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# Current Status and Challenges of *BRCA1* and *BRCA2* Genetic Testing for Hereditary Breast and Ovarian Cancer in Japan

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## Abstract

*Background/Aim*: In patients with breast cancer, breast cancer gene 1 and 2 (*BRCA1/2*) genetic testing is used to diagnose hereditary breast and ovarian cancer (HBOC) and guide appropriate risk management for patients and their relatives. In Japan, this testing has been covered by the national health insurance system since 2020 for patients with breast cancer who meet specific eligibility criteria. However, insufficient implementation of genetic testing may lead to missed opportunities for appropriate risk-reducing strategies and early clinical intervention in patients with pathogenic variants. Therefore, we retrospectively evaluated the implementation status of *BRCA1/2* testing and the prevalence of pathogenic variants at our institution.

*Patients and Methods*: We analyzed 354 patients with breast cancer who underwent insurance-covered *BRCA1/2* genetic testing between July 2018 and September 2024. Patients were classified into three groups: a newly diagnosed group (diagnosed after the introduction of insurance coverage for HBOC testing in April 2020), a postoperative follow-up group (diagnosed before April 2020 and tested during follow-up), and a companion diagnostic group for metastatic breast cancer. Clinicopathological characteristics, fulfilled eligibility criteria, and positivity rates were compared.

*Results*: Of the 354 patients, 238 (67.3%) were newly diagnosed, 60 (16.9%) were in postoperative follow-up, and 56 (15.8%) underwent companion diagnostic testing. Overall, 43 patients (12.1%) harbored pathogenic *BRCA1/2* variants (*BRCA1*, n=21; *BRCA2*, n=22). Variant positivity rates were 10.1% in the newly diagnosed group, 20.0% in the postoperative follow-up group, and 12.5% in the companion diagnostic group.

*Conclusion*: The higher prevalence of pathogenic *BRCA1/2* variants in the postoperative follow-up group suggests that genetic testing for hereditary breast and ovarian cancer (HBOC) may be underutilized among eligible breast cancer patients during follow-up. Proactive testing recommendations by healthcare providers and improved patient understanding are essential.

**Keywords:** *BRCA1/2* pathogenic variants, hereditary breast and ovarian cancer (HBOC), germline genetic testing, breast cancer, testing implementation.

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## Introduction

Approximately 5-10% of breast cancers are considered hereditary (1-3). Hereditary breast and ovarian cancer (HBOC) syndrome is caused by pathogenic variants in the breast cancer genes 1 and 2 (*BRCA1/2*) and is characterized by an increased susceptibility to breast and ovarian cancers, accounting for approximately half of hereditary breast cancers (3, 4). In individuals carrying pathogenic variants in *BRCA1* and *BRCA2*, the cumulative lifetime risk of developing breast cancer by the age of 80 is estimated to be 72% and 69%, respectively, while the corresponding cumulative risk of ovarian cancer is 44% and 17% (5).

In Japan, *BRCA1/2* genetic testing was approved for insurance coverage in July 2018 as a companion diagnostic to determine eligibility for PARP inhibitor therapy in patients with metastatic breast cancer, and subsequently in April 2020 for the purpose of diagnosing HBOC in breast cancer patients who meet specific criteria. If the uptake of *BRCA1/2* genetic testing is low, opportunities for appropriate surveillance and risk-reducing surgery in patients with pathogenic variants may be compromised. Furthermore, identification of a pathogenic *BRCA* variant enables genetic testing of blood relatives, facilitating preventive interventions and early diagnosis before disease onset. Therefore, improving the implementation rate of *BRCA1/2* genetic testing is essential to ensure the appropriate delivery of these medical services. However, documentation of family history and related information in medical records often relies on patient self-reporting, and key information required to identify candidates for *BRCA1/2* testing is frequently incomplete. As a result, eligible patients may not be appropriately identified. In this context, we conducted a retrospective study to assess the current implementation of *BRCA1/2* genetic testing at our institution and to identify the associated challenges.

## Patients and Methods

*Patients.* A total of 354 patients with breast cancer who underwent *BRCA1/2* genetic testing at our Genetic Medicine Center between July 2018 and September 2024 were included in this study. The indications for testing and patient categorization are presented in Figure 1.

