

## High Frequency of *BRCA2* c.5576\_5579del Carriers in Kakogawa, Japan

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**Abstract.** *Background/Aim:* Certain germline pathogenic variants (PVs), known as founder mutations, have been frequently observed in specific regions and ethnic groups. In Japan, several pathogenic variants of *BRCA1/2* have been identified as founder mutations, with their distribution varying across different regions. This retrospective study aimed to further investigate the detailed distribution and correlation between genotype and clinical features among breast cancer patients. *Patients and Methods:* This study was conducted at Kobe University Hospital and three collaborating institutions. It included breast cancer patients who underwent *BRCA1/2* genetic testing between July 1, 2018, and March 31, 2021, and were found to have germline PVs. Clinical characteristics and breast cancer subtypes were compared between carriers of *BRCA2* c.5576\_5579del and those with other PVs. Additionally, the detection rate of *BRCA2* c.5576\_5579del was compared

with that observed in a previous report. *Results:* A total of 38 breast cancer patients were included; PVs in *BRCA1* and *BRCA2* were detected in 12 and 26 patients, respectively, 12 of whom were *BRCA2* c.5576\_5579del carriers. *BRCA2* c.5576\_5579del carriers were more likely to develop triple negative breast cancers among all *BRCA2* PV carriers. *BRCA2* c.5576\_5579del accounted for 30.8% of the PVs detected, with a particularly high frequency of 72.7% at Kakogawa Central City Hospital. *Conclusion:* *BRCA2* c.5576\_5579del was detected with a particularly high frequency in Hyogo Prefecture, especially in Kakogawa city. In the future, a survey of the distribution of the *BRCA2* c.5576\_5579del carriers may provide more clarity regarding their localization.

It has been reported that approximately 300,000 women in the United States were diagnosed with breast cancer in 2023, making it the most common of all cancers (1). Breast cancer prevalence is not limited to the United States; it is also widespread in Asia, where the number of breast cancer patients is increasing (1, 2). Of these, hereditary breast and ovarian cancer (HBOC) patients with pathogenic variants (PVs), mainly in the *BRCA1* and *BRCA2*, are especially known to have an elevated cumulative lifetime risk of breast and ovarian cancer, with a higher incidence at younger ages (3-5). Phenotypic characteristics of breast cancer in *BRCA1* PV carriers have been reported to be different from those in *BRCA2* PV carriers (6): *BRCA1* PV carriers are more likely to develop estrogen receptor (ER) negative, progesterone receptor (PgR) negative, and human epidermal growth factor receptor 2 (HER2) negative breast cancer (triple negative breast cancer), whereas *BRCA2* PV carriers are more likely to develop ER positive, HER2 negative breast cancer

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*Key Words:* Breast cancer, hereditary breast and ovarian cancer, Japan, *BRCA2* c.5576\_5579del, founder mutation.

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Table I. Clinical characteristics of patients who underwent *BRCA1/2* genetic testing.

Metastatic or inoperable breast cancer	14
Early breast cancer	24
Family history of breast cancer	18
Breast cancer at less than 45 years old	13
Family history of ovarian cancer, fallopian tube cancer, or peritoneal cancer	6
History of multiple incidences of breast cancer	5
History of triple negative breast cancer	5
History of ovarian cancer, fallopian tube cancer, or peritoneal cancer	1
Male breast cancer	1

(luminal type breast cancer). To date, various *BRCA1/2* germline variants have been reported and information on the variants has been accumulated in public disease databases. Some variants have been observed with high frequency in certain regions and races and are called founder mutations (7). Founder mutations in *BRCA1/2* have been reported in Ashkenazi Jewish (8-11) and Europeans (12-14), whereas there are still few reports in Asian countries (15, 16).

In Japan, owing to the development of the HBOC Consortium (4, 17), several PVs have been reported to exhibit founder effects, including *BRCA1* c.188T>A (p.Leu63\*) (4, 5, 17, 18), *BRCA2* c.5576\_5579del (p.Ile1859fs), *BRCA2* c.6952C>T (p.Arg2318\*) (4, 5, 18). Among them, *BRCA2* c.5576\_5579del has a higher carrier frequency in the Kinki region including Hyogo Prefecture than in other regions (5). Therefore, we conducted a retrospective observational study to investigate its distribution in Hyogo Prefecture.

