Germline Pathogenic Variants in 7636 Japanese Patients With Prostate Cancer and 12 366 Controls

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Abstract

Background: Genetic testing has been conducted in patients with prostate cancer (PCa) using multigene panels, but no centralized guidelines for genetic testing exist. To overcome this limitation, we investigated the demographic and clinical characteristics of patients with pathogenic variants.

Methods: We sequenced eight genes associated with hereditary PCa in 7636 unselected Japanese patients with PCa and 12 366 male, cancer-free control individuals. We assigned clinical significance for all 1456 variants using the American College of Medical Genetics and Genomics guidelines and ClinVar. We compared the frequency of carriers bearing pathogenic variants between cases and control participants with calculated PCa risk in each gene and documented the demographic and clinical characteristics of patients bearing pathogenic variants. All statistical tests were two-sided.

Results: We identified 136 pathogenic variants, and 2.9% of patients and 0.8% of control individuals had a pathogenic variant. Association with PCa risk was statistically significant for variants in \( \text{BRCA2} \) (\( P < .001 \), odds ratio \( \text{OR} = 5.65 \), 95% confidence interval \( \text{CI} = 3.55 \) to \( 9.32 \)), \( \text{HOXB13} \) (\( P < .001 \), OR \( = 4.73 \), 95% CI \( = 2.84 \) to \( 8.19 \)), and \( \text{ATM} \) (\( P < .001 \), OR \( = 2.86 \), 95% CI \( = 1.63 \) to \( 5.15 \)). We detected recurrent new pathogenic variants such as p.Gly132Glu of \( \text{HOXB13} \). Patients with pathogenic variants were 2.0 years younger at diagnosis and more often had smoking and alcohol drinking histories as well as family histories of breast, pancreatic, lung, and liver cancers.

Conclusions: This largest sequencing study of PCa heredity provides additional evidence supporting the latest consensus among clinicians for developing genetic testing guidelines for PCa.

Prostate cancer (PCa) is the second most common cancer in men worldwide and has the highest incidence rate in developed countries (1). Among common cancers at 11 anatomical sites, PCa was found to be the most heritable (2), and genome-wide association studies have identified more than 150 variants associated with PCa (3). However, the identified variants were common and had low penetrance, limiting the clinical utility of genetic risk scores (4,5). Familial clustering of PCa has been reported (6), and around 5% of PCa cases could be primarily attributable to rare, highly penetrant mutations in genes such as \( \text{BRCA1} \), \( \text{BRCA2} \), and \( \text{HOXB13} \) (7).

Genetic testing using multigene panels has the potential to guide PCa screening, targeted treatment, and surveillance for patients and their relatives (8). Because variants in genes such as \( \text{BRCA1} \) and \( \text{BRCA2} \) are associated with increased risk of multiple cancer types including PCa (9), identifying pathogenic variants in patients with PCa has implications for surveillance of various cancer types in relatives. Patients with a pathogenic variant in \( \text{ATM} \), \( \text{BRCA2} \), and \( \text{CHEK2} \) are reported to have a higher risk for metastatic PCa (10). Patients with metastatic PCa who have germline or somatic mutations in DNA-repair machinery have sustained responses to poly–adenosine diphosphate

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ribose polymerase inhibitors (11) and platinum-based chemotherapy (12). The ongoing IMPACT study (NCT00261456) is evaluating the use of targeted PCa screening in men with BRCA1/2 mutations (13). However, no centralized guidelines for PCa genetic testing exist.

Guidelines for genetic testing serve as a resource to identify individuals who may benefit from cancer-risk assessment and genetic counseling, to guide decisions related to genetic testing, and to facilitate a multidisciplinary approach in managing individuals at increased risk (9). In contrast to breast, ovarian (9), and colon cancers (14), studies on PCa have been limited, and information regarding the clinical significance of genetic variants in ClinVar is much sparser than information available for other cancers. In this setting, a large-scale, case-control study could provide important information on classifications of individual germline variants, PCa disease risk for each gene, and demographic and clinical characteristics of patients bearing pathogenic variants. Although most studies have analyzed only patients with PCa (8), our previous study on breast cancer (15) showed that population-matched control individuals were indispensable because 5% or fewer variants found in Japanese patients were registered in the most closely matched population in ExAC (16). Therefore, various types of information from a large-scale, case-control study would help in developing guidelines for genetic testing in PCa.

