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Brief Communication

Somatic Mutations of *TP53* Identified by Targeted Next-Generation Sequencing Are Poor Prognostic Factors for Primary Operable Breast Cancer: A Single-Center Study

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ABSTRACT

Few studies have reported on the clinical utility of targeted next-generation sequencing (NGS) for breast cancer in Korea. We retrospectively reviewed the targeted NGS data of 219 patients with breast cancer who underwent surgical resection between August 2018 and April 2021. Here, we described the mutational profiles of breast cancer and examined their prognostic implications. The most frequently mutated gene was *PIK3CA* (n = 97/219, 44.3%), followed by *TP53* (n = 79/219, 36.1%), *AKT1* (n = 23/219, 10.5%), and *GATA3* (n = 20/219, 9.1%). *TP53* mutations were associated with aggressive histologic features. We followed up for 31 (range, 1–39) months and observed 11 (5.0%) recurrences: nine were *TP53* mutant and two were *TP53* wild-type. Multivariable analysis revealed that *TP53* mutation was an independent prognostic factor for recurrence ($p = 0.012$). Although no drug is currently available for *TP53* mutations, it is valuable to know the mutational status of *TP53* for the precise management of breast cancer.

Keywords: Breast Neoplasms; Disease-Free Survival; Genes, p53; High-Throughput Nucleotide Sequencing; Mutation

INTRODUCTION

Molecular studies have shown that breast cancer is a heterogeneous disease. Each breast cancer subtype has diverse biologic characteristics [1]. The development of next-generation sequencing (NGS) has reduced the time and cost of genomic analyses. Targeted NGS enables genomic analysis and is readily available in clinical settings. Several platforms for targeted NGS have been commercialized and used in clinical practice.

Since 2017, targeted NGS for solid cancers has been partially covered by the national health insurance in Korea [2]. However, the mutational profiles of Korean patients with breast cancer have been poorly characterized. Moreover, the clinical utility of targeted NGS for

Conflict of Interest
The authors declare that they have no competing interests.

Author Contributions
Conceptualization: Kim LS; Data curation: Kim HY; Methodology: Seo J, Min SK; Project administration: Kim LS; Resources: Seo J, Min SK; Supervision: Kim HY, Kim LS; Writing - original draft: Park JH; Writing - review & editing: Kwon MJ.

primary operable breast cancer remains unclear [3]. To fill the gap between widespread clinical use and unproven clinical benefits, we aimed to describe our experience with targeted NGS for primary operable breast cancer.

METHODS

Patient selection and data acquisition

Targeted NGS was initiated at our institution in August 2018. We retrospectively reviewed the electronic medical records of patients with breast cancer who underwent surgical resection between August 2018 and April 2021. We included patients with stage I–III breast cancer and collected the available NGS data. Patients who underwent neoadjuvant chemotherapy and those with recurrent tumors, distant metastasis, and occult breast cancer were excluded from the study. We collected clinicopathological data, including age at diagnosis, menopausal status, body mass index, histologic subtype, nuclear grade, histologic grade, lymphovascular invasion, lymph node metastases, and immunohistochemical staining. Pathological data included estrogen receptor (ER), progesterone receptor, human epithelial growth factor receptor 2 (HER2), and Ki-67 index. According to the Saint Gallen consensus [4], we classified the patients into five subtypes: luminal A, luminal B/HER2-negative, luminal B/HER2-positive, HER2-enriched, and triple-negative breast cancers. We adopted a cut-off value of Ki-67 as 20% for distinguishing between the luminal A and luminal B/HER2-negative subtypes.

NGS protocol

All NGS procedures were performed in accordance with the institutional protocols. Formalin-fixed paraffin-embedded tissue blocks were dissected to 10-μm thickness. Tumor areas with high cellularity were selected and manually dissected for further analysis. The DNA was extracted and purified in a standard manner.

For sequencing, we used MiSeqDx (Illumina, San Diego, CA, USA), according to the manufacturer's protocol. We selected 50 cancer-related genes and customized a pan-cancer panel. The genes included in the NGS panel were as follows: *AKT1*, *ALK*, *APC*, *ARID1A*, *ATRX*, *BRAF*, *BRCA1*, *BRCA2*, *CDH1*, *CDK4*, *CDK6*, *CDKN2A*, *CTNNB1*, *EGFR*, *HER2*, *ERBB3*, *ERBB4*, *ESR1*, *FBXW7*, *FGFR1*, *FGFR2*, *FGFR3*, *FOXA1*, *GATA3*, *H3F3A*, *IDH1*, *IDH2*, *KIT*, *KRAS*, *MAP2K1*, *MET*, *MLH1*, *MTOR*, *MYC*, *MYCN*, *NRAS*, *PDGFRA*, *PIK3CA*, *PTEN*, *RB1*, *RELA*, *RET*, *RHOA*, *RICTOR*, *ROS1*, *SMAD4*, *SMARCB1*, *SMO*, *STK11*, and *TP53*. All coding exons of the genes were included in the panel.

