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Germline Mutations Related to Complete Remission After Neoadjuvant Chemotherapy in Patients With Triple-negative Breast Cancer

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ABSTRACT

Purpose: Triple-negative breast cancer (TNBC) is a frequent phenotype of *BRCA*-mutant tumors. Tumors with BRCAness may show characteristics of *BRCA*-mutant tumors and respond to similar treatments. Next-generation sequencing is an efficient and cost-effective method for simultaneously sequencing multiple cancer susceptibility genes, surpassing conventional Sanger testing.

Methods: A total of 148 women with TNBC were recruited from December 2015 to November 2018, as part of a sub-analysis based on the PEARLY trial data. Of them, 103 patients received neoadjuvant chemotherapy (NCT). The targeted genes related to hereditary cancers were sequenced using the 65-gene germline next-generation sequencing (gNGS) panel pathogenic and likely pathogenic variants (P&LPs) were determined by Sanger sequencing. We examined the occurrence of pathologic complete remission (ypCR) in patients with P&LPs.

Results: The patients' median age was 47 years (range, 27–69 years). Twenty (13.7%) of 148 patients had P&LP in six genes, including *BARD1* (n = 2), *BRCA1* (n = 9), *BRCA2* (n = 5), *CHEK2* (n = 1), *RAD51C* (n = 1), and *RAD51D* (n = 2). Among the 103 patients with NCT, 43 (41.7%) achieved ypCR (P&LPs; 9 individuals vs. non-variants; 34 individuals). Among the 103 patients with NCT, 14 (9.3%) had P&LPs. Nine of 14 patients with P&LPs, including *BARD1* (n = 2), *BRCA1* (n = 4), *BRCA2* (n = 1), *RAD51C* (n = 1), and *RAD51D* (n = 1), achieved ypCR, showing a trend toward statistical significance ($p = 0.066$).

Conclusion: Germline P&LP mutations in TNBC patients can be detected by gNGS. This panel test can identify *BRCA* and BRCAness mutations that may predict ypCR in TNBC.

Keywords: Gene Components; Genes, *BRCA1*; Genes, *BRCA2*; Germ-line Mutation; Triple Negative Breast Neoplasms

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Conflict of Interest

The authors declare that they have no competing interests.

Data Availability

The datasets generated or analyzed during the study are not publicly available as they contain information that could compromise the privacy of the research participants but are available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization: Park HS; Data curation: Ahn JH; Formal analysis: Ahn JH; Investigation: Ahn JH, Lee SJ, Yang SH, Kim MH, Park HS; Methodology: Ahn JH, Park HS; Project administration: Park HS; Resources: Park JS, Won D, Lee ST, Kim JY, Park S, Kim SI, Park BW, Kim MH, Kim GM, Sohn J, Park HS; Supervision: Park HS; Visualization: Ahn JH; Writing - original draft: Ahn JH; Writing - review & editing: Park HS.

INTRODUCTION

Triple-negative breast cancer (TNBC) accounts for approximately 10%–20% of all breast malignancies and is characterized by biological and clinical heterogeneity [1,2]. TNBC has aggressive features and an unfavorable prognosis. TNBC has a limitation in primary therapeutic choices, primarily relying on surgery with neoadjuvant chemotherapy (NCT) or adjuvant chemotherapy. However, recent advancements in the understanding of TNBC have led to the emergence of some therapeutic possibilities in specific cases.

Variants in cancer predisposition genes contribute to the elevation in TNBC risk, with notable relevance attributed to *BRCA1* and *BRCA2* [3,4]. Approximately 5% of breast cancer patients carry a germline deleterious mutation in *BRCA1* and *BRCA2* (*BRCA1/2*). This prevalence is significantly increased to approximately 20% in patients with TNBC [5,6]. *BRCA1/2* function as tumor-suppressor genes essential for maintaining genome integrity by facilitating homologous recombination, a significant pathway for repairing DNA damage [7]. Defects in *BRCA* genes lead to increased cell susceptibility to chromosomal instability due to compromised DNA strand break repair. This elevates the risk of breast cancer [8]. Patients with *BRCA* gene mutations are recommended to consider additional treatments and enhanced surveillance beyond standard care. Opting for bilateral prophylactic mastectomy is a robust consideration [9], and the addition of poly (ADP-ribose) polymerase (PARP) inhibitors, which target the single-strand repair PARP gene, can be strongly considered in both adjuvant and metastatic settings [4]. For carriers who choose to preserve their breasts while undergoing surveillance, a comprehensive screening involving annual mammography alongside magnetic resonance imaging should be performed at a younger age [10,11].