## Patients and Methods

This study was conducted at Kobe University Hospital and three collaborating institutions: Kakogawa Central City Hospital, Hyogo Prefectural Harima-Himeji General Medical Center, and Hyogo Prefectural Nishinomiya Hospital. Breast cancer patients with germline PVs detected by *BRCA1/2* genetic testing between July 1, 2018, and March 31, 2021 were included. *BRCA1/2* genetic testing was performed for companion diagnostic purpose to determine Olaparib, a poly (adenosine diphosphate ribose) polymerase inhibitor, dosing for patients with unresectable or metastatic breast cancer or for diagnosis of HBOC in patients with early breast cancer. Patients with early breast cancer had to meet at least one of the following criteria for public health care in Japan; (i) breast cancer diagnosed before age 45, (ii) triple negative breast cancer diagnosed before age 60, (iii) two or more primary breast cancers, (iv) family history of breast or ovarian cancer in the third degree, (v) male breast cancer, (vi) history of the ovarian, fallopian tube, or peritoneal cancer. Before *BRCA1/2* genetic testing, patients received an explanation about the genetic testing and its implications at each institute, then a 7 ml blood sample was collected from those who requested testing. Blood samples were anonymized and sent to Myriad Genetics (Salt Lake City, UT, USA) via SRL (Fukuoka, Japan). The results of the genetic testing were returned to each institute and disclosed to the patients. In this study, variants reported

as ‘Positive for a deleterious mutation’ or ‘Positive for a suspected deleterious mutation’ were defined as PVs.

The information collected from medical records included: age at breast cancer onset, sex, history of other cancers, breast cancer subtype (status of ER, PgR, and HER2), details of detected PVs, and family history of breast, ovarian, peritoneal, and fallopian tube cancer. The clinical characteristics such as breast cancer subtypes were evaluated between carriers of *BRCA2* c.5576\_5579del and those of other *BRCA1/2* PVs. We did not perform a rigorous statistical analysis because of the very small sample size. The detection rate of *BRCA2* c.5576\_5579del in the *BRCA1/2* genetic testing at each institution was compared with that in the previous report (4).

All patients were aged 20 years or older. All eligible patients were informed about the testing results and subsequently informed about associated cancer risks and recommended medical management options, including risk-reducing surgery.

This study was approved by the ethics committee of Kobe University and all collaborating institutions. Informed consent was obtained in the form of opt-out.

## Results

A total of 38 breast cancer patients were included in this study. Their clinical characteristics are shown in Table I. Among them, 14 patients underwent *BRCA1/2* genetic testing for companion diagnostic purposes for Olaparib and 24 patients underwent testing for the diagnosis of HBOC. All 24 patients met the criteria for *BRCA1/2* genetic testing in public health care: 13 were diagnosed with breast cancer under the age of 45 years, 5 were diagnosed with triple negative breast cancer under the age of 60, five were diagnosed with multiple primary breast cancer, one had a personal history of ovarian cancer, and one was a male breast cancer patient. Regarding family history, 18 and 6 of the 24 patients had a family history of breast and ovarian cancer among third-degree relatives, respectively.

PVs in *BRCA1* and *BRCA2* were detected in 12 and 26 of the 38 patients, respectively. The most frequently detected PVs in *BRCA1* was *BRCA1* c.4357+2T>G, which was detected in two patients. *BRCA1* c.188T>A, which is common in Japanese, was not observed in this study. The

Table II. Clinicopathological characteristics of the patients with pathogenic variants (PVs) in *BRCA1* and those with pathogenic variants in *BRCA2*.

	<i>BRCA 1</i> (12 patients)	<i>BRCA 2</i> (26 patients)	
		All <i>BRCA 2</i> (26 patients)	<i>BRCA2</i> c.5576_5579del (12 patients)
Age, mean (range)	41.7 (33-51)	49.0 (28-73)	50.2 (28-73)
Sex, n (%)			
Female	12 (100)	25 (96.2)	11 (91.7)
Male	0 (0)	1 (3.8)	1 (8.3)
History of cancer, n (%)			
Ovarian cancer, fallopian tube cancer, or peritoneal cancer	0 (0)	1 (3.8)	1 (8.3)
Other cancer	0 (0)	2 (7.7)	1 (8.3)
Family history, n (%)			
Breast cancer	9 (75)	14 (53.8)	9 (75)
Ovarian cancer, fallopian tube cancer, or peritoneal cancer	4 (33.3)	3 (11.5)	1 (8.3)
Pancreatic cancer	0 (0)	4 (15.4)	3 (25)
Prostate cancer	0 (0)	1 (3.8)	1 (8.3)
	<i>BRCA 1</i> (15 breasts)	<i>BRCA 2</i> (32 breasts)	
		All <i>BRCA 2</i> (32 breasts)	<i>BRCA2</i> c.5576_5579del (14 breasts)
Subtypes, n (%)			
Luminal type	5 (33.3)	23 (71.8)	8 (57.1)
Luminal-HER2	0 (0)	4 (12.5)	2 (14.3)
HER2	2 (13.3)	1 (3.1)	0 (0)
Triple negative	8 (53.3)	3 (9.4)	3 (21.4)
Unknown	0 (0)	1 (3.1)	1 (7.1)