In this study, we performed the largest case-control sequencing study on PCa heredity (to the best of our knowledge), involving 7636 unselected Japanese patients with PCa and 12366 control participants. We sequenced coding regions of eight genes (7), assigned clinical significance for all variants detected, and calculated PCa risk estimates for presumed pathogenic variants in each gene. We investigated the demographic and clinical characteristics of patients with pathogenic variants.

**Methods**

**Study Population**

We obtained all study samples from BioBank Japan (17,18), which is a multi-institutional, hospital-based registry that collects DNA and clinical information from patients with various common diseases, including PCa (19), from all over Japan between 2003 and 2018. Clinical characteristics of cases and control individuals were collected by interview or medical record survey using a standard questionnaire at the point of entry to Biobank Japan. These PCa samples are considered likely to be representative of Japanese patients because the age-specific distribution of PCa patients in BioBank Japan was similar to that described in the Japanese Ministry of Health, Labour, and Welfare Patient Survey (19). In this study, we performed a hospital registry-based study in 7744 patients with PCa and 12520 male controls. Among the 7744 patients with PCa, 7229 individuals were diagnosed before enrollment, and the remaining 515 patients were diagnosed during a follow-up period. We used the same 12520 male controls age 60 years and older with no personal or family history of cancer from our previous study on breast cancer (15). Owing to this selection criterion, the control group may exhibit a lower frequency of pathogenic variants than that observed in the general controls individuals, and as a result, disease risk may be calculated to be higher. All participants provided their written informed consent. The study was approved by the ethical committees of the Institute of Medical Sciences, the University of Tokyo, and the RIKEN Center for Integrative Medical Sciences.

**Sequencing and Bioinformatics Analysis**

We selected eight genes (ATM, BRCA1, BRCA2, BRCA1 interacting protein C-terminal helicase 1 [BRCAP1], CHEK2, HOXB13, NBN, and PALB2) whose rare germline variants were reported to show high penetrance for PCa in a review article (7) because there were no guidelines about gene selection for genetic testing. We analyzed the complete coding regions and 2-bp flanking intronic sequences of all eight genes (37982 bp) by a multiplex polymerase chain reaction–based target sequence method (20) (Supplementary Methods, available online). Finally, we identified 1456 genetic variants in 7636 patients and 12366 control individuals, and 99.98% of the target region was covered by at least 20 sequence reads.

**Annotation of Variants**

We assigned clinical significance (pathogenic, benign, or uncertain) for all variants as in our previous study (15) (Supplementary Methods, available online). Briefly, we determined clinical significance using the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) guidelines (21,22) (Supplementary Tables 1 and 2, available online) as well as pathogenicity assertions registered in ClinVar (23). We used the same procedure for all genes except HOXB13 because a gain-of-function missense variant in HOXB13 was considered pathogenic (24). We considered variants as pathogenic based on classification as pathogenic by the ACMG/AMP guidelines and/or classification as pathogenic in ClinVar. Specific details are described in Supplementary Methods (available online). Variants not registered in ClinVar on August 1, 2017, were considered novel.

**Statistical Analysis**

Case-control association analysis was performed using Fisher exact test under a dominant model. To investigate the association of pathogenic variants with demographic and clinical characteristics, we used t tests for continuous variables and Fisher exact tests or Cochran-Armitage tests for discrete variables. All statistical tests were two-sided, and P less than .05 was considered statistically significant except when Bonferroni correction was applied for the association analysis between each of the eight genes and PCa (P < .006 = .05/8). All analyses were performed using R statistical package (ver. 3.1.3).

