Research Square

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Prevalence and Predictors of Additional Variants Identified by Whole- Genome Sequencing in BRCA1/2 Mutation-Negative Breast Cancer Patients

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Abstract

Background:

The aim of this study was to evaluate the prevalence and clinical significance of non-BRCA germline pathogenic variants (PVs) or likely pathogenic variants (LPVs) identified by whole-genome sequencing (WGS) in Korean BRCA1/2 mutation-negative breast cancer patients.

Methods:

A total of 871 BRCA1/2 mutation-negative breast cancer patients underwent WGS between May 2020 and December 2022. The frequency of PVs or LPVs was analyzed, and clinicopathologic characteristics, treatment patterns, and oncologic outcomes were compared between variant-detected and non-detected groups.

Results:

In 43 of 871 patients (4.9%), at least one PV or LPV was identified across 16 genes, with PALB2 and ATM being most frequently detected. Detected variants were significantly associated with advanced tumor stage, younger age, premenopausal status, and higher rates of neoadjuvant chemotherapy. Patients aged ≤ 40 years with ≥ 2 affected family members showed a detection rate of 20.0% (OR = 5.10, p = 0.034). Distinct genotype-phenotype correlations were identified, with PALB2, BARD1, and MSH2 variants linked to triple-negative breast cancer and TP53 mutations to HER2-positive disease.

Conclusions:

WGS identified clinically significant non-BRCA germline variants in 4.9% of BRCA1/2-negative breast cancer patients, with distinct genotype-phenotype correlations and significant associations with adverse clinicopathologic features. These findings support the integration of WGS into hereditary breast cancer risk assessment, particularly in patients with early-onset disease or strong family history, where conventional panel testing may fail to capture the full spectrum of germline risk.

Background

Genetic testing for breast cancer susceptibility is now widely practiced. However, there has been growing concern over the potential role of germline pathogenic variants associated with hereditary breast cancer and other malignancies, such as ovarian cancer. As the diagnosis of genetic disorders becomes more common, the shift from group-centered treatment to personalized treatment and preventive care has become a critical point in precision medicine services.

The evaluation of breast cancer risk, particularly with germline pathogenic variants beyond the *BRCA1/2* mutations, is essential. Some multicenter retrospective studies have provided estimates of breast cancer risk associated with these variants. Identifying breast cancer susceptibility genes and recognizing the significantly elevated breast cancer risks in individuals carrying pathogenic variants (PVs) or likely pathogenic variants (LPVs) have become crucial for clinical practice.

Many studies have used hereditary breast cancer multigene panels to assess the risk of breast cancer associated with germline variants[1–5]. One large study demonstrated that after excluding *BRCA1*, *BRCA2*, and syndromic breast cancer genes (*CDH1*, *PTEN*, and *TP53*), genes such as *ATM*, *BARD1*, *CHEK2*, *PALB2*, and *RAD51D* were associated with high or moderate increases in breast cancer risk. On the other hand, variants in genes such as *BRIP1*, *RAD51C*, *MRE11A*, *RAD50*, *MLH1*, *NF1* were not associated with increased breast cancer risk. These findings, when combined, have helped shape current guidelines for estimating breast cancer risk based on genetic testing results[2, 6–8][2, 6–8]. Approximately 10% of breast cancer patients are found to have germline (L)PVs. As studies continue to reveal the prevalence and clinical impact of (L)PVs, demonstrating their significant influence on surgical and systemic treatment decisions, there is a growing need for further research to reinforce the importance of genetic testing and clarify the clinical significance of these variants [9].

For more precise clinical data, it is essential to consider subtype-specific risks. An analysis of 34 putative susceptibility genes in breast cancer patients and controls showed that *ATM* and *CHEK2* mutations with protein-truncating variants were more strongly associated with estrogen receptor (ER)-positive disease, while *BARD1*, *PALB2*, *RAD51C*, and *RAD51D* mutations were more frequently linked to ER-negative disease[1, 10–14].

In this study, even *BRCA1/2* mutation-negative breast cancer patients underwent whole-genome sequencing (WGS) rather than conventional multigene panel testing, enabling unbiased detection of variants across both coding and non-coding regions. Although previous studies have reported the prevalence and gene spectrum of non-BRCA pathogenic variants in BRCA1/2-negative breast cancer patients, a comprehensive comparison of clinicopathologic characteristics, treatment patterns, and oncologic outcomes between variant-detected and non-detected groups has not been performed[15, 16]. Furthermore, no prior study has utilized WGS in this clinical context, which allows unbiased detection of variants across both coding and non-coding regions beyond the constraints of predefined gene panels. The present study aims to address this gap by providing a comprehensive clinical and genomic characterization of BRCA1/2-negative breast cancer patients using WGS.

