

Germline variant spectrum and pragmatic family history assessment in prostate cancer: a 250-patient Turkish cohort

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Abstract

Germline genetic testing is increasingly incorporated into prostate cancer care, but data from underrepresented populations remain limited and optimal approaches to family history assessment are uncertain. We retrospectively evaluated 250 consecutive patients with histologically confirmed prostate adenocarcinoma who underwent germline testing using a 60-gene hereditary cancer panel. Pathogenic or likely pathogenic (P/LP) variants were identified in 34 patients (13.6%), most frequently in *ATM* (n = 9), *BRCA2* (n = 8), and *MUTYH* (n = 5). P/LP variant detection was not significantly associated with age at diagnosis, metastatic disease, or ISUP grade group. In contrast, a pragmatic study-defined family history was more frequent among patients with P/LP variants than among those without such variants (89.7% vs 54.1%, $p < 0.001$) and remained independently associated with P/LP variant detection in multivariable analysis (adjusted OR 8.31, 95% CI 2.35–29.38; $p = 0.001$). Among 18 P/LP variant carriers who could be classified using both approaches, 83.3% met the study-defined family history criteria compared with 38.9% meeting National Comprehensive Cancer Network family history criteria ($p = 0.008$). These findings demonstrate a broad spectrum of germline P/LP variants in Turkish patients with prostate cancer and suggest that a pragmatic family history assessment may complement guideline-based approaches to germline testing.

1. Introduction

Prostate cancer is the second most commonly diagnosed cancer in men worldwide and remains a major cause of cancer-related mortality [1]. A clinically relevant proportion of patients carry germline pathogenic or likely pathogenic (P/LP) variants in cancer predisposition genes. Reported germline yields vary considerably with cohort selection and panel composition [2–4]. Many of these variants affect DNA damage response and repair genes, particularly *BRCA2*, *ATM*, and other genes involved in homologous recombination repair (HRR). Their identification has implications beyond inherited cancer risk. Germline findings may influence treatment options, including the use of poly(ADP-ribose) polymerase (PARP) inhibitors in selected patients with HRR gene alterations, and may also identify families who could benefit from cascade testing and cancer surveillance [2–5].

Family history is an important component of hereditary cancer risk assessment in men with prostate cancer. Because germline cancer predisposition may involve multiple organ systems, histories of breast, ovarian, pancreatic, colorectal, and endometrial cancer in relatives may also be informative when assessing inherited susceptibility [6]. In routine clinical practice, however, guideline-based criteria may require detailed information such as relatives' age at diagnosis or tumour characteristics that is not always available. This creates a need to evaluate whether simpler, pragmatic family history definitions can complement guideline-based selection for germline testing.

Data on the germline genetic landscape of prostate cancer in Türkiye remain limited despite the substantial national disease burden [7]. We therefore aimed to characterize the prevalence and spectrum of germline P/LP variants in a Turkish prostate cancer cohort and to examine their associations with

clinical characteristics. We also evaluated whether a pragmatic, predefined family history definition could identify germline variant carriers and compared it with National Comprehensive Cancer Network (NCCN) family history criteria.

2. Materials and methods

2.1. Study population and clinical data

This retrospective, single-centre study included 250 consecutive patients with histologically confirmed prostate adenocarcinoma who underwent germline genetic testing at the Department of Medical Genetics, Ankara Etlik City Hospital, Türkiye, between September 2022 and June 2026.

Clinical data were obtained from medical records and genetic counselling files. Variables included age at prostate cancer diagnosis, metastatic status, Gleason score/International Society of Urological Pathology (ISUP) grade group, personal history of a secondary malignancy, and family history of cancer.

The study was approved by the Ankara Etlik City Hospital Clinical Research Ethics Committee (approval no. AEŞH-BADEK-2025-0177). Written informed consent for germline genetic testing was obtained from all patients.

2.2. Family history and NCCN-based assessment

For the study-defined family history, positivity was defined as at least one first- or second-degree relative with prostate, breast, ovarian, pancreatic, colorectal, or endometrial cancer. No age or disease-stage restrictions were applied.