**Results**

**Demographic and Clinical Characteristics of Participants**

The mean age at PCa diagnosis was 71.0 years (SD = 6.9) (Table 1). Positive smoking history in cases (69.4%) was statistically significantly lower than that in controls (76.1%, P < .001). This reflects the fact that this proportion was the fifth smallest among 42 male diseases registered in the BioBank Japan (17), whereas control participants consisted of patients with complex diseases other than cancer in the same biobank. Family history of prostate, breast, or pancreatic cancers was observed in 6.8%, 4.7%, and 3.3% of patients, respectively. Other clinical characteristics are shown in Table 1.

**Pathogenic Germline Variants**

Sequencing of the eight PCa-relevant genes identified 1456 germline variants in total. We categorized the variants
Demographic and clinical characteristics of study participants

| Variable                                      | PCa patients | Controls |
|-----------------------------------------------|--------------|----------|
| No. of participants                           | 7744 (100)   | 12,520 (100) |
| Mean age at entry, (SD), y                    | 72.9 (7.1)   | 70.4 (7.0) |
| Mean age at diagnosis, (SD), y*               | 71.0 (6.9)   | —        |
| Smoking history                               |              |          |
| Yes                                           | 5263 (69.4)  | 9490 (76.1) |
| No                                            | 2322 (30.6)  | 2984 (23.9) |
| Missing                                       | 159          | 46       |
| Alcohol drinking history                      |              |          |
| Yes                                           | 5307 (70.0)  | 8698 (69.9) |
| No                                            | 2270 (30.0)  | 3751 (30.1) |
| Missing                                       | 167          | 71       |
| Body mass index, (SD) kg/m²*                  | 23.4 (2.9)   | 23.4 (3.1) |
| Family history of PCa                         |              |          |
| Yes                                           | 530 (6.8)    | 0† (0)   |
| No                                            | 7214 (93.2)  | 12,520 (100.0) |
| Missing                                       | 621          | —        |
| Family history of breast cancer               |              |          |
| Yes                                           | 362 (4.7)    | 0† (0)   |
| No                                            | 7382 (95.3)  | 12,520 (100.0) |
| Missing                                       |              |          |
| Family history of pancreatic cancer           |              |          |
| Yes                                           | 255 (3.3)    | 0† (0)   |
| No                                            | 7489 (96.7)  | 12,520 (100.0) |
| Histological type                             |              |          |
| Adenocarcinoma                                | 7085 (99.5)  | —        |
| Others                                        | 38 (0.5)     | —        |
| Missing                                       | 621          | —        |
| TNM classification: T                         |              |          |
| T4                                            | 172 (4.5)    | —        |
| T3                                            | 805 (20.9)   | —        |
| T2                                            | 1794 (46.5)  | —        |
| T1                                            | 1080 (28.0)  | —        |
| T0                                            | 9 (0.2)      | —        |
| Missing                                       | 3884         | —        |
| TNM classification: N                         |              |          |
| N1                                            | 229 (6.1)    | —        |
| N0                                            | 3517 (93.9)  | —        |
| Missing                                       | 3998         | —        |
| TNM classification: M                         |              |          |
| M1                                            | 297 (8.0)    | —        |
| M0                                            | 3397 (92.0)  | —        |
| Missing                                       | 4050         | —        |
| Gleason score                                 |              |          |
| Aggressive (≥8)                               | 1713 (29.7)  | —        |
| Indolent (<8)                                 | 4064 (70.3)  | —        |
| Missing                                       | 1967         | —        |
| Maximum value of serum PSA before treatment, ng/mL |          |          |
| >20                                           | 1470 (31.0)  | —        |
| 10–20                                         | 1117 (23.5)  | —        |
| 4–10                                          | 1991 (42.0)  | —        |
| ≤4                                            | 166 (3.5)    | —        |
| Missing                                       | 3000         | —        |
| Complicated with benign prostatic hypertrophy |              |          |
| Yes                                           | 2722 (57.8)  | —        |
| No                                            | 1985 (42.2)  | —        |
| Missing                                       | 3037         | —        |

Note: For variables with missing data, the number of missing data is 311 in mean age at diagnosis; 268 in cases and 753 in controls in body mass index. PCa = prostate cancer; PSA = prostate-specific antigen. Em dashes (--) indicate no information for control participants.