BRCAness describes a phenotype characterized by homologous recombination repair (HRR) deficiency that functionally resembles the loss-of-function mutations of *BRCA1/2* [12]. Several genes that induce BRCAness have been identified, and various mechanisms such as *BRCA1* methylation and EMSY overactivation lead to impaired *BRCA* function as part of the mechanism of BRCAness. Cancers with a BRCAness feature also exhibit sensitivity to PARP inhibitors [13].

To expand the scope of treatment options for TNBC, a comprehensive understanding of BRCAness-related genes including *BRCA1/2* is imperative. The use of next-generation sequencing (NGS) enables rapid detection and facilitates the identification of numerous BRCAness-associated genes, including *BRCA1/2* [14]. In the past, Sanger sequencing (SGS) served as the primary method for identifying DNA mutations [15]. However, SGS has limited sensitivity and cannot simultaneously analyze multiple targets. Additionally, identifying somatic cancer mutations through SGS can be challenging without microdissections due to the heterogeneous nature of tumors, frequently intertwined with normal tissues.

Our study aimed to employ a germline next-generation sequencing (gNGS) panel to identify reproductive organ mutations associated with BRCAness-related genes including *BRCA1/2* in TNBC patients and explore the potential for developing a gene panel test for detecting BRCAness. In addition, we sought to investigate the association between BRCAness-related genes including *BRCA1/2* genes and pathological complete response (ypCR), which is an independent prognostic factor for treatment outcomes in clinical practice.

METHODS

Patients

A total of 148 patients with TNBC who consented to gNGS testing for clinical research were included in this study. All patients were recruited from 13 multicenter hospitals in South Korea between December 2015 and November 2018. The gNGS in patients with TNBC was carried out through a *post hoc* examination of the PEARLY trial (NCT02441933). This phase III, multicenter, randomized, and open-label study evaluated the efficacy and safety of incorporating carboplatin into NCT. This study compared anthracycline-based regimens followed by taxane versus those followed by taxane plus carboplatin as NCT. Specifically, the neoadjuvant regimen comprised four cycles of anthracycline and cyclophosphamide followed by taxane, administered to patients with clinical stage II–III TNBC. Patients in the PEARLY trial were randomly allocated to study groups according to institution, treatment setting (neoadjuvant vs. adjuvant), presence of clinical axillary lymph node metastasis for neoadjuvant setting or pathological axillary lymph node metastasis for adjuvant setting, and *BRCA* mutation status. The post hoc multiple panel testing conducted in this study involved 103 patients who underwent NCT and 45 patients who underwent surgical treatment followed by adjuvant chemotherapy. The following clinical and pathologic data were obtained from the registry information of the PEARLY study: personal and family cancer history, cancer multiplicity, histologic type, histologic grade, NCT status, types of surgery, and the results of gNGS. The case of each breast cancer patient was thoroughly evaluated by a panel of pathologists within the same institute.

Ethics

This study was approved by the Institutional Review Board of the Yonsei University College of Medicine (4-2018-0774). Written informed consent was obtained from patients who provided agreed to undergo multi-gene panel testing after receiving a comprehensive explanation regarding the extensive use of the testing results. The results of breast cancer-related gene mutations in multi-gene panel testing were reflected in the treatment of patients.