Patients were also assessed according to NCCN Version 2.2026 family history criteria and overall germline testing indications. When relevant family history was known but information required for NCCN classification was unavailable, status was recorded as *unknown*; absence of family history data was treated as missing. The same approach was applied to overall NCCN testing indications.

2.3. Germline genetic testing and variant interpretation

Genomic DNA was extracted from peripheral blood samples and analysed using the SOPHiA Custom Hereditary Cancer Solution (CHCS_C_v2), a targeted next-generation sequencing panel covering 60 hereditary cancer genes (**Supplementary Table 1**). Sequencing was performed on the Illumina NextSeq 2000 platform, and bioinformatic analysis was carried out using SOPHiA DDM.

Sequence variants were interpreted according to the 2015 American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) standards, together with gene- or disease-specific recommendations when applicable [8]. Variants classified as pathogenic (P) or likely pathogenic (LP) were considered positive findings. Variants of uncertain significance (VUS) and cases without a P/LP variant were considered negative for the primary statistical analyses.

A subset of nine genes represented in the panel and previously evaluated in PARP inhibitor trials (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CHEK2*, *PALB2*, *RAD51C*, and *RAD51D*) was analysed separately [5]. This grouping was descriptive and did not imply treatment eligibility.

2.4. Statistical analysis

Continuous variables were summarized as mean $\pm$ SD or median (IQR), as appropriate, and categorical variables as n (%). Germline P/LP positivity was the primary outcome. Age at diagnosis was compared using an independent-samples *t* test, and categorical variables using Pearson's chi-square or Fisher's exact test, as appropriate.

Binary logistic regression was used to assess independent associations with P/LP positivity. The multivariable model included age at diagnosis, metastatic disease, and study-defined family history; overlapping family history variables were not entered simultaneously. The two distinct family history definitions were compared among classifiable P/LP-positive patients using the exact McNemar test. Missing data were handled on a variable-specific basis, and NCCN classifications recorded as unknown were excluded from binary comparisons.

Exploratory analyses compared age, metastatic status, and ISUP grade group between *BRCA2* or *ATM* carriers and non-carriers. All tests were two-sided, with $p < 0.05$ considered statistically significant. Analyses were performed using IBM SPSS Statistics version 31 (IBM Corp., Armonk, NY, USA).

3. Results

3.1 Cohort characteristics and germline findings

A total of 250 patients with prostate cancer were included. The median age at diagnosis was 63 years (IQR, 56-70), and 63.6% of patients with available data had metastatic disease. Cohort characteristics are summarized in **Table 1**.

At least one germline pathogenic or likely pathogenic (P/LP) variant was identified in 34 of 250 patients (13.6%). Among the remaining patients, 106 (42.4%) had at least one VUS without a P/LP variant, while 110 (44.0%) had no reportable P/LP or VUS finding. Four patients carried P/LP variants in two genes, resulting in 38 P/LP findings overall. The most frequently affected genes were *ATM* ($n = 9$), *BRCA2* ($n = 8$), and *MUTYH* ($n = 5$), followed by *BRCA1*, *CHEK2*, *ERCC3*, and *NBN* ($n = 2$ each). Individual P/LP variants and associated clinical characteristics are provided in **Table 2** and **Supplementary Table 2**, respectively. VUS findings are listed in **Supplementary Table 3**.

Twenty-two of the 34 P/LP-positive patients (64.7%) carried at least one variant in a gene involved in homologous recombination repair or related DNA double-strand break response pathways. Using the predefined nine-gene PARP inhibitor-related set, 20 of 250 patients (8.0%) carried a germline P/LP variant.

Table 1: Clinical characteristics and germline P/LP variant status of the study cohort

Characteristic	Value
Age at diagnosis, median (IQR), years	63 (56-70)
Metastatic disease, n/N (%)	133/209 (63.6)
Study-defined positive family history, n/N (%)	131/223 (58.7)
First-degree relative with prostate cancer, n/N (%)	51/223 (22.9)
NCCN family history criteria fulfilled, n/N (%)	29/223 (13.0)
NCCN germline testing indication fulfilled, n/N (%)	168/200 (84.0)
Personal history of a secondary malignancy, n/N (%)	35/228 (15.4)
Germline P/LP variant, n/N (%)	34/250 (13.6)

Percentages were calculated using the number of patients with available data for each variable.