Control participants with no past history or family history of cancers were selected for this study. TNM = Tumor, Node, Metastasis.

Sensitivity Analyses Regarding the Annotation of Variants

Various procedures of the ACMG/AMP guidelines (21) followed in different laboratories have resulted in different interpretations of variants (27). We performed two types of sensitivity analyses. The first sensitivity analysis compared our method to ClinVar. We performed gene-based association analysis using pathogenic variants registered in ClinVar (n = 58, Supplementary Table 3, available online) and determined by the
ACMG/AMP guidelines (n = 122, Supplementary Table 8, available online). The odds ratio of all genes was comparable (ClinVar: OR = 3.99, 95% CI = 2.68 to 6.07; ACMG/AMP: OR = 3.66, 95% CI = 2.84 to 4.74). For each gene, similar odds ratios were observed, with the exception of HOXB13–0/58 pathogenic ClinVar records vs 5/122 ACMG/AMP classifications. These data suggest that our interpretation of the ACMG/AMP guidelines would be comparable with that of ClinVar.

The second sensitivity analysis involves gene-based association analysis of rare benign variants exhibiting Minor allele frequency less than 0.01 (n = 248, Supplementary Table 9, available online) and of rare VUS (n = 1036, Supplementary Table 10, available online). The gene-based association test using benign variants actually showed no genes possessing a P less than .05. Conversely, the gene-based association test using VUS indicated that CHEK2 exhibited a P less than .001 and an OR = 1.62 (95% CI = 1.30 to 2.00). Three missense variants possessed a P less than .05, and these included p.Ala496Pro (P = .006, OR = 4.22, 95% CI = 1.41 to 15.11), p.Arg223Cys (P = .03, OR = 1.98, 95% CI = 1.01 to 3.92), and p.His414Tyr (P = .03, OR = 2.25, 95% CI = 1.04 to 4.99). Although p.Arg223Cys possessed sufficient pathogenic (PS3, PM1, and PP3) as well as benign evidence (BS1 and BP5), the others lacked sufficient evidence. Therefore, certain variants within CHEK2 may be pathogenic, and CHEK2 may contribute to the development of PCa, although additional research, including functional tests, is required to clarify this issue. It might also suggest further improvement of the ACMG/AMP guidelines.

### Demographic and Clinical Characteristics of Patients, With Pathogenic Variants

To investigate the association of pathogenic variants with demographic and clinical characteristics of PCa, we compared these between the 219 carrier patients and the 7417 noncarrier patients (Table 3). The carriers were on average 2.0 years younger at PCa diagnosis (P < .001) and more often had histories of smoking (77.0% in carriers vs 69.2% in noncarriers, P = .02) and...
### Table 2. Results of gene-based association test using pathogenic variants

| Gene     | No. of pathogenic variants | Case (n = 7636) | Control (n = 12 366) | P* | OR† (95% CI) |
|----------|----------------------------|----------------|----------------------|----|--------------|
| BRCA2    | 52                         | 83             | 0.8                  | <.001 | 5.65 (3.55 to 9.32) |
| HOXB13   | 5                          | 61             | 0.2                  | <.001 | 3.73 (2.64 to 5.31) |
| ATM      | 31                         | 37             | 0.5                  | <.001 | 2.86 (1.63 to 5.15) |
| BRCA1    | 14                         | 14             | 0.2                  | <.001 | 2.27 (0.94 to 5.71) |
| CHEK2    | 9                          | 12             | 0.2                  | .06  | 2.43 (0.91 to 6.86) |
| PALB2    | 6                          | 4              | 0.1                  | .06  | 1.62 (0.30 to 8.70) |
| BRIP1    | 12                         | 6              | 0.1                  | .58  | 1.39 (0.39 to 4.83) |
| NBN      | 7                          | 3              | 0.0                  | .00  | 1.21 (0.18 to 7.18) |
| Sum      | 136                        | 219‡           | 2.9                  | <.001 | 3.66 (2.87 to 4.69) |

*Two-sided Fisher exact test was used. BRIP1 = BRCA1 interacting protein C-terminal helicase 1; CI = confidence interval; OR = odds ratio. †Odds ratio for cases bearing pathogenic variants vs controls bearing pathogenic variants.
‡Because one patient had a pathogenic variant both in BRCA2 and HOXB13, the total number of carriers was one smaller than the sum of carriers in each gene.

