. Prostate 2015;75:390-8.
5. Bratt O, Drevin L, Akre O, Garmo H, Stattin P. Family history and probability of prostate cancer, differentiated by risk category: a nationwide population-based study. J Natl Cancer Inst 2016;108:djw110.
6. Giri VN, Obeid E, Gross L, Bealin L, Hyatt C, Hegarty SE, et al. Inherited mutations in men undergoing multigene panel testing for prostate cancer: emerging implications for personalized prostate cancer genetic evaluation. JCO Precis Oncol 2017;1:PO.16.00039.
7. Ryan S, Jenkins MA, Win AK. Risk of prostate cancer in Lynch syndrome: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014;23:437-49.
8. Cancer Genome Atlas Research Network. The molecular taxonomy of primary prostate cancer. Cell 2015;163:1011-25.
9. Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015;161:1215-28. Erratum in: Cell 2015;162:454.
10. Armenia J, Wankowicz SAM, Liu D, Gao J, Kundra R, Reznik E, et al. The long tail of oncogenic drivers in prostate cancer. Nat Genet 2018;50:645-51. Erratum in: Nat Genet 2019;51:1194.

11. Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375:443-53.
12. Wu Y, Yu H, Li S, Wiley K, Zheng SL, LaDuca H, et al. Rare germline pathogenic mutations of DNA repair genes are most strongly associated with grade group 5 prostate cancer. Eur Urol Oncol 2020;3:224-30.
13. Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T, et al. Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2019;17:479-505.
14. Spratt DE, Chan T, Waldron L, Speers C, Feng FY, Ogunwobi OO, et al. Racial/ethnic disparities in genomic sequencing. JAMA Oncol 2016;2:1070-4.
15. Zhu Y, Mo M, Wei Y, Wu J, Pan J, Freedland SJ, et al. Epidemiology and genomics of prostate cancer in Asian men. Nat Rev Urol 2021;18:282-301.
16. Momozawa Y, Iwasaki Y, Hirata M, Liu X, Kamatani Y, Takahashi A, et al. Germline pathogenic variants in 7636 Japanese patients with prostate cancer and 12 366 controls. J Natl Cancer Inst 2020;112:369-76.
17. Nicolosi P, Ledet E, Yang S, Michalski S, Freschi B, O'Leary E, et al. Prevalence of Germline variants in prostate cancer and implications for current genetic testing guidelines. JAMA Oncol 2019;5:523-8.
18. Wei Y, Wu J, Gu W, Qin X, Dai B, Lin G, et al. Germline DNA repair gene mutation landscape in Chinese prostate cancer patients. Eur Urol 2019;76:280-3.
19. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-24.
20. Abou Tayoun AN, Pesaran T, DiStefano MT, Oza A, Rehm HL, Biesecker LG, et al.; ClinGen Sequence Variant Interpretation Working Group (ClinGen SVI). Recommendations for interpreting the loss of function PVS1 ACMG/AMP variant criterion. Hum Mutat 2018;39:1517-24.
21. Ewing CM, Ray AM, Lange EM, Zuhlke KA, Robbins CM, Tembe WD, et al. Germline mutations in HOXB13 and prostate-cancer risk. N Engl J Med 2012;366:141-9.
22. Cheng HH, Sokolova AO, Schaeffer EM, Small EJ, Higano CS. Germline and somatic mutations in prostate cancer for the clinician. J Natl Compr Canc Netw 2019;17:515-21.
23. Giri VN, Knudsen KE, Kelly WK, Cheng HH, Cooney KA, Cookson MS, et al. Implementation of germline testing for prostate cancer: Philadelphia Prostate Cancer Consensus Conference 2019. J Clin Oncol 2020;38:2798-811.
24. Hayano T, Matsui H, Nakaoka H, Ohtake N, Hosomichi K, Suzuki K, et al. Germline variants of prostate cancer in Japanese families. PLoS One 2016;11:e0164233.
25. Boyle JL, Hahn AW, Kapron AL, Kohlmann W, Greenberg SE, Parnell TJ, et al. Pathogenic germline DNA repair gene and *HOXB13* mutations in men with metastatic prostate cancer. JCO Precis Oncol 2020;4:PO.19.00284.
26. Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature 2016;536:285-91.
27. Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. J Clin Oncol 2004;22:735-42.
28. Gallagher DJ, Gaudet MM, Pal P, Kirchhoff T, Balistreri L, Vora K, et al. Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. Clin Cancer Res 2010;16:2115-21.
29. Blackford AN, Jackson SP. ATM, ATR, and DNA-PK: the trinity at the heart of the DNA damage response. Mol Cell 2017;66:801-17.
30. Chi KN, Rathkopf DE, Smith MR, Efstathiou E, Attard G, Olmos D, et al. Phase 3 MAGNITUDE study: first results of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) as first-line therapy in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without homologous recombination repair (HRR) gene alterations. J Clin Oncol 2022;40(6 Suppl):12.

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