Each variant was compared with known mutations stored in web-based databases, such as COSMIC (https://cancer.sanger.ac.uk/cosmic), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), and OncoKB (https://www.oncokb.org/). According to the guidelines [5], the variants were classified into three groups: tier 1, variants with strong clinical significance; tier 2, variants with potential clinical significance; and tier 3, variants with unknown clinical significance. The variants of tiers 1 and 2 were included in the analysis.

Statistical analysis

Comparisons between categorical variables were performed using the χ^2 test or Fisher's exact test. Comparisons between continuous variables were performed using the Student's *t*-test. Disease-free survival (DFS) was compared using the Kaplan-Meier product limit method and log-rank test. The Cox proportional hazards model was used for the multivariable analysis.

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All statistical analyses were performed using SPSS (version 27.0; IBM Corporation, Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

This study was reviewed and approved by the Institutional Review Board of Hallym University Sacred Heart Hospital (IRB number: 2019-05-009). The requirement for informed consent was waived due to the retrospective study design.

RESULTS

Clinicopathological characteristics

A total of 801 patients underwent surgery for breast cancer between August 2018 and April 2021. Among 258 patients who underwent NGS for breast cancer, 219 were included in the analysis (**Supplementary Figure 1**). *TP53* mutations were significantly associated with aggressive histologic features, such as high nuclear grade, high histologic grade, and high Ki-67 index (**Table 1**). Adjuvant chemotherapy showed no significant differences between *TP53* wild-type and mutant tumors (**Supplementary Table 1**).

Table 1. Comparison between *TP53* wild-type and mutant tumors

Variables	*TP53* wild-type (n = 140)	*TP53* mutant (n = 79)	*p*
Age (yr)	55.09 ± 11.56	54.77 ± 12.82	0.857
Menopausal status			0.158
Premenopausal	66 (47.1)	30 (38.0)	
Postmenopausal	72 (51.4)	45 (57.0)	
Perimenopausal	2 (1.4)	4 (5.1)	
BMI (kg/m^2)	24.49 ± 3.91	25.03 ± 4.52	0.375
Operation			0.501
BCS	100 (71.4)	53 (67.1)	
TM	40 (28.6)	26 (32.9)	
T stage			0.029
1	79 (56.4)	30 (38.0)	
2	49 (35.0)	42 (53.2)	
3	10 (7.1)	4 (5.1)	
4	2 (1.4)	3 (3.8)	
N stage			0.024
0	86 (61.4)	39 (49.4)	
1	27 (19.3)	14 (17.7)	
2	15 (10.7)	21 (26.6)	
3	12 (8.6)	5 (6.3)	
Nuclear grade			< 0.001
1	19 (13.9)	2 (2.5)	
2	78 (56.9)	17 (21.5)	
3	40 (29.2)	60 (75.9)	
Histologic grade			< 0.001
1	38 (27.9)	5 (6.3)	
2	72 (52.9)	21 (26.6)	
3	26 (19.1)	53 (67.1)	
Lymphovascular invasion			0.041
Absent	92 (67.2)	42 (53.2)	
Present	45 (32.8)	37 (46.8)	
Ki-67 index	20.06 ± 16.15	40.98 ± 16.69	< 0.001

Values are expressed as mean ± standard deviation or number (%).
BMI = body mass index; BCS = breast conserving surgery; TM = total mastectomy.

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Table 2. Classification of the identified mutations based on the molecular subtypes

Genes	Luminal A (n = 83)	Luminal B/HER2-negative (n = 38)	Luminal B/HER2-positive (n = 35)	HER2-enriched (n = 22)	Triple-negative (n = 41)	Total (n = 219)	*p*	*p* for trend
PIK3CA	55 (66.3)	12 (31.6)	11 (31.4)	10 (45.5)	9 (22.0)	97 (44.3)	< 0.001	< 0.001
TP53	5 (6.0)	11 (28.9)	18 (51.4)	17 (77.3)	28 (68.3)	79 (36.1)	< 0.001	< 0.001
AKT1	10 (12.0)	7 (18.4)	2 (5.7)	0 (0.0)	4 (9.8)	23 (10.5)	0.184	0.221
GATA3	10 (12.0)	4 (10.5)	6 (17.1)	0 (0.0)	0 (0.0)	20 (9.1)	0.041	0.023
PTEN	8 (9.6)	2 (5.3)	1 (2.9)	0 (0.0)	4 (9.8)	15 (6.8)	0.380	0.582
CDH1	5 (6.0)	1 (2.6)	1 (2.9)	1 (4.5)	3 (7.3)	11 (5.0)	0.838	0.836
BRCA2	2 (2.4)	3 (7.9)	3 (8.6)	0 (0.0)	1 (2.4)	9 (4.1)	0.288	0.843
HER2	1 (1.2)	0 (0.0)	2 (5.7)	1 (4.5)	1 (2.4)	5 (2.3)	0.452	0.332
BRCA1	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	3 (7.3)	4 (1.8)	0.047	0.024
FOXA1	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.9)	4 (1.8)	0.276	0.547