Study-defined family history was considered positive when at least one first- or second-degree relative had prostate, breast, ovarian, pancreatic, colorectal, or endometrial cancer at any age.

NCCN status was unknown in 66/223 patients for family history and 17/200 for overall testing indications; these patients were included in the descriptive denominator but were not classified as negative or included in binary comparisons.

Abbreviations: IQR, interquartile range; NCCN, National Comprehensive Cancer Network; P/LP, pathogenic/likely pathogenic.

Table 2: Germline pathogenic and likely pathogenic variants identified in the study cohort

Case(s)	Gene	Germline variant
6	<i>APC</i>	NM_000038.6: c.6709C>T; p.(Arg2237Ter)
11	<i>ATM</i>	NM_000051.4: c.6082C>T; p.(Gln2028Ter)
18	<i>ATM</i>	NM_000051.4: c.967A>G; p.(Ile323Val)
22, 178	<i>ATM</i>	NM_000051.4: c.6047A>G; p.(Asp2016Gly)
35, 39	<i>ATM</i>	NM_000051.4: c.4909+1G>A
42	<i>ATM</i>	NM_000051.4: c.6415_6416del; p.(Glu2139IlefsTer6)
216	<i>ATM</i>	NM_000051.3: c.2838+1G>A
231	<i>ATM</i>	NM_000051.3: c.2754del; p.(Phe918LeufsTer11)
49	<i>BRCA1</i>	NM_007294.4: c.5467+2T>A
178	<i>BRCA1</i>	NM_007294.4: c.3624dup; p.(Leu1209IlefsTer10)
50	<i>BRCA2</i>	NM_000059.4: c.471del; p.(Lys157AsnfsTer15)
52, 223	<i>BRCA2</i>	NM_000059.4: c.3751dup; p.(Thr1251AsnfsTer14)
56	<i>BRCA2</i>	NM_000059.4: c.6468_6469del; p.(Gln2157IlefsTer18)
57	<i>BRCA2</i>	NM_000059.4: c.4284dup; p.(Gln1429SerfsTer9)
58	<i>BRCA2</i>	NM_000059.4: c.9097dup; p.(Thr3033AsnfsTer11)
244	<i>BRCA2</i>	NM_000059.4: c.3720_3721del; p.(Phe1241Ter)
249	<i>BRCA2</i>	NM_000059.3: c.2970_2975delinsTATTAATGATTAC; p.(Met990fs)
83	<i>CHEK2</i>	NM_007194.4: c.721+3A>T
217	<i>CHEK2</i>	NM_001005735.1: c.628G>A; p.(Gly210Arg)
95	<i>DDB2</i>	NM_000107.3: c.730_733del; p.(Lys244Ter)
99	<i>ERCC3</i>	NM_000122.2: c.1533G>A; p.(Trp511Ter)
115	<i>ERCC3</i>	NM_000122.2: c.325C>T; p.(Arg109Ter)
35	<i>FANCA</i>	NM_000135.4: c.3788_3790del; p.(Phe1263del)
113	<i>GALNT12</i>	NM_024642.5: c.394del; p.(Tyr132MetfsTer11)
115	<i>MSH2</i>	NM_000251.3: c.421dup; p.(Met141AsnfsTer11)
120, 127	<i>MUTYH</i>	NM_001048174.2: c.1395_1397del; p.(Glu466del)
128	<i>MUTYH</i>	NM_001048171.1: c.1145G>A; p.(Gly382Asp)
167	<i>MUTYH</i>	NM_001048171.1: c.1395_1397del; p.(Glu466del)

198	<i>MUTYH</i>	NM_001048174.2: c.135del; p.(Glu46ArgfsTer17)
135	<i>NBN</i>	NM_001024688.3: c.1894C>T; p.(Arg632Ter)
139	<i>NBN</i>	NM_002485.5: c.247dup; p.(Met83AsnfsTer23)
142	<i>NTHL1</i>	NM_001318194.2: c.191G>A; p.(Trp64Ter)
42	<i>RAD51C</i>	NM_058216.3: c.709C>T; p.(Arg237Ter)
151	<i>VHL</i>	NM_000551.4: c.37del; p.Val13Ter

All listed variants were heterozygous and classified as pathogenic or likely pathogenic according to ACMG/AMP standards.