Process of NGS assay and BRCAness

The genomic DNA isolated from the patient's blood specimens underwent library preparation and target enrichment through a gNGS panel designed for candidate genes. Massively parallel sequencing was carried out on the MiSeq System (Illumina, San Diego, CA, USA). Quality assessment and sequence analysis were performed utilizing the BaseSpace (Illumina) and NextGENe (SoftGenetics, State College, PA, USA) software. Customized targeted capture sequencing panel (OncoRisk; Celemics, Seoul, Korea) was used to detect coding sequences and intron-exon boundaries of the coding exons of 65 cancer susceptibility genes, including *APC*, *ATM*, *BARD1*, *BLM*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A*, *CHEK2*, *EPCAM*, *MEN1*, *MLH1*, *MRE11A*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PMS2*, *POLE*, *PRSS1*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *RET*, *SLX4*, *SMAD4*, *STK11*, *TP53*, *VHL*, *WT1*, *NF1*, *NF2*, *RB1*, *RUNX1*, *KRAS*, *NRAS*, *PTCH1*, *SDHA*, *SDHB*, *ALK*, *PHOX2B*, *KIF1B*, *LMO1*, *PAX6*, *CTNNB1*, *AXIN1*, *NTRK1*, *AXIN2*, *EXO1*, *FANCM*, *FLCN*, *GALNT12*, *GPC3*, *GREM1*, *MLH3*, *PMS1*, *POLD1*, *PPM1D*, *SDHAF2*, and *RAD51*. Among these, the primary genes of interest in this study are *BRCA1*, *BRCA2*, and other BRCAness genes such as *BARD1*, *CHEK2*, *RAD51C*, and *RAD51D*. According to the American College of Medical Genetics and Genomics classification, genetic mutation results were divided into five categories: pathogenic (P), likely pathogenic (LP), variants of unknown significance (VOUS), likely benign (LB), and benign (B) [16]. Among these, patients requiring active treatment or intervention were grouped under

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P&LPs. VOUS and benign variants (VOUS&Bs) were combined into the VOUS&B group, given the absence of established clinical guidelines. All patients with P&LPs were identified by conducting an additional SGS. The types of genes associated with BRCAness were determined based on previous research findings [17].

Criteria for assessing pathologic complete remission after NCT

The tumor volume was determined by dividing the tumor tissue by the total tissue volume. Tumor response to NCT was assessed by preoperative radiologic evaluation, according to the Response Evaluation Criteria in Solid Tumors [18,19]. The tumor response to NCT was evaluated partial response (PR) as a ≥ 30% reduction in total tumor lesions based on two evaluations separated by at least four weeks, stable disease as the absence of PR or progressive disease (PD), and PD as a ≥ 20% increase in the size of one or more measurable lesions or the appearance of new lesions. ypCR was defined as the absence of breast invasive carcinoma (Tis/T0) and absence of lymph node involvement (N0).

Statistical analysis

Categorical variables comparisons of clinicopathologic characteristics between the P&LP group and VOUS&B group were compared using the χ^2 test or Fisher's exact test. The correlation between variables was quantified using Pearson's correlation analysis. Frequency analyses, including cumulative frequency assessments, were applied to demonstrate the distribution of genes in the entire and specific target regions. A *p*-value of less than 0.05 was considered statistically significant. The statistical analyses were conducted using the IBM SPSS software (version 25.0; IBM Corp., Armonk, NY, USA).

RESULTS

Study cohort

The clinicopathologic features of the study participants based on their mutation status are presented in **Table 1**. The patients' median age at breast cancer diagnosis was 47 years (range, 27–69 years). One hundred forty-six patients were diagnosed with invasive ductal carcinoma, while two individuals were diagnosed with metaplastic carcinoma with osseous differentiation and invasive carcinoma with apocrine differentiation. Over two-thirds of the patients received NCT. Among the 148 patients included in this study, 72 (49.6%) received a regimen incorporating carboplatin. More than half of the patients were eligible for partial mastectomy. All patients in the P&LP group had BRCAness-related gene mutations. Patients classified as pathologic T0/Tis included not only the 43 patients who achieved ypCR but also five patients with confirmed node metastasis.

Prevalence of P&LP variants of the cancer predisposition genes

Of the 148 patients, 20 (13.5%) comprised the *BRCA1/2* mutation and BRCAness-related genes in P&LP group. In 136 patients aged ≤ 60 years, the proportion of those in P&LP increased to 14.7%. Among the 148 patients, 14 (9.5%) had P&LP with *BRCA 1/2* mutation alone. In 136 patients aged ≤ 60 years, the proportion of those with P&LP increased to 10.3% (**Figure 1**).

Distribution of variants

The results of the gNGS are presented in **Figure 2**. Among the patients who received NCT, nine who achieved ypCR exhibited P&LP variants in *BARD1*, *BRCA1*, *BRCA2*, *RAD51C*, and *RAD51D* genes. *BRCA1* mutations were the most prevalent and were observed in four patients.