In Japan, insurance reimbursement for *BRCA1/2* genetic testing with the purpose of diagnosing HBOC was approved in April 2020. Therefore, before this period, only companion diagnostics were included, whereas both companion diagnostics and HBOC diagnosis were included thereafter. Among patients tested for HBOC diagnosis, those who visited our institution for breast cancer after April 2020 were defined as the initial diagnosis group, and those who had been diagnosed with breast cancer before this period and underwent testing during postoperative follow-up were defined as the postoperative follow-up group. Patients tested solely for companion diagnostics were classified as the companion diagnostic testing group. Clinical and pathological characteristics as well as the prevalence of pathogenic variants were retrospectively compared among these groups.

This study was approved by the Ethics Committee of Tokyo Medical University Hospital (approval number: T2024-0060) and the need for written informed consent was waived due to the retrospective nature of the study. Patients could see the research plan on the website of the hospitals and were offered the choice to opt out of the study at any time.

*Statistical analysis.* Statistical analyses were performed using JMP 14.2 statistical software (SAS Institute Inc., Cary, NC, USA). The chi-square test was used to assess the independence between variables. A $p$-value of $<0.05$ was considered statistically significant.

## Results

*Indications for BRCA genetic testing and prevalence of pathogenic variants.* Among the 354 eligible patients, 238 (67.3%) were included in the initial diagnosis group, 60 (16.9%) in the postoperative follow-up group, and 56 (15.8%) in the companion diagnostic testing group. Approximately 85% of all cases underwent testing for

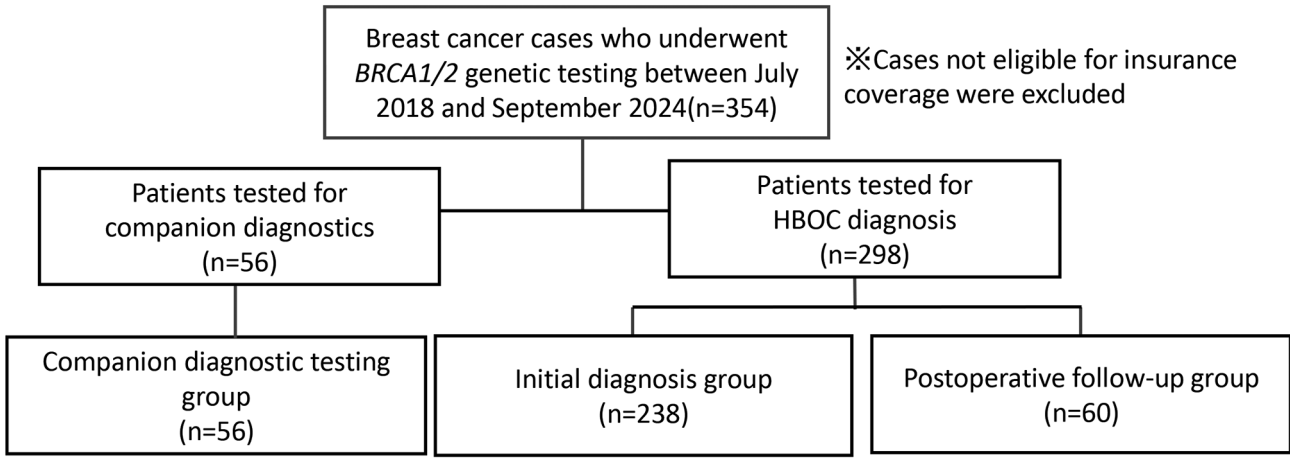


Figure 1. *Study design and patient classification for BRCA1/2 genetic testing. Patients were categorized into three groups according to the indication for testing and the timing of breast cancer diagnosis: the initial diagnosis, postoperative follow-up, and companion diagnostic testing groups. BRCA1/2: breast cancer gene 1 and 2.*

the purpose of HBOC diagnosis, with the initial diagnosis group accounting for the largest proportion. In total, pathogenic *BRCA1/2* variants were detected in 43 patients (*BRCA1*: 21 cases, *BRCA2:* 22 cases), yielding an overall positivity rate of 12.1%. When stratified by patient group, the positivity rates were 10.1% in the initial diagnosis group, 20% in the postoperative follow-up group, and 12.5% in the companion diagnostic testing group, with the postoperative follow-up group showing the highest proportion (Figure 2).