Cases 35, 42, 115, and 178 each carried P/LP variants in two genes. Recurrent identical variants are listed once, with all corresponding case numbers.

3.2 Clinical factors associated with germline P/LP positivity

P/LP positivity was not significantly associated with age at diagnosis, metastatic status, or ISUP grade group (**Table 3A**). In contrast, study-defined family history was more frequent among P/LP-positive patients than among those without a P/LP variant (89.7% vs 54.1%, $p < 0.001$). First-degree family history of prostate cancer (41.4% vs 20.1%, $p = 0.011$) and fulfilment of NCCN family history criteria (38.9% vs 15.8%, $p = 0.046$) were also associated with P/LP positivity. Other clinical comparisons were not statistically significant.

In multivariable logistic regression, study-defined family history remained independently associated with P/LP positivity (adjusted OR, 8.31; 95% CI, 2.35-29.38; $p = 0.001$), whereas age and metastatic disease were not significant (**Table 3B**).

Exploratory analyses showed numerically younger age among *BRCA2* carriers (58.0 vs 63.1 years), with metastatic disease in 5/6 and ISUP grade group 4-5 in 3/4 evaluable carriers; none of these differences reached statistical significance. No comparable pattern was observed for *ATM* carriers (all $p > 0.05$).

Table 3: Clinical characteristics associated with germline P/LP variant positivity

A. Group comparisons			
Variable	P/LP positive[⊠]	No P/LP variant[⊠]	p value
Age at diagnosis, mean ± SD, years	61.47 ± 8.76	63.22 ± 9.44	0.312
Metastatic disease, n/N (%)	20/31 (64.5)	113/178 (63.5)	0.912
ISUP grade group 4-5, n/N (%)	11/20 (55.0)	76/121 (62.8)	0.506
Study-defined positive family history, n/N (%)	26/29 (89.7)	105/194 (54.1)	<0.001
First-degree relative with prostate cancer, n/N (%)	12/29 (41.4)	39/194 (20.1)	0.011
NCCN family history criteria fulfilled, n/N (%) [⊠]	7/18 (38.9)	22/139 (15.8)	0.046
NCCN germline testing indication fulfilled, n/N (%) [⊠]	27/28 (96.4)	141/155 (91.0)	0.474
Personal history of a secondary malignancy, n/N (%)	4/32 (12.5)	31/196 (15.8)	0.794
B. Multivariable logistic regression			
Variable	Adjusted OR[⊠]	95% CI	p value
Age at diagnosis, per year	1.01	0.96-1.05	0.811
Metastatic disease	1.82	0.74-4.49	0.191
Positive family history, study definition	8.31	2.35-29.38	0.001

⊠ For categorical variables, percentages were calculated among patients with available data for the corresponding characteristic within each P/LP group.

⊠ Patients with an unknown NCCN classification were excluded from the corresponding binary comparison and were not classified as negative.

⊠ The multivariable logistic regression model included age at diagnosis, metastatic disease, and study-defined family history. The model was based on 193 patients with complete data, including 27 P/LP-positive patients.

Abbreviations: CI, confidence interval; ISUP, International Society of Urological Pathology; NCCN, National Comprehensive Cancer Network; OR, odds ratio; P/LP, pathogenic/likely pathogenic; SD, standard deviation.

3.3 Comparison of family history definitions

Among P/LP-positive patients with sufficient information for binary classification by both family history definitions (n = 18), the study-defined criteria was positive in 15 patients (83.3%), whereas the NCCN family history definition was positive in 7 (38.9%). Eight patients were classified as positive only by the

study-defined criteria, while none were classified as positive only by the NCCN definition. The paired difference was statistically significant (exact McNemar test, $p = 0.008$).