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Table 1. Clinicopathologic characteristics of the study participants

Characteristics	P&LP group (n = 20)	VOUS&B group (n = 128)	*p*-value
Age			0.755
< 40 yr	5 (25.0)	28 (21.9)	
≥ 40 yr	15 (75.0)	100 (78.1)	
Multiplicity			0.832
Single	16 (80.0)	100 (78.2)	
Multifocal/multicentric	4 (20.0)	28 (21.9)	
Histology			0.574
Invasive ductal carcinoma	20 (100.0)	126 (98.4)	
Other	-	2 (1.6)	
Neoadjuvant chemotherapy			0.966
None	6 (30.0)	39 (30.5)	
Done	14 (70.0)	89 (69.5)	
Breast surgery			0.027
Conserving surgery	17 (85.0)	76 (59.4)	
Total mastectomy	3 (15.0)	52 (40.6)	
Axillary surgery			0.611
SLNB	12 (60.0)	69 (53.9)	
ALND	8 (40.0)	59 (46.1)	
Histological grade			0.308
1	-	1 (0.8)	
2	5 (25.0)	33 (25.8)	
3	6 (30.0)	61 (47.7)	
Unknown	9 (45.0)	33 (25.8)	
Pathologic T stage			0.396
T0/Tis	9 (45.0)	39 (30.5)	
T1	4 (20.0)	39 (30.5)	
T2/T3	7 (35.0)	50 (39.1)	
Number of metastatic lymph nodes			0.017
None	19 (95.0)	89 (69.5)	
≥ 1	1 (5.0)	39 (30.5)	
BRCAness gene			< 0.001
No	-	85 (66.5)	
Yes	20 (100.0)	43 (33.6)	

Values are presented as number of patients (%).
P = pathogenic; LP = likely pathogenic; VOUS = variants of unknown significance; B = benign; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection.

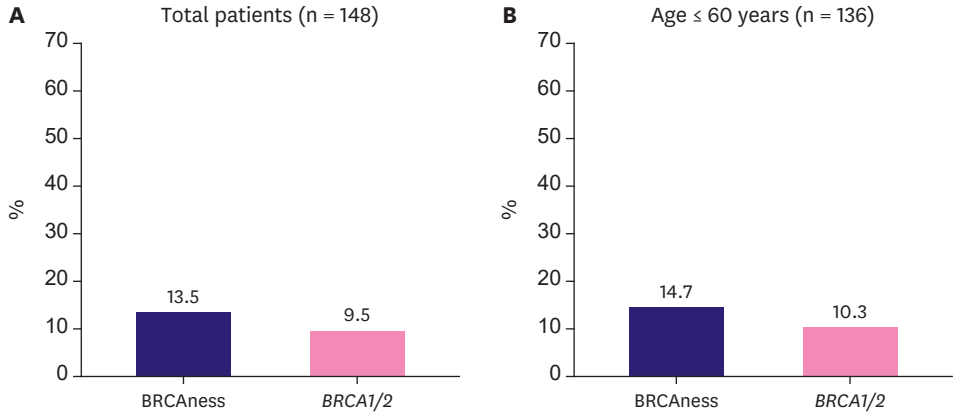

Figure 1. Proportion of germline pathogenic & likely pathogenic variants of BRCAness and *BRCA1/2* gene. In the entire patient cohort (A) and in patients aged < 60 years (B).

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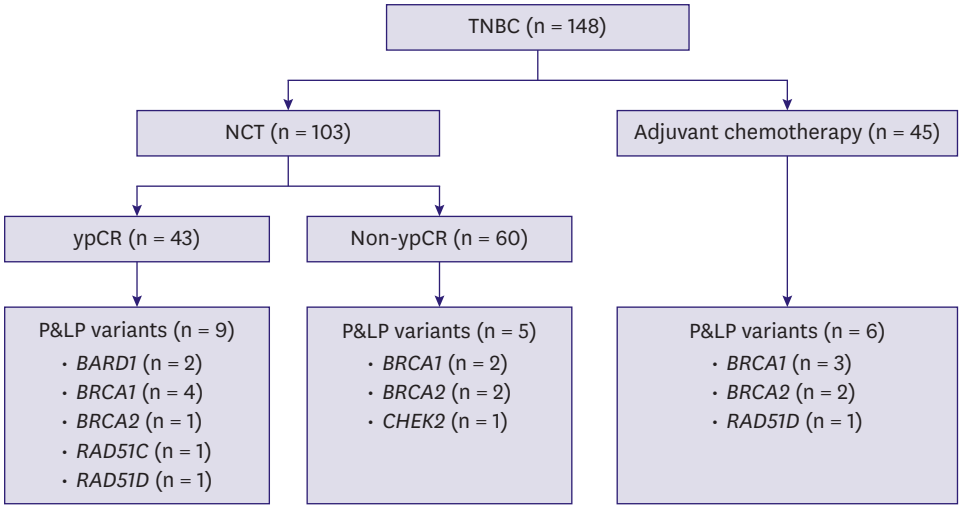