Values are presented as number (%) not otherwise specified.
HER2 = human epithelial growth factor receptor 2.

Mutational profiles

The most commonly mutated gene was *PIK3CA* in 97 (44.3%) patients, followed by *TP53* in 79 (36.1%), *AKT1* in 23 (10.5%), and *GATA3* in 20 (9.1%). The less commonly mutated genes included *PTEN*, *CDH1*, *BRCA2*, *HER2*, and *BRCA1* mutations in 15 (6.8%), 11 (5.0%), 9 (4.1%), 5 (2.3%), and 4 (1.8%) patients, respectively.

Each breast cancer subtype exhibited different mutational characteristics (**Table 2**). *PIK3CA* mutations were more commonly found in the luminal A subtype (n = 55/83, 66.3%) than in the luminal B/HER2-negative (12/38, 31.6%), luminal B/HER2-positive (11/35, 31.4%), HER2-enriched (10/22, 45.5%), or triple-negative (9/41, 22.0%) subtypes (p<0.001). *TP53* mutations were more commonly found in the HER2-enriched (17/22, 77.3%) and triple-negative (28/41, 68.3%) subtypes than in the luminal B/HER2-positive (18/35, 51.4%), luminal B/HER2-negative (11/38, 28.9%), and luminal A (5/83, 6.0%) subtypes (p < 0.001). *GATA3* mutations were exclusively found in luminal breast cancers (p = 0.023). *BRCA1* mutations were more likely to be found in the triple-negative subtype (p = 0.024).

Survival analysis

We compared survival outcomes between wild-type and mutant tumors. Overall, there were 11 (5.0%) recurrences during 31 (range, 1–39) months of follow-up. *TP53* mutations were significantly associated with worse short-term DFS (**Figure 1**). For the other genes, there were no significant differences in survival (**Supplementary Figure 2**).

Multivariable analysis was performed to further validate the prognostic implications of *TP53* mutations (**Supplementary Table 2**). Univariable analysis revealed that high nodal stage, high nuclear grade, high histologic grade, ER negativity, and *TP53* mutations were associated with recurrence. Multivariable analysis showed that *TP53* mutations were independently associated with short-term DFS in breast cancer (hazard ratio, 7.23; 95% confidence interval, 1.55–33.77; p = 0.012).

DISCUSSION

We showed that somatic mutations of *TP53*, which can be identified by targeted NGS, are poor prognostic factors for breast cancer in a curative setting. Among the various genetic alterations, only *TP53* mutations were associated with poor short-term DFS in patients with primary operable breast cancer. *TP53* mutations are associated with poor prognostic factors,

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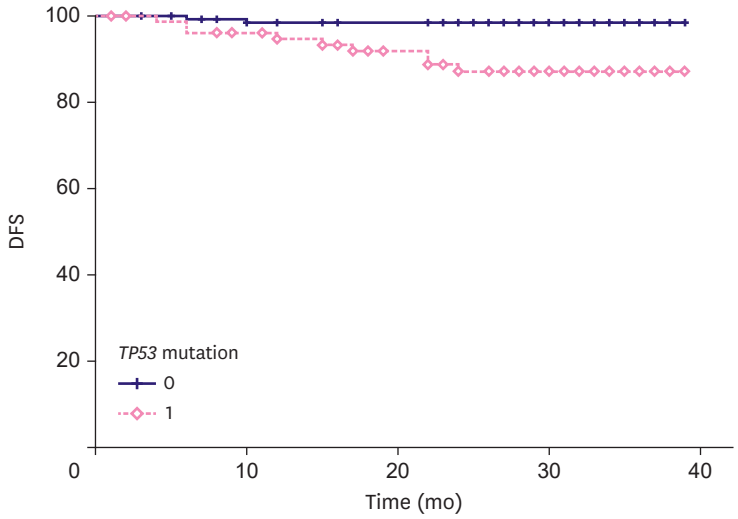

Figure 1. Kaplan-Meier survival analysis of the study patients.
TP53 mutations were associated with poor short-term DFS of primary operable breast cancer patients (p = 0.001).
DFS = disease-free survival.

such as high histologic grade, high Ki-67 index, and non-luminal subtype. Multivariable analysis showed that *TP53* mutations were independent prognostic factors for recurrence.