4. Discussion

In this cohort of 250 patients with prostate cancer, germline P/LP variants were identified in 13.6%, with *ATM* and *BRCA2* accounting for the largest proportion of findings. Family history was the strongest clinical correlate of germline positivity and remained independently associated with P/LP status.

Reported germline yields vary across prostate cancer cohorts because of differences in patient selection and panel composition. P/LP variants have been reported in 11.8% of men with metastatic disease, 17.2% of a referral-based cohort, and 7.7% of unselected patients [2,3,9]. A recent Turkish series using a 42-gene panel reported a rate of 9.8% [10]. Our 13.6% rate reflects the yield of a broad 60-gene hereditary cancer panel and should not be interpreted as the prevalence of established prostate cancer-susceptibility variants alone.

Twenty patients (8.0%) carried P/LP variants in the predefined PARP inhibitor-related gene set. This proportion indicates potential therapeutic relevance but should not be interpreted as a treatment-eligibility rate, as PARP inhibitor benefit varies by gene and clinical setting [5,11,12]. Current guidelines recommend interpretation within the specific molecular and clinical context [13,6].

Family history was the strongest clinical correlate of P/LP positivity. Study-defined family history was positive in 89.7% of evaluable carriers and remained independently associated with P/LP positivity (adjusted OR, 8.31). Previous studies have reported inconsistent associations between family history and germline findings [14-16], which may partly reflect differences in the cancers considered, degree of relationship, and completeness of family history information. In hereditary cancer practice, detailed information on relatives' age at diagnosis, tumour characteristics, or disease stage is frequently unavailable, particularly when diagnoses occurred many years earlier or in extended family members.

Among the 18 carriers classifiable by both definitions, 83.3% met the study-defined criteria compared with 38.9% meeting NCCN family history criteria. However, the broader definition was also positive in 54.1% of patients without a P/LP variant and should therefore not be considered superior to, or a replacement for, guideline-based criteria. Its practical advantage is that it does not require detailed information on relatives' age at diagnosis or tumour characteristics. Our findings support pragmatic family history assessment as a complement to current guideline-based testing [9,13,6].

Overall P/LP positivity was not associated with age at diagnosis, metastatic disease, or ISUP grade group, consistent with some clinically tested cohorts [14,16], but contrasting with large studies reporting enrichment of selected DNA-repair variants in metastatic or aggressive prostate cancer [2,17]. This apparent discrepancy may reflect the heterogeneity of genes combined under an overall P/LP-positive category, since individual susceptibility genes may differ substantially in their association with disease aggressiveness. In exploratory analyses, *BRCA2* carriers were numerically younger and more frequently

had metastatic or ISUP grade group 4–5 disease, whereas no comparable pattern was observed for *ATM*. This direction is compatible with previous evidence linking *BRCA2* particularly strongly to aggressive prostate cancer, but the very small number of evaluable carriers in our cohort precludes gene-specific conclusions.

Nearly two-thirds of P/LP-positive patients (64.7%) carried variants in homologous recombination repair or related DNA double-strand break response genes, consistent with previous prostate cancer germline studies [2-4,18]. Less frequent findings in *NBN*, *FANCA*, and *RAD51C* further illustrate that the germline DNA-repair spectrum extends beyond the genes most commonly represented in prostate-focused testing panels.

The five monoallelic *MUTYH* findings deserve a different interpretation. They represented 2.0% of the entire cohort, closely matching the 2.1% *MUTYH* P/LP frequency reported in a previous Turkish hereditary cancer panel study of 1,254 patients [19] and the approximately 1-in-45 carrier frequency estimated in broader populations [20]. Thus, our findings do not support enrichment of monoallelic *MUTYH* variants in prostate cancer, for which a predisposition association is not established [20]. Any potential contribution to tumorigenesis would require evidence of a somatic second hit, such as loss of the wild-type allele [21].