*Clinicopathological characteristics of patients tested for HBOC diagnosis.* The clinicopathological characteristics of the 238 patients in the initial diagnosis group and 60 patients in the postoperative follow-up group who underwent *BRCA* testing for the diagnosis of HBOC are summarized in Table I. The median age at breast cancer onset was 45 years in the initial diagnosis group and 42 years in the postoperative follow-up group, with the latter being significantly younger ($p<0.05$). Among the 298 patients, 70 had two or more primary breast cancers. In such cases, clinical stage and subtype were determined based on the more advanced lesion. Clinical stage I was observed in 35.3% of patients in the initial diagnosis group and 51.7% in the postoperative follow-up group, showing a tendency to be more frequent in the postoperative follow-up group. No significant differences were observed between the two groups regarding breast cancer subtype.

*Comparison of eligibility criteria for HBOC testing.* A comparison of the eligibility criteria for *BRCA1/2* testing between the initial diagnosis group and the postoperative follow-up group is presented in Table II. Early onset breast cancer (≤45 years) was significantly more frequent in the postoperative follow-up group (57.6% *vs*. 76.7%, $p<0.01$). In contrast, no significant differences were observed between the two groups regarding the proportion of patients aged ≤60 years, history of multiple primary breast cancers, family history of breast or ovarian cancer, male breast cancer, or a history of ovarian cancer–related tumors. Furthermore, when comparing the number of eligibility criteria met, the majority of patients in the initial diagnosis group met only one criterion, whereas those in the postoperative follow-up group frequently met three or more. Overall, the postoperative follow-up group had a significantly higher number of fulfilled criteria ($p<0.01$).

*Association between the number of eligibility criteria met and the presence of pathogenic BRCA1/2 variants.* We

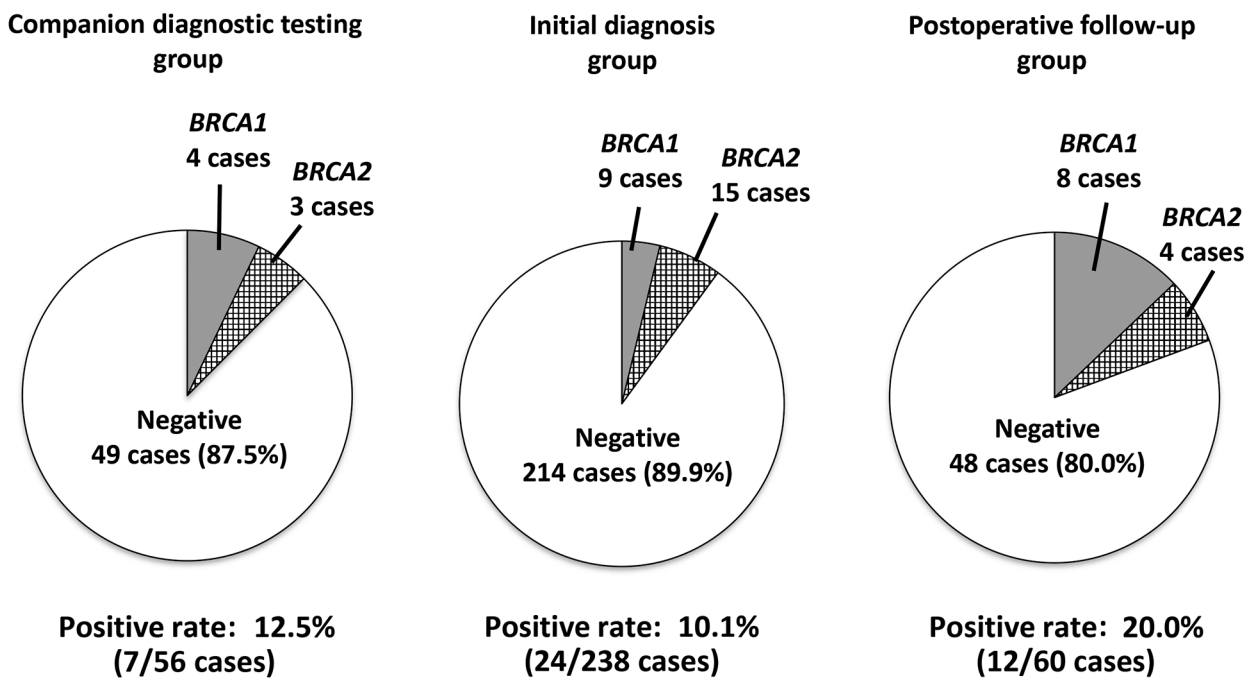


Figure 2. *Prevalence of pathogenic BRCA1/2 variants by indication for genetic testing. The positivity rates of BRCA1/2 pathogenic variants are shown for the initial diagnosis, postoperative follow-up, and companion diagnostic testing groups. BRCA1/2: breast cancer gene 1 and 2.*