TP53 mutations are driver mutations in various cancer types. *TP53* mutations are closely related to aggressive histologic features and poor survival in breast cancer [6-8]. Paired analysis of primary breast tumors and metastatic samples showed that *TP53* mutations were more commonly identified in metastatic samples [9,10]. However, it is unclear whether *TP53* mutations are predictive factors. *TP53* mutations were not predictive factors in a randomized controlled trial comparing taxane versus non-taxane neoadjuvant chemotherapy [11]. In hormone receptor-positive breast cancers, *TP53* mutations were associated with resistance to hormonal treatment [12,13]. Another study suggested that tamoxifen is effective against breast cancer with wild-type *TP53* [14]. There are no drugs available that target *TP53* mutations; however, such drugs are currently under investigation [15-17].

The most commonly mutated gene in our study was *PIK3CA*. *PIK3CA* mutations were commonly identified in the luminal A subtype and were associated with indolent histologic features in our cohort. However, we were unable to demonstrate their prognostic value. In contrast to early breast cancer, *PIK3CA* mutations are poor prognostic factors for advanced breast cancer [12,18]. Drugs that target the PI3K/Akt/mTOR pathway are available for treating metastatic breast cancer [18-20]. Notably, alpelisib is an oral PI3Kα inhibitor that has recently been approved for hormone receptor-positive, HER2-negative metastatic breast cancers.

Although various genetic alterations can be identified through targeted NGS, there is insufficient evidence to guide treatment through NGS. All patients in our study received standard treatments. Only two genetic alterations, *BRCA1* and *BRCA2* mutations, can guide the surgical treatment of breast cancer. Mutations in *BRCA1* or *BRCA2* can cause hereditary breast and ovarian cancer syndromes. For patients with pathogenic germline mutations of *BRCA1* or *BRCA2*, risk-reducing mastectomy may be recommended. We identified four (1.8%) *BRCA1* and nine (4.1%) *BRCA2* mutations. Among the three patients who underwent the germline *BRCA* test, two were confirmed to have germline *BRCA* mutations, and the other

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patient was confirmed to have a somatic mutation (**Supplementary Table 3**). The results of this study are consistent with those of a previous study that demonstrated that approximately one-third of *BRCA* mutations are of somatic origin [21]. Genetic counseling should be performed before initiating targeted NGS, and germline testing should be performed for all patients with *BRCA* mutations.

Some of the identified mutations have been associated with treatment resistance. We identified a patient with an *ESR1* (p.Y537C) mutation located in the ligand-binding domain of ESR1 [22]. *ESR1* mutations have rarely been identified in treatment-naïve breast cancers. In metastatic cohorts, *ESR1* mutations have been identified in up to 25% of cases [12,23,24]. Activating mutations in *HER2* can be identified by NGS. *HER2* mutations are not detectable by immunohistochemistry and are resistant to trastuzumab [25,26]. In our cohort, there were five cases of *HER2* mutations. One case was a pleomorphic lobular carcinoma for which the pan-HER inhibitor neratinib could be applied [26].

Our study had several limitations. We only included patients with primary operable breast cancer for whom investigational drugs were not applicable. Due to the short observation period, we could not observe any late recurrences. Long-term follow-up is required to observe the recurrence of ER-positive breast cancer. Because our gene panel included only 50 genes, some important genetic alterations could not be identified. Despite these limitations, we demonstrated that *TP53* mutations identified using targeted NGS can serve as independent prognostic markers for primary operable breast cancer. This study provides valuable real-world data on the genomic profiles of breast cancer in Korea.

In conclusion, targeted NGS can be used to identify genetic alterations that may serve as prognostic factors for primary operable breast cancer. Knowledge of the *TP53* mutational status is valuable for the precise management of breast cancer and for designing clinical trials. Although there are no clinically available drugs that target *TP53* mutations, such drugs are currently being investigated.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Adjuvant chemotherapeutic regimens recommended by the clinicians

Click here to view

Supplementary Table 2
Factors associated with the short-term DFS

Click here to view

Supplementary Table 3
Clinical characteristics of the patients with *BRCA* mutations

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Supplementary Figure 1

Flow diagram of the study design.

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Supplementary Figure 2

Kaplan-Meier survival analysis of the patients with mutations other than *TP53*. There are no significant differences in (A) *PIK3CA* mutations (n = 97), (B) *AKT1* mutations (n = 23), (C) *GATA3* mutations (n = 20), (D) *PTEN* mutations (n = 15), (E) *CDH1* mutations (n = 11), and *BRCA2* mutations (n = 9).

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