A P/LP variant was also identified in *MSH2*. Prostate cancer is increasingly recognized within the Lynch syndrome tumor spectrum, with the strongest evidence reported for *MSH2* carriers [22,23]. Although only one *MSH2* carrier was identified, this finding illustrates that germline evaluation in prostate cancer may uncover hereditary cancer syndromes with implications extending beyond the affected patient. Identification of a mismatch repair gene P/LP variant may have consequences for cancer surveillance and cascade testing in relatives, in addition to its potential relevance to tumour-directed therapy [24].

The broader panel also identified P/LP variants in *ERCC3*, *DDB2*, *NTHL1*, *APC*, *VHL*, and *GALNT12*, none of which are established prostate cancer susceptibility genes [25]. *ERCC3* and *DDB2* participate in nucleotide excision repair, while biallelic *NTHL1* variants cause a recessive multi-tumour predisposition syndrome; the relevance of heterozygous variants in these genes to prostate cancer remains uncertain [25-27]. *APC*, *VHL*, and *GALNT12* are associated with other hereditary cancer phenotypes but not with established germline prostate cancer predisposition [28-30]. Although alterations in Wnt, HIF, and glycosylation pathways have been implicated in prostate cancer biology, current evidence is insufficient to assign a causal role to these germline findings [31,32]. These findings should not be assumed to explain the patients' prostate cancer solely on the basis of their pathogenic classification. Rather, they exhibit an important challenge of broad hereditary cancer testing: variant pathogenicity and gene-disease validity are distinct considerations. Clinical interpretation therefore requires assessment of the established phenotype and inheritance pattern associated with each gene.

No P/LP variant was detected in *HOXB13*, despite its inclusion in the panel. The well-established G84E risk allele shows marked ancestry-dependent variation and is most frequent in populations of Northern

European origin [33,34]. Its absence in our cohort may therefore reflect population-specific differences in the germline genetic architecture of prostate cancer.

The high frequency of VUS findings also deserves consideration. At least one VUS without a P/LP variant was identified in 42.4% of the cohort, illustrating a common challenge of broad hereditary cancer panel testing. VUS should not be used to guide clinical management or predictive testing of relatives, and their interpretation may change as additional population, segregation, functional, and clinical evidence becomes available [8,35,36]. This is particularly relevant for broad multigene panels, in which increasing numbers of genes and variants may increase the likelihood of uncertain findings. Periodic reassessment may therefore be important, particularly for VUS identified in clinically relevant cancer predisposition genes [36]. Reporting the VUS spectrum of our cohort may also provide useful population-specific data for future reinterpretation.

This study has several limitations. Its retrospective, single-centre design and incomplete clinical data, particularly for ISUP grade and NCCN family history classification, limited some analyses. The paired family history comparison included only 18 P/LP-positive patients, and family history was largely patient-reported. The broad panel also included genes with uncertain relevance to prostate cancer, while tumour analyses were unavailable to assess somatic second hits. Small gene-specific subgroups further limited genotype-phenotype analyses. Nevertheless, the consecutive real-world cohort and standardized germline testing provide useful data from an underrepresented population.

5. Conclusion

Germline P/LP variants were identified in 13.6% of patients with prostate cancer, with DNA damage response genes predominating among the findings. A pragmatic family history definition was strongly associated with germline positivity and may complement current guideline-based testing criteria. The broad variant spectrum, including findings of uncertain prostate cancer relevance, also highlights the need for gene-specific interpretation when translating multigene panel results into clinical practice.

Declarations

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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Author Contribution

Z.Ö.P. contributed to protocol/project development, data collection and management, data analysis, and manuscript writing/editing. E.Ç.D. and A.B. contributed to data collection and management. T.B. and H.S. contributed to genetic analysis and interpretation. Ö.A.Y., F.O., and A.N.K. contributed to patient recruitment and critically reviewed the manuscript. H.B.E. contributed to protocol/project development, study supervision, and critical revision of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets generated and analysed during the current study are not publicly available because they contain potentially identifiable clinical and genetic information. De-identified data may be available from the corresponding author on reasonable request, subject to institutional and ethical requirements.

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