Table I. *Patient characteristics of cases tested for hereditary breast and ovarian cancer diagnosis.*

| Factors | | Initial diagnosis group (n=238) | Postoperative follow-up group (n=60) | *p*-Value |
|---|---|---|---|---|
| Age at breast cancer diagnosis (median, years) | | 45 | 42 | 0.01 |
| cStage, n (%) | 0 | 41 (17.2%) | 8 (13.3%) | 0.07 |
| | I | 84 (35.3%) | 31(51.7%) | |
| | II | 92 (38.7%) | 15 (25.0%) | |
| | III | 19 (8.0%) | 5 (8.3%) | |
| | IV | 2 (0.8%) | 0 | |
| | NA | 0 | 1 (1.7%) | |
| Subtype, n(%) | HR+/HER2– | 163 (68.5%) | 41 (68.3%) | 0.44 |
| | HR+/HER2+ | 12 (5.0%) | 6 (10.0%) | |
| | HR–/HER2+ | 7 (2.9%) | 2 (3.3%) | |
| | HR–/HER2– | 56 (23.5%) | 11 (18.3%) | |

NA: Not available; HR: hormone receptor; HER2: human epidermal growth factor receptor 2.

next examined the relationship between the number of eligibility criteria met and the presence of pathogenic *BRCA1/2* variants. The prevalence of pathogenic variants was 5% in patients who met one criterion, 14.3% in those who met two criteria, and 39.4% in those who met three or more (Table III). Thus, a clear trend was observed in which the positivity rate increased with the number of fulfilled criteria. When comparing the number of criteria between patients with and without pathogenic variants, the median number was higher in variant-positive patients (2.0) than in variant-negative patients (1.0) ($p$<0.01), indicating that variant-positive

Table II. *Comparison of testing eligibility criteria for hereditary breast and ovarian cancer diagnosis.*

| Factors | | Initial diagnosis group (n=238), n (%) | Postoperative follow-up group (n=60), n (%) | *p*-Value |
|---|---|---|---|---|
| Age ≤45 years old at breast cancer diagnosis | Yes | 137 (57.2%) | 46 (74.2%) | <0.01 |
| | No | 101 (42.8%) | 14 (25.8%) | |
| TNBC ≤60 years old at diagnosis | Yes | 46 (19.3%) | 12 (20.0%) | 0.85 |
| | No | 192 (80.7%) | 48 (80.0%) | |
| Two or more primary breast cancers | Yes | 51 (21.4%) | 19 (31.7%) | 0.12 |
| | No | 187 (78.6%) | 41 (68.3%) | |
| Family history of breast, ovarian, pancreatic, and prostate cancer | Yes | 117 (49.2%) | 33 (55.0%) | 0.47 |
| | No | 121 (50.8%) | 27 (45.0%) | |
| Male breast cancer | Yes | 1 (0.4%) | 0 | 1.00 |
| | No | 237 (99.6%) | 60 (100%) | |
| Personal history of ovarian, peritoneal, or pancreatic cancer | Yes | 7 (2.9 %) | 1 (1.7%) | 1.00 |
| | No | 231 (97.1%) | 59 (98.3%) | |
| Number of eligibility criteria met | 1 criterion | 136 (57.1%) | 24 (40.0%) | <0.01 |
| | 2 criteria | 84 (35.3%) | 21 (35.0%) | |
| | ≥3 criteria | 18 (7.6%) | 15 (25.0%) | |

TNBC: Triple negative breast cancer.

cases tended to fulfil a greater number of criteria. Among the *BRCA1/2* pathogenic variant–positive cases, 8, 15, and 13 patients met one, two, and three or more eligibility criteria, respectively. The specific criteria fulfilled by these patients are presented in Table IV. When only one eligibility criterion was met, most *BRCA1/2* pathogenic variant–positive cases had a family history.