### Table 3. Statistically significant differences in demographic and clinical characteristics between patients with PCa with and without pathogenic variants

| Variable                                      | No. of patients with pathogenic variants (%) | No. of patients without pathogenic variants (%) | P*   | OR (95% CI) |
|-----------------------------------------------|---------------------------------------------|-----------------------------------------------|------|-------------|
| No. of patients                               | 219 (100)                                   | 7417 (100)                                    |      |             |
| Age at diagnosis, mean (SD), y                | 69.0 (7.7)                                  | 71.0 (6.9)                                    | <.001|             |
| Smoking history                               |                                             |                                               |      |             |
| Yes                                           | 167 (77.0)                                  | 5046 (69.2)                                   | .02  | 1.48 (1.07 to 2.09) |
| No                                            | 50 (23.0)                                   | 2243 (30.8)                                   | 1.00 (Referent) |
| Alcohol drinking history                      |                                             |                                               |      |             |
| Yes                                           | 180 (82.6)                                  | 5078 (69.8)                                   | <.001| 2.05 (1.44 to 3.01) |
| No                                            | 38 (17.4)                                   | 2202 (30.2)                                   | 1.00 (Referent) |
| Family history of PCa†                         |                                             |                                               |      |             |
| Yes                                           | 18 (8.2)                                    | 505 (6.8)                                     | .41  | 1.23 (0.71 to 2.01) |
| No                                            | 201 (91.8)                                  | 6912 (93.2)                                   | 1.00 (Referent) |
| Family history of breast cancer               |                                             |                                               |      |             |
| Yes                                           | 26 (11.9)                                   | 333 (4.5)                                     | <.001| 2.87 (1.80 to 4.40) |
| No                                            | 193 (88.1)                                  | 7084 (95.5)                                   | 1.00 (Referent) |
| Family history of pancreatic cancer           |                                             |                                               |      |             |
| Yes                                           | 19 (8.7)                                    | 234 (3.2)                                     | <.001| 2.92 (1.69 to 4.78) |
| No                                            | 200 (91.3)                                  | 7183 (96.8)                                   | 1.00 (Referent) |
| Family history of lung cancer                 |                                             |                                               |      |             |
| Yes                                           | 27 (12.3)                                   | 553 (7.5)                                     | .01  | 1.73 (1.10 to 2.64) |
| No                                            | 192 (87.7)                                  | 6864 (92.5)                                   | 1.00 (Referent) |
| Family history of liver cancer                |                                             |                                               |      |             |
| Yes                                           | 17 (7.8)                                    | 340 (4.6)                                     | .03  | 1.75 (0.99 to 2.92) |
| No                                            | 202 (92.2)                                  | 7077 (95.4)                                   | 1.00 (Referent) |
| TNM classification: T                         |                                             |                                               |      |             |
| T3/T4                                         | 37 (33.6)                                   | 902 (24.6)                                    | .03  | 1.56 (1.01 to 2.36) |
| T0-2                                          | 73 (66.4)                                   | 2769 (75.4)                                   | 1.00 (Referent) |
| TNM classification: M                         |                                             |                                               |      |             |
| M1                                            | 14 (13.2)                                   | 270 (7.7)                                     | .04  | 1.83 (0.95 to 3.28) |
| M0                                            | 92 (86.8)                                   | 3244 (92.3)                                   | 1.00 (Referent) |
| Gleason score                                 |                                             |                                               |      |             |
| Aggressive (≥8)                               | 66 (41.0)                                   | 1610 (29.1)                                   | .002 | 1.70 (1.21 to 2.36) |
| Indolent (<8)                                 | 95 (59.0)                                   | 3930 (70.9)                                   | 1.00 (Referent) |
| Maximum value of serum PSA before treatment, ng/mL |                                             |                                               |      |             |
| >10                                           | 87 (64.0)                                   | 2461 (54.1)                                   | .02  | 1.51 (1.04 to 2.19) |
| ≤10                                           | 49 (36.0)                                   | 2087 (45.9)                                   | 1.00 (Referent) |