Methods

This study was performed under the National Project of Bio Big Data in South Korea and was approved by the Institutional Review Board of the Samsung Medical Center, Seoul, South Korea (IRB No.: SMC 2020–10–042).

Whole genome sequencing (WGS)

One microgram of genomic DNA was isolated from whole blood specimens. A WGS library preparation was constructed using a TruSeq DNA PCR-Free Library Preparation Kit (Illumina, San Diego, CA, USA) in accordance with the manufacturer's instructions. WGS was performed using NovaSeq6000 platform (Illumina) with paired-end reads of 150 bp, in accordance with the manufacturer's instructions. The samples were sequenced with a mean depth of ≥ 30×, with more than 97% showing a coverage of ≥ 10×. The bioinformatics process was as previously described[17]. Sequence reads were mapped and aligned to the human reference genome (hg38). The HaplotypeCaller of the Genome Analysis Toolkit, version 4.2.6.1 was used for variant calling[18]. Parliament2 was used to call structural variants (SVs) and copy number variants (CNVs)[19]. Variants were annotated using the ANNOVAR software and AnnotSV [20, 21]. For in-silico prediction, rare exome variant ensemble learnerand SpliceAI were used for missense and intronic/synonymous variants[22, 23]. Variants presumed to be false positives were excluded from the analysis, such as those with i) alternative depth ≤ 5, ii) variant allele frequency < 0.1, or iii) genotype quality < 10. Common variants with the minor allele frequency ≥ 0.05 were filtered out using the Genome Aggregation Database (gnomAD, https://gnomad.broadinstitute.org/) and the Korean Reference Genome Database (KRGDB)[24]. During the SV analysis, CNVs smaller than 30 bp and larger than 1.5 Mb were excluded for the interpretation.

For prioritization of variants, both genotype-driven and phenotype-driven approaches were performed[25]. Genotype-driven analyses included prioritization of previously reported disease-causing variants using ClinVar and Human Gene Mutation Database, predicted loss-of-function (pLOF) variants (e.g. nonsense, frameshift, and essential splice sites), variants compatible with inheritance pattern (e.g. de novo variants for dominant disorders or biallelic variants for recessive disorders) and SpliceAI score ≥ 0.2. For phenotype-driven approach, we constructed a virtual panel consisted of 78 genes (Supplementary Table S1) using panelAPP database (https://panelapp.genomicsengland.co.uk/panels) and Human Phenotype Ontology database (https://hpo.jax.org/app). Variants from candidate gene lists were classified according to the 2015 American College of Medical Genetics (ACMG)/Association for Molecular Pathology variant interpretation guidelines and the ClinGen Sequence Variant Interpretation Recommendations[26, 27]. The strength of evidence for PVS1 was in accordance with recommendations by Tayoun et al[28]. CNVs were prioritized containing coding regions with OMIM morbid genes. During the analysis, CNVs smaller than 30 bp and larger than 1.5 Mb were excluded for the interpretation. Candidate CNVs were classified according to the ACMG/ClinGen guideline for CMA interpretation[29].

Patient selection

BRCA1/2 gene testing is supported by National Health Insurance in Korea if the patient has a risk of hereditary breast and ovarian cancer. Patients with a family history of breast cancer, those diagnosed with breast cancer before the age of 40, or those who developed triple-negative breast cancer (TNBC) before the age of 60 were considered to have a high likelihood of hereditary breast cancer and

underwent *BRCA1/2* sequencing tests. The patients who were strong suspicion of genetic breast disease, but with *BRCA1/2*-negative in sequencing test were enrolled in WGS Pilot Study conducted between May 2020 and December 2021, as part of National Project of Bio Big Data (www.cirn.re.kr). A total of 890 *BRCA1/2* sequencing negative breast cancer patients in the construction were received WGS. *BRCA1/2* sequencing negative patients was supposed to have the results with PV or LPV not detected in sequencing tests. Patients who were not applicable with clinical diagnosis and who had insufficient medical records were excluded. Finally, a total of 871 patients were analyzed focused on the occurrence of pathogenic and likely pathogenic variants in WGS (Supplementary Figure S1).

Statistics

The chi-square test and Fisher's exact test were used to statistically analyze differences in clinicopathological characteristics, treatment patterns, and oncologic outcomes between the variant-detected and non-detected groups. Logistic regression was used to calculate odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was defined as $p < 0.05$. To formally evaluate the interaction between age at diagnosis and family history on variant detection, a logistic regression model including an age-by-family history interaction term was fitted. All statistical analyses were executed using R (version 4.5.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 871 *BRCA1/2*-negative patients were identified as having undergone WGS. Among the cohort, 43 patients (4.9%) were found to harbor a PV or LPV based on WGS results (Table 1).

