

Case Report

Genetic Analysis of a Family with Multiple Incidences of Prostate Cancer

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Keywords

Prostate cancer · Predisposition · Genetic · Mutation · Germline

Abstract

A family with multiple members diagnosed with prostate cancer was identified, and genetic variants were analyzed. Three brothers were diagnosed with prostate cancer. Germline variants in *BRCA1*, *BRCA2*, *TINF2*, and *CD19* were found through next-generation DNA sequencing using a hereditary cancer panel. The *BRCA1* G275D variant was present in patients, but absent in the healthy member. An *ELAC2* variant was found in 1 patient. Several mutations were predicted to be deleterious by a set of computation programs. Multiple gene mutations might contribute to the overall predisposition to prostate cancer in the family. Even in cases with potentially deleterious variants in *BRCA1* or *BRCA2*, there could be diverse clinical manifestations.

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Introduction

Prostate cancer (Pca) is one of the most common cancers in men in the USA. In China, Pca is among the top 10 of the most common cancers in men [1]. About 10% of Pca was considered hereditary [2, 3]. Some common genes of which mutations cause predisposition to Pca include *BRCA1*, *BRCA2*, *CHEK2*, *ATM*, *HOXB13*, *BRIP*, *PALB2*, and mismatch repair genes (MMR) [2–4]. The American College of Medical Genetics recommend genetic testing when three or more first-degree relatives are with Pca or two or more first-degree relatives

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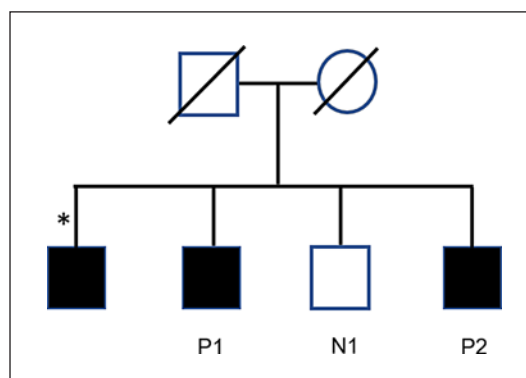


Fig. 1. Family pedigree. *This subject was out of contact.

Table 1. Distribution of rare germline variants from NGS

Subject	<i>BRCA1</i> NM_007300 p.G275D	<i>BRCA2</i> NM_000059 p.V2109I	<i>TINF2</i> NM_001099274 p.T100I	<i>CD19</i> NM_001178098 p.P471L	Others
N1	–	+	+	+	<i>MSH3</i> NM_002439:p.D620N
P1	+	+	+	+	
P2	+	+	+	+	<i>ELAC2</i> NM_018127:p.R464W

All variants were of heterozygous type.

N1, healthy brother; P1 and P2, two brothers with Pca.

*Mutation present.

–Mutation absent.

are diagnosed with Pca at age 55 or younger [5]. We performed genetic analysis of a family in which three out of four brothers suffered from Pca and found variants in *BRCA1* and *BRCA2*, together with some other putatively related genes, and the clinical characteristics also less aggressive.

Case Report

Two brothers were diagnosed with Pca in 2020 at the local hospital through prostate biopsies and pathological exams. Main symptom is difficulty in urination. History tracing revealed that another brother from the family was also diagnosed with Pca a few years ago, but lost contact since then. Pca was not diagnosed before the age of 60. One brother remains healthy. The family pedigree is shown in Figure 1.

Blood specimens were taken from the three brothers available for genetic tests with consent. NGS was performed with a hereditary panel of 219 predisposition genes in cancers. The gene list of the panel and experimental details are provided in online supplementary file S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000521122). Six rare germline gene variants were identified, and all were of heterozygous type (Table 1). All variants were verified by Sanger sequencing. No other variants were found in *CHEK2*, *ATM*, *BRIP1*, *PALB2*, *HOXB13*, or other MMR genes. Panel gene list, NGS experimental, and bioinformatics details are given in online supplementary File 1. *BRCA1* G275D was noticeably absent in the healthy brother but present in the two brothers with Pca, while *BRCA1* V2109I was found in all the three brothers (Table 1).