most frequently detected PV in *BRCA2* was *BRCA2* c.5576\_5579del, in 12 patients. The second most common PV in *BRCA2* were *BRCA2* c.6952C>T (p.Arg2318\*) and *BRCA2* c.9382C>T (p.Arg3128\*), with 2 each. To investigate the impact of PVs in each gene on the clinical features of breast cancer, we compared the clinicopathological characteristics between the patients with PVs in *BRCA1* and those with PVs in *BRCA2* (Table II). *BRCA1* PV carriers were more likely to be diagnosed with triple negative breast cancer and to have a family history of ovarian cancer. *BRCA2* PV carriers were diagnosed with breast cancer at a higher age than *BRCA1* PV carriers and were more likely to have a family history of prostate or pancreatic cancer. Triple negative breast cancer tended to be more common in *BRCA2* c.5576\_5579del carriers compared to all *BRCA2* PV carriers (21.4% vs. 9.4%).

The carrier frequency was compared among the four participating hospitals, as shown in Figure 1. We also compared the observed frequency with that of Japanese patients reported by Yoshimura *et al.* (4). *BRCA2* c.5576\_5579del accounted for 30.8% of the PVs detected in this study, and it was detected with a particularly high frequency of 72.7% at Kakogawa Central City Hospital.

## Discussion

Here, we have reported a surprisingly high detection rate of *BRCA2* c.5576\_5579del carriers among breast cancer patients at Kakogawa Central City Hospital. Globally, *BRCA2* c.5576\_5579del is most frequently reported in Asia (15, 16), especially in Japan (4, 5, 15, 18), Korea (15, 19, 20) and China (21). *BRCA2* c.5576\_5579del has been reported as a Japanese founder mutation; however, in these previous reports, *BRCA2* c.5576\_5579del accounts only for approximately 10% of breast cancer patients diagnosed as *BRCA1/2* PV carriers (4, 5). Geographically, there were fewer *BRCA2* c.5576\_5579del carriers in areas west of Kakogawa, and more in areas east of Kakogawa. It is difficult to confirm that this PV originated in Kakogawa without investigating the family trees, but *BRCA2* c.5576\_5579del carriers were found in a large proportion of the PVs in Kakogawa. *BRCA1* c.188T>A carriers, common in Japanese, were not detected in this study. In previous studies, *BRCA1* c.188T>A carriers were relatively rare in the Kinki region (5). Since this study involved a small number of carriers, we consider this result reasonable, along with the small number of *BRCA2* c.6952C>T carriers, the second most common *BRCA2* PV in Japan.