Figure 2. Flowchart showing the results of the analysis of patients by chemotherapy status and distribution of pathogenic & likely pathogenic variants.
TNBC = triple-negative breast cancer; NCT = neoadjuvant chemotherapy; ypCR = pathologic complete remission; P = pathogenic; LP = likely pathogenic.

Among the patients who received NCT but did not achieve ypCR, five showed P&LP variants in *BRCA1*, *BRCA2*, and *CHEK2* genes. Among the five patients who underwent surgery and received adjuvant chemotherapy, P&LP variants were identified in *BRCA1* and *BRCA2* genes.

The overall gene frequency is depicted in **Figure 3**. In the entire patient cohort, *BRCA1* was observed in nine patients (6.0%), *BRCA2* in five (3.3%), *BARD1* in two (1.3%), *RAD51D* in one, *RAD51C* in one, and *CHEK2* in one. VOUS were found across 41 genes, with a prevalence of 66.2% (98 patients) in the entire cohort.

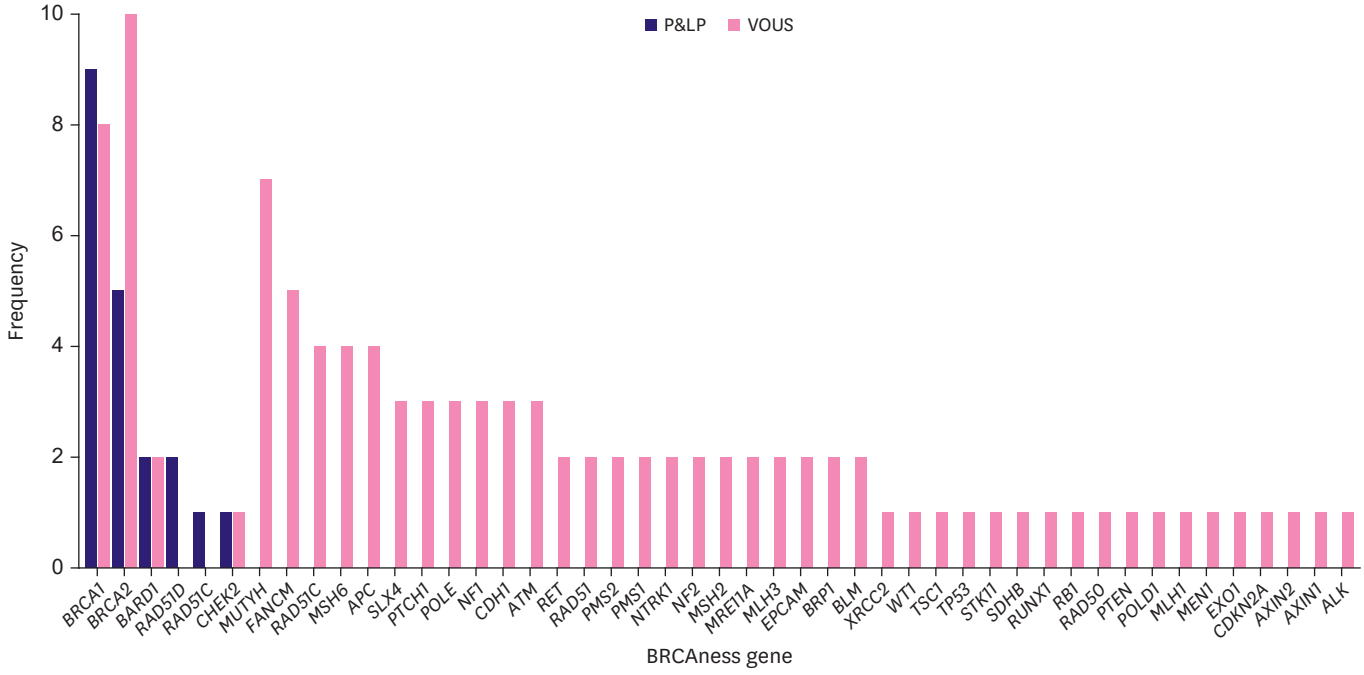

Figure 3. Frequency of BRCAness gene according to pathogenic & likely pathogenic variants or variants of uncertain significance in the entire cohort.
P = pathogenic; LP = likely pathogenic; VOUS = variants of unknown significance.