Table 2. Population frequencies of the variants

Gene	SNP rs#	ChinaMAP	1000G EAS	ExAC EAS	GenomeAD EAS
<i>BRCA1</i>	rs397509327	0.00179448	NA	0.0014	0.0011
<i>BRCA2</i>	rs79456940	0.00236116	0.002	0.0038	0.0032
<i>CD19</i>	rs147626581	NA	NA	0	0
<i>ELAC2</i>	rs200149324	0.0083113	0.0109	0.0093	0.0103
<i>MSH3</i>	rs200337887	0.000708349	NA	0.0006	0.0006
<i>TINF2</i>	NA	NA	NA	NA	NA

NA, information not found.

Table 3. Functional effect prediction by computational programs

Variant	SIFT	Polyphen2	MutationTaster	MutationAssessor	Provean
<i>BRCA1</i> G275D	D	B	D	H	D
<i>BRCA2</i> V2109I	T	B	N	N	N
<i>CD19</i> P471L	D	D	N	L	D
<i>ELAC2</i> R464W	D	D	N	M	D
<i>MSH3</i> D620N	D	D	D	M	D
<i>TINF2</i> T100I	D	P	D	M	D

D, damaging; P, probably damaging; T, tolerant; B, benign; N, neutral; M, moderate; L, low; H, high.

All variants were rare with population allele frequencies between 0.001 and 0.01 (Table 2). Population frequency information for *TINF2* was absent from the databases. NGS data from over 200 Pca patients collected in the laboratory were also analyzed, and the *BRCA1* variant was found in another patient with Pca, and no other *BRCA1* or *BRCA2* variant was found recurrent except the family in this report.

The functional consequences of the variants were analyzed by some commonly used *in silico* tools, SIFT, Polyphen2, MutationTaster, MutationAssessor, and Provean [6]. The predicted effects are summarized in Table 3. The results show that the *BRCA1* G275D might have a higher functional impact, and the *BRCA2* V2109I might have limited functional effect. The glycine at position 275 of *BRCA1* is conserved among multiple species, including human, monkey, and mouse (data not shown). None of the variants was classified as *pathogenic* or *likely pathogenic* in the Clinvar database (<https://www.ncbi.nlm.nih.gov/clinvar/>).

In this family, Pca was not diagnosed before the age of 60. One brother remains healthy at the age over 70. The two brothers with Pca with clinical information available had adenoma of the prostate by pathological exams, and the Gleason scores were 6 and 7, respectively. No metastasis was found. PSA level was between 4 and 10 ng/mL. Both received radical prostatectomy treatment, and the disease remain stable with PSA less than 4 ng/mL up to the point of this report.

Discussion/Conclusions

BRCA1 and *BRCA2* genes are tumor suppressors, involved in cellular DNA damage repair. *BRCA1* and *BRCA2* gene germline mutations are the most common and major drivers of familial Pca [2–4, 7, 8]. The types of *BRCA2* gene germline mutations include frameshift (64%),

missense (31%), and splicing (5%). For the *BRCA1* gene, the mutation types are missense (63%), frameshift (31%), and splicing (6%) [7]. It is estimated that germline mutations of *BRCA1* and *BRCA2* could increase Pca risk by 3.8- and 8.6-fold, respectively [9, 10]. Clinically, Pcas in *BRCA*-mutated carriers are associated with early onset, higher Gleason score, more aggressive clinical course, and shorter survival time [9, 11, 12]. Pca patients with mutations in DNA damage repair genes respond favorably to PARP inhibitors such as olaparib and rucaparib [13]. In this family however, the onset of age is older than 60 years old. Gleason scores and PSA level were at moderate levels. Aggressive clinical features were not shown.

In summary, multiple brothers in this family were diagnosed with Pca, and *BRCA1* G275D appeared having high impact on the pathogenesis. Early onset and aggressive clinical manifestations did not display in this family. It appears that at least in some families, variants in multiple genes might contribute together to the predisposition to Pca, and even in cases with potentially deleterious variants in *BRCA1* or *BRCA2*, there could be diverse clinical manifestations.

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Statement of Ethics

The subjects of this case report have given their written informed consent for the study and for publication of the research findings. The study was approved by the Ethics Committee of Affiliated Wuxi No. 2 Hospital, Nanjing Medical University.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Project conception and overall organization of the research: N.H.F., F.P.L., and Q.S.S.; clinical materials and information collection: X.Y.X. and Y.W.; experimental design and performing data analysis and manuscript preparation: K.C.Z.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding authors.

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