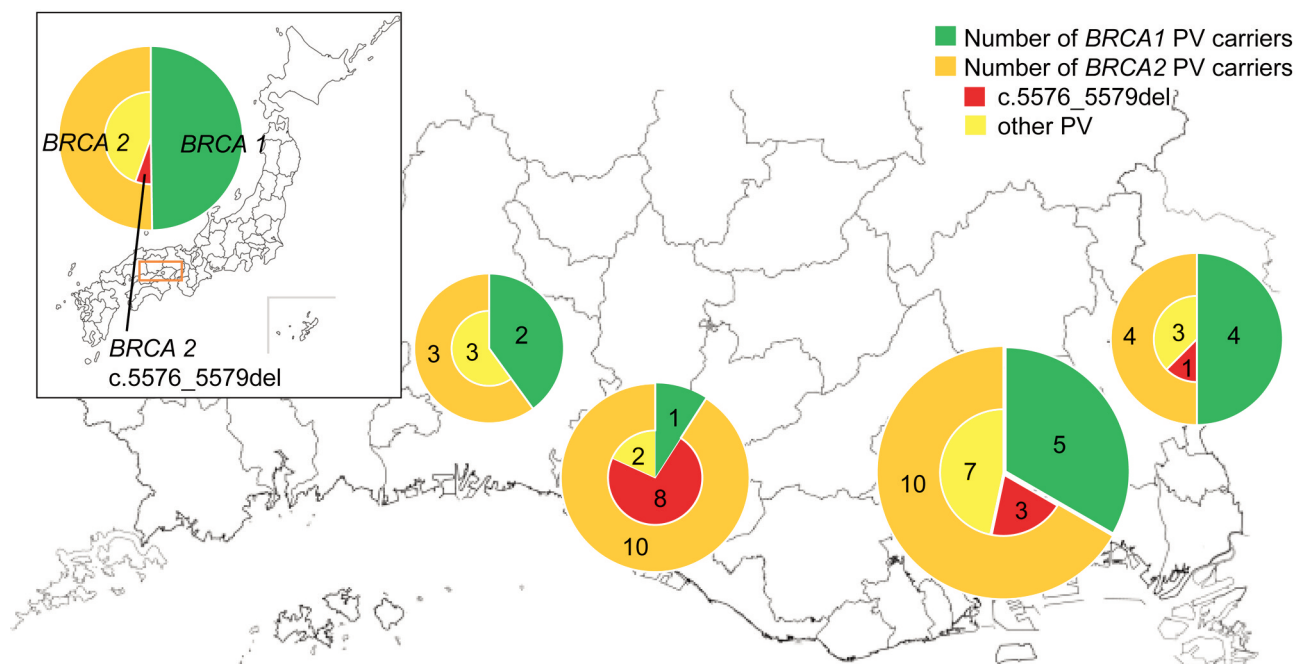


Figure 1. The carrier frequency among the four participating hospitals. The BRCA1/2 carrier frequency was compared in patients among four hospitals. The frequency of PVs in the observed patients was also compared with that in Japanese patients reported by Yoshimura et al. (4). A pie chart was used to compare the proportion of PVs at each hospital. BRCA2 c.5576\_5579del accounted for 30.8% of the PVs detected in this study and was detected with a particularly high frequency at Kakogawa Central City Hospital, accounting for 72.7% of the PVs observed there.

There have been very few reports of the phenotypic characteristics according to the genotype of *BRCA2*. *BRCA2* PV carriers are more likely to develop luminal type breast cancer than triple negative breast cancer, with the proportion of triple negative breast cancer patients reported to be approximately 14% (6). However, the present study shows a higher incidence of triple negative breast cancer in *BRCA2* PV carriers than in the previous study of *BRCA2* phenotypes. There is also a report that *BRCA2* c.5576\_5579del is involved in the development of ovarian cancer at a younger age, although the number of cases is small (22). This suggests that *BRCA2* c.5576\_5579del carriers may have similar clinical features to *BRCA1* carriers. However, these studies were limited to Hyogo Prefecture, and genetic traits other than *BRCA1/2* variants in that district may be also responsible.

The strength of this study is that it is one of the few reports of *BRCA1/2* variants in Japan. In addition, *BRCA2* c.5576\_5579del carriers were found at the Kakogawa Central City Hospital at an unprecedentedly high frequency of 72.7% of all *BRCA1/2* PV carriers. However, this study has several limitations. The number of patients was small, and the study was conducted in a limited number of hospitals in Hyogo Prefecture. Also, no family tree was created in this study, and no information was collected on birthplace or place of

residence of the patients. It is necessary to collect such information from a larger number of cases to demonstrate the founder effect of *BRCA2* c.5576\_5579del in Kakogawa.

Decades ago, it was considered nearly taboo to talk about genetic diseases in Japan. In recent years, as various benefits of recognizing one's own genetic information have become better known, genetic testing and genetic research have become more prevalent in Japan. In the future, *BRCA1/2* variants will be studied more widely and in larger numbers, and the distribution and the characteristics of the variants will be more precisely elucidated.

### Conclusion

*BRCA2* c.5576\_5579del accounted for 30.8% of the *BRCA1/2* PVs detected in this study conducted in the Hyogo Prefecture, Japan. It was detected with a particularly high frequency of 72.7% in Kakogawa. Future investigation of the distribution of the *BRCA2* c.5576\_5579del carriers may clarify their localization.

### Conflicts of Interest

Sachiko Mizumoto, Hirokazu Tanino and Tomonari Kunihisa received a research grant from Ono Pharmaceutical Co. Ltd. Tomonari Kunihisa

is a lecturer in an endowed chair founded by Hyogo Prefecture. The other Authors declare no conflicts of interest in relation to this study.

## Authors' Contributions

Conceptualization, H.N. (lead), S.M. (supporting), H.T. (supporting), T.K. (Supporting); data curation, H.N., S.M., H.T., Y.N., M.O., Y.S., K.T., S.K., M.K.; formal analysis, H.N., S.M., H.T., Y.N., S.U., T.K.; investigation, H.N., S.M., H.T., Y.N., M.O., Y.S., K.T., S.K., M.K., T.K.; methodology, H.N., S.M., H.T.; project administration, H.N., S.M., H.T., T.K.; resources, H.N., S.M., H.T., Y.N., M.O., Y.S., K.T., S.K., M.K., T.K.; supervision, H.T., M.O., S.U., T.K.; validation, H.N., S.M., H.T., S.U.; visualization, H.N., S.M., H.T.; writing – original draft, H.N. (lead), S.M. (supporting), H.T. (supporting); writing – review & editing, S.M., H.T., Y.N., M.O., Y.S., K.T., S.K., M.K., S.U., T.K.

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