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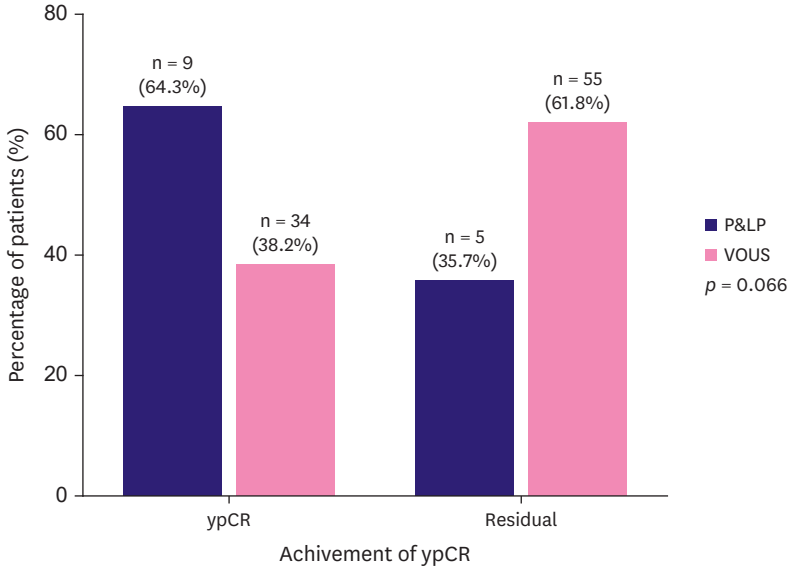

Figure 4. Analysis of the correlation between pathologic complete remission and variant types in patients treated with neoadjuvant chemotherapy.
P = pathogenic; LP = likely pathogenic; VOUS = variants of uncertain significance; ypCR = pathologic complete remission.

Relationship variants and complete remission

The results of ypCR in 103 patients who underwent NCT according to P&LP status are shown in **Figure 4**. A total of 43 patients achieved ypCR (41.7%), and 14 of them exhibited P&LP variants (13.6%). A cross-analysis between the presence of P&LP variants and ypCR status was performed, which revealed that among patients with P&LP variants, nine achieved ypCR. This association determined by Pearson's correlation analysis demonstrated a statistically significant tendency ($p = 0.066$). In a subanalysis, we also evaluated the ypCR rates in patients with *BRCA1/2* mutations and those with BRCAness excluding *BRCA1/2* mutations, with comparable results observed in each group (5 vs. 4 patients, $p = 0.36$).

DISCUSSION

The present study revealed that genetic mutations observed in TNBC patients originate from BRCAness-related genes. Additionally, it underscores a tendency for patients undergoing NCT with genetic mutations to achieve ypCR. Patients exhibiting BRCAness without *BRCA1/2* mutations achieved ypCR at a rate similar to those harboring *BRCA1/2* mutations, indicating that this phenotype represents a clinically meaningful subgroup. It is well established that achieving ypCR through NCT indicates a favorable prognosis [20]. Comprehensive NGS profiling of BRCAness can therefore help identify additional patients who may derive benefit from DNA-damaging agents, including carboplatin. Accordingly, gene panel testing for genetic variants can be regarded as a meaningful approach to identifying suitable candidates for tailored therapeutic interventions.

TNBC is characterized by its rapid progression, aggressive behavior, and poor prognosis. Traditional treatment modalities have typically been limited to surgery and chemotherapy. Recently, the benefits of genetic testing for *BRCA1/2* mutations in TNBC have been well established. The presence of *BRCA* mutations has shown improved outcomes with PARP inhibitors. Additionally, targeted therapy against programmed death-ligand 1 has gained

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recognition as an emerging treatment option for TNBC [21,22]. To expand personalized treatment options for TNBC, the proactive consideration of multiple panel testing for BRCAness is essential. In addition to the well-known *BRCA* genes, the likelihood of cancer development increases due to defects in BRCAness-related genes involved in HRR [17]. Furthermore, cancers with defects in BRCAness-related genes, along with the presence of such defects, exhibit sensitivity to PARP inhibitor treatment known to be effective for *BRCA*-mutated cancers. When accompanying mutations are present, tailoring therapeutic interventions based on the mutated gene's associated risks could contribute to enhanced patient outcomes.