Table III. *Comparison of breast cancer gene 1 and 2 (BRCA1/2) pathogenic variant status and the number of eligibility criteria in cases tested for hereditary breast and ovarian cancer diagnosis.*

| Number of eligibility criteria met | Positive rate of pathogenic BRCA1/2 variants |
|---|---|
| 1 | 8/160 (5.0%) |
| 2 | 15/105 (14.3%) |
| 3 of more | 13/33 (39.4%) |

*Contralateral risk-reducing mastectomy (CRRM) and salpingo-oophorectomy (RRSO) in patients with pathogenic BRCA1/2 variants.* Finally, among the 36 patients who underwent *BRCA1/2* genetic testing for the diagnosis of HBOC and were found to carry pathogenic variants, we investigated the implementation of CRRM and RRSO. The median observation period, calculated from the date of genetic testing until the 30$^{th}$ of August 2025, was 32.5 months. Because CRRM became available at our institution only in August 2025, none of the patients included in the present study underwent CRRM at our institution. During the study period, three patients underwent CRRM at other institutions, and no incidental breast cancer was detected in the resected contralateral breast tissue. The remaining patients have been followed with annual imaging surveillance including contrast-enhanced breast magnetic resonance imaging (MRI). Among the 36 patients, 16 (44%) underwent RRSO. Excluding two patients whose clinical course was unknown due to transfer to other institutions, the remaining patients have been followed by gynecology departments.

## Discussion

In the present study, the prevalence of pathogenic variants among the 298 patients who underwent *BRCA1/2* genetic testing for the diagnosis of HBOC was 12.1%, which was comparable to previously reported rates (6-9). However, when patients tested for HBOC were stratified into the initial diagnosis group and the postoperative follow-up

Table IV. *Comparison of eligibility criteria in cases positive for pathogenic BRCA1/2 variants.*

| Factors | | 1 criterion (n=8) | 2 criteria (n=15) | ≥3 criteria (n=13) |
|---|---|---|---|---|
| Age ≤45 years old at breast cancer diagnosis | Yes | 2 (25%) | 13 (86.7%) | 10 (76.9%) |
| | No | 6 (75%) | 2 (13.3%) | 3 (23.1%) |
| TNBC ≤60 years old at diagnosis | Yes | 0 | 4 (26.7%) | 11 (84.6%) |
| | No | 8 (100%) | 11 (73.3%) | 2 (15.4%) |
| Two or more primary breast cancers | Yes | 0 | 4 (26.7%) | 6 (46.2%) |
| | No | 8 (100%) | 11 (73.3%) | 7 (53.8%) |
| Family history of breast, ovarian, pancreatic, and prostate cancer | Yes | 5 (62.5%) | 9 (60%) | 12 (92.3%) |
| | No | 3 (37.5%) | 6 (40%) | 1 (7.7%) |
| Male breast cancer | Yes | 0 | 0 | 0 |
| | No | 8 (100%) | 15 (100%) | 13 (100%) |
| Personal history of ovarian, peritoneal, or pancreatic cancer | Yes | 1 (12.5%) | 0 | 0 |
| | No | 7 (87.5%) | 15 (100%) | 13 (100%) |

TNBC: Triple negative breast cancer; BRCA1/2: breast cancer gene 1 and 2.

group, the prevalence of pathogenic variants tended to be higher in the postoperative follow-up group (20%). The postoperative follow-up group consisted of patients who had been diagnosed with breast cancer before *BRCA1/2* genetic testing became covered by public health insurance in Japan; therefore, this difference in clinical background may have contributed to the observed disparity in positivity rates. The higher prevalence of pathogenic variants in the follow-up group may suggest that some patients who met the eligibility criteria for testing might not have undergone *BRCA1/2* genetic testing during the postoperative follow-up period. Potential reasons for insufficient testing among eligible patients include inadequate assessment of personal and family history by healthcare providers, which may limit appropriate test recommendations. In addition, patients with a stable postoperative course may not fully understand the clinical significance and benefits of genetic testing.