PV/LPV detection genes

Figure 1 illustrates the distribution of Pathogenic Variants (PV) or Likely Pathogenic Variants (LPV) identified across various genes based on WGS results. Excluding *BRCA1* and *BRCA2*, the detection rate was highest in the *PALB2* gene at 20.9% (9/43), followed by *ATM* at 16.3% (7/43) and *TP53* at 7.0% (3/43). Other identified variants included *MSH2*, *PTEN*, *SDHC*, *MSH6*, and *BARD1* (each at 4.7%), as well as *NF1*, *MLH1*, *RAD51C*, *APC*, *CHEK2*, and *RAD51D* (each at 2.3%).

The distribution of breast cancer intrinsic subtypes associated with these genetic variants is presented in Supplementary Figure S2. In the overall PV carriers group (n = 43), the HR+ HER2 negative subtype was the most prevalent at 60.5%, followed by TNBC at 23.3% and HER2 positive at 14.0%. Subtype distribution varied notably by individual gene; specifically, *PALB2* carriers exhibited a higher proportion of TNBC (33.3%) compared to the overall carrier group, whereas *ATM* carriers were predominantly associated with the HR+ HER2 negative subtype at 85.7%.

Supplementary Table S1 summarizes the clinicopathologic characteristics associated with each detected gene, revealing distinct patterns of receptor expression among different genotypes.

Immunohistochemistry (IHC) profiles indicated that variants in *BRCA1* (40.0%), *BARD1* (100.0%), and *MSH2* (100.0%) were predominantly associated with ER negative tumors. In contrast, *ATM* and *PTEN* variants were exclusively or highly associated with ER positive disease, at 85.7% and 100.0%, respectively, as were *BRCA2* and *MSH6*, which both showed 100.0% positivity.

Progesterone receptor (PR) expression followed a similar trend, where *BARD1* and *MSH2* variants were linked entirely to PR negative status at 100.0%, while *ATM* (71.4%) and *TP53* (66.7%) showed a higher frequency of PR positive tumors. Regarding HER2 status, most pathogenic variants were identified in HER2 negative tumors, including 80.0% of *BRCA1* and 77.8% of *PALB2* cases. However, *TP53* (33.3%), *MSH2* (50.0%), and *MSH6* (50.0%) variants exhibited relatively higher rates of HER2 positive expression compared to other genes.

Patient Demographics – clinicopathologic characteristics.

The demographic and clinical characteristics of these patients are summarized in Table 1. The median follow-up duration was 45.0 months (interquartile range [IQR], 28.0–70.0 months), and the median age at diagnosis was 46 years (range, 20–73 years). The mean age of patients with detected variants was significantly lower than that of patients without detected variants ($p = 0.025$). When examining the association between family history and WGS detection results, family history was categorized as having a single affected family member, two or more affected family members, or unknown family history. In the detected group, 9 patients (20.9%) had a family history of two or more affected members, compared to 72 patients (8.7%) in the non-detected group. It revealed a statistically significant association between a number of family history and WGS results ($p = 0.011$). These findings suggest that patients with a family history of two or more relatives affected by breast or ovarian cancer are more likely to have pathogenic variants detected through WGS. To further illustrate the combined effect of age and family history on variant detection, subgroup analysis was performed stratifying patients by age (≤ 40 vs. >40 years) and family history (≥ 2 affected members vs. others). As shown in Fig. 2, the highest detection rate of 20.0% was observed in patients aged ≤ 40 years with a family history of two or more affected relatives ($n = 15$), compared to 3.3% in patients aged > 40 years without a significant family history ($n = 512$). This difference was statistically significant (OR = 5.10, $p = 0.034$), suggesting that young age at diagnosis and multiple affected family members may independently contribute to the likelihood of detecting pathogenic variants through WGS. However, formal logistic regression incorporating an age-by-family history interaction term did not demonstrate a statistically significant interaction effect (OR = 1.32, $p = 0.745$), indicating that the elevated detection rate in this subgroup likely reflects the additive contributions of each factor rather than a synergistic interaction, and should be interpreted with caution given the limited sample size ($n = 15$). Additionally, WGS detection status was significantly associated with cancer stage and menopausal status. The variant-detected group had a higher proportion of patients with advanced-stage disease ($p < 0.001$). Premenopausal status was also significantly more common in patients with detected variants ($p = 0.029$). In contrast, WGS detection was not significantly associated with breast cancer subtypes as defined by IHC profiles.