The onset age of breast cancer patients with *BRCA1/2* mutations is known to be relatively younger compared with that of patients without mutations [6]. Based on the American Society of Breast Surgeons and National Comprehensive Cancer Network guidelines, *BRCA1/2* mutation testing is recommended for patients diagnosed with TNBC at the age of 60 years [23,24]. When analyzing the age range of those aged < 60 years, both *BRCA1/2* mutations and genetic mutations showing BRCAness-related genes including *BRCA1/2* were detected within this age range. The conduct of NGS in TNBC patients aged < 60 years can enhance understanding of genetic alterations related to BRCAness-related genes including *BRCA1/2*, thus enabling the appropriate management of hereditary cancers. The 2013 National Institute for Health and Care Excellence guidelines suggest that individuals without a history of breast or ovarian cancer should consider genetic testing if their combined likelihood of carrying mutations in both *BRCA1* and *BRCA2* genes is 10% or higher [25]. This recommendation becomes pertinent in cases where testing a family member affected by these cancers is not feasible.

In our study, VOUS were identified in 41 genes and observed in 98 patients (66.2%), which aligns closely with the findings of another study that conducted a multigene panel testing [26-28]. Until their clinical significance is thoroughly understood, the identification of VOUS should not influence clinical decision-making. The accumulation of clinical data may result in the reclassification of genes initially identified as VOUS to P or LP, especially 5%–11% in *BRCA1* and *BRCA2* genes [29,30]. This, in turn, necessitates reevaluation and consultation for treatment decisions in patients carrying these genes. Furthermore, attempts are being made to detect multiple susceptible genes by mapping numerous risk regions simultaneously [31]. Fachal et al. [31] conducted a mapping of breast cancer risk variants in over 150 genomic regions and identified 191 likely target genes.

Studies exploring the prevalence of genes and their clinical utility using NGS in various cancer types are actively underway. In the field of gynecology, genetic mutations in reproductive cells are directly associated with cancer, making genetic analysis crucial [32]. Eoh et al. [28] conducted an NGS panel analysis of 35 cancer susceptibility genes in 117 epithelial ovarian cancer (EOC) patients. Apart from *BRCA1/2* gene mutations, P&LP variants were observed in *BRIP1*, *CHEK2*, *MSH2*, *POLE*, *RAD51C*, and *RAD51D*. This broader spectrum of variant detection, beyond just *BRCA*1/2 testing, enhances the potential for better patient-tailored treatment in EOC.

The current study presents several advantages. First, we conducted an analysis using data extracted from a prospective study database. This approach facilitated data analysis without the unnecessary inclusion of data or omission of essential data. Additionally, there was no mixing of patients with different subtypes of breast cancer. All the study participants were homogeneously diagnosed with TNBC, reducing the confounding effects in the results.

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Second, comprehensive information was obtained from a single analysis of each patient by utilizing a panel with various genes. This approach enhanced the understanding of the overall landscape of high-risk cancer-associated genes carried by patients, surpassing the scope of single-gene data.

This study has several limitations. First, the number of samples was relatively small. The study did not include all patients from the clinical trial, but rather focused on analyzing only a subset of participants. This study involved patients who had consented to participate in the prospective research. Therefore, it should be considered less for yielding confirmative results and more as a study for hypothesis generation, as the findings may not reach statistical significance. Additional studies targeting a larger population are needed to approach a more representative distribution. Second, the selection of the entire population cannot be considered well-executed. The results are based on the analysis of a subset of patients who agreed to participate in the study. Hence, further research is required, utilizing methods that can represent the entire population for patient selection and analysis.

In conclusion, genetic mutations were predominantly observed in the *BRCA1/2* genes or genes exhibiting similar *BRCA*-mutant patterns in TNBC. When gNCT is administered to TNBC patients with accompanying genetic mutations, the attainment of ypCR can be anticipated. The implementation of gNGS in studying BRCAness-associated genetic variations among TNBC patients holds the potential for effective hereditary cancer management.

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