In this study, the proportion of patients who developed breast cancer at or below the age of 45 years was higher in the postoperative follow-up group. While age can be readily ascertained from medical records, family history and past medical history are often incompletely documented. This may have led to a tendency for genetic testing to be offered primarily based on the clear criterion of early-onset disease. As a result, patients aged over 45 years who nevertheless met other eligibility criteria may not have been sufficiently offered opportunities to undergo genetic testing. Indeed, in the postoperative follow-up group, patients who met multiple eligibility criteria and were therefore considered to be at clearly higher risk were more likely to undergo testing compared with those in the initial diagnosis group. This pattern is consistent with previous reports showing that the prevalence of *BRCA1/2* pathogenic variants increases with the number of eligibility criteria fulfilled (8). However, a non-negligible prevalence of pathogenic variants has also been reported even among patients who meet only a single eligibility criterion (6, 7), suggesting that genetic testing should be considered whenever anyone criterion is fulfilled. Taken together, these findings suggest that periodic reassessment of eligibility criteria, including family and personal medical history, during the postoperative follow-up period, as well as the standardization of eligibility assessment using tools such as checklists, may facilitate the appropriate delivery of genetic testing.

In Japan, the implementation rate of *BRCA1/2* genetic testing among patients with breast cancer who meet the insurance coverage criteria has been reported to be 55.4% (10), whereas the corresponding rate among patients meeting NCCN guideline criteria in the United States is 72.1% (11). Although this difference may partly reflect variations in healthcare systems, simple

international comparisons should be interpreted with caution, as patients deemed to be at higher clinical risk may be selectively tested in settings with limited testing opportunities.

International clinical guidelines for *BRCA1/2* testing were systematized by Pujol *et al.* (12). However, subsequent real-world studies have demonstrated substantial variation in the uptake of genetic testing across countries and regions (13-15), indicating that guideline dissemination alone is insufficient to ensure adequate testing. The NCCN guidelines recommend multi-gene panel testing for patients with relevant personal or family histories (16), yet not all eligible patients undergo testing in routine practice, resulting in missed carriers of pathogenic variants (17). To address these challenges, De Jong *et al.* reported in a nationwide Dutch study that institutions implementing mainstream genetic testing (MGT) achieved significantly higher testing uptake than conventional pathways [78% *vs*. 63%; odds ratio (OR)= 2.48, 95% confidence interval (CI)=2.14-2.87] (18). MGT refers to a model in which treating physicians directly order genetic testing within routine clinical care, without referral to specialized genetics clinics.

In Japan, although clinical guidelines for HBOC have been developed and awareness-raising activities are ongoing, decisions regarding testing eligibility and recommendations still largely depend on the discretion of treating physicians, and test ordering most commonly requires referral to specialized genetics clinics, which may create psychological and time-related barriers to undergoing testing. Therefore, to improve the uptake of *BRCA1/2* genetic testing, it is important to implement stepwise, feasible measures within the current healthcare system, including education, periodic reassessment of testing eligibility during postoperative follow-up, and standardization of eligibility assessment. Given Japan's healthcare and genetic counseling infrastructure, immediate implementation of MGT may be constrained by human resources and institutional factors, and thus requires careful consideration.

*Limitations*. First, it was a single-center, retrospective study, and therefore the findings may have been influenced by institution-specific characteristics, including the study population and clinical practice patterns. In addition, decisions regarding the implementation of examinations were left to the discretion of the attending physicians. As a result, differences in risk assessment and perceptions of test indications among physicians may have led to preferential testing of high-risk patients who met multiple eligibility criteria, particularly in the postoperative follow-up group. Consequently, the possibility of selection bias cannot be excluded.

## Conclusion

In this study, the prevalence of pathogenic *BRCA1/2* variants tended to be higher in the follow-up group, suggesting that *BRCA1/2* genetic testing may not be sufficiently implemented among eligible patients in the postoperative follow-up setting. These results highlight the importance of more proactive test recommendations by healthcare providers, as well as the need for adequate patient education to improve the uptake of genetic testing.

## Conflicts of Interest

The Authors have no potential conflicts of interest to disclose in relation to this study.

## Authors' Contributions

Kayono Onishi and Yoshiya Horimoto designed the study. Yoichi Koyama, Kyoko Orimoto, Natsuki Uenaka, Hiroki Kusama, and Takahiko Kawate collected clinical data. Natsuko Inagaki and Kazuyo Kiribayashi contributed genetic expertise to this study. Kayono Onishi and Yoshiya Horimoto performed data analysis and statistical analysis. Kayono Onishi and Yoshiya Horimoto drafted the original manuscript, and Kimito Yamada, Hiroshi Kaise, and Takashi Ishikawa substantively revised it. All Authors have read and approved the manuscript.

## Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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