*Two-sided Fisher exact test was used for all analyses except for age at diagnosis. Two-sided t test was used for age at diagnosis. CI = confidence interval; OR = odds ratio; PCa = prostate cancer; PSA = prostate-specific antigen; TNM = Tumor, Node, Metastasis.
†Family history of PCa was not associated with carrier status but is shown because its association was expected.
alcohol drinking (82.6% vs 69.8%, P < .001). Carriers also more often had a family history of breast (11.9% vs 4.5%, P < .001), pancreatic (8.7% vs 3.2%, P < .001), lung (12.3% vs 7.5%, P = .01), or liver (7.8% vs 4.6%, P = .03) cancers. There was no difference between carriers (8.2%) and noncarriers (6.8%) in family history of PCa (P = .41). The carriers also showed worse clinical characteristics in terms of Tumor, Node, Metastasis (TNM) classifications (P = .03 and P = .04 for T and M, respectively), Gleason score of at least 8 (41.0% vs 29.1%, P = .002), and prostate-specific antigen (PSA) greater than 10 (64.0% vs 54.1%, P < .001). Carriers also more often had a family history of breast cancer (15.7% vs 4.5% in noncarriers, P < .001) and in HOXB13 (16.4%, P < .001). Family history of pancreatic cancer was associated with variants in BRCA2 (16.9% in BRCA2 variant carriers vs 3.2% in noncarriers, P < .001). Patients bearing pathogenic variants of BRCA2 alone showed worse clinical characteristics as shown by TNM classifications (T: P = .001, M: P = .008), Gleason score of at least 8 (51.7% in BRCA2 carriers vs 29.1% in noncarriers, P < .001), and PSA greater than 10 (70.2% vs 54.1%, P = .03).

## Discussion

We identified 136 pathogenic variants in eight genes in 7636 patients with PCa and 12366 control individuals. Finally, 33.8% of the pathogenic variants were newly identified in this study. Pathogenic variants were found in 2.9% of unselected Japanese PCa patients; HOXB13, BRCA2, and ATM were the statistically significant causative genes. Patients with pathogenic variants showed specific demographic and clinical characteristics.

The Philadelphia Prostate Cancer Consensus 2017 (the Consensus) was recently published to establish a genetic evaluation framework for inherited PCa (8). We investigated if our study results could add more evidence to the Consensus. Regarding gene selection, the Consensus considered that both BRCA1 and BRCA2 had high-grade evidence for being related to PCa. However, our results revealed that only BRCA2 showed a statistically significant contribution to PCa, and patients carrying a pathogenic variant in this gene showed worse clinical characteristics. BRCA1 pathogenic variants, altogether or considering only the most frequent pathogenic variant observed in patients with breast cancer (15), p.Leu639*, showed no statistically significant association with PCa risk. PCa disease risks were calculated as 5.65 for BRCA2 and 2.27 for BRCA1. This is consistent with results of previous studies (28) (BRCA2: 4.7–8.6 and BRCA1: 1.1–3.8). Therefore, our results suggest that BRCA1 and BRCA2 should be separately considered in genetic testing among Japanese patients with PCa.

We validated the importance of HOXB13, although its main pathogenic variant in our population, p.Gly132Glu, was different from those in European (p.Gly84Glu) (24) and Chinese (p.Gly135Glu) populations (29). According to the Genome Aggregation Database (16), p.Gly84Glu was also observed in African, Ashkenazi Jewish, and Latino populations, but p.Gly132Glu and p.Gly135Glu were found only in East Asian populations. However, p.Gly132Glu and p.Gly135Glu may be subpopulation specific, given that p.Gly132Glu was not observed in 96 Chinese patients (29) and p.Gly135Glu was not found in our Japanese cohort, suggesting that the existence of frequent pathogenic variants in each subpopulation would strongly affect the importance of HOXB13 in genetic testing for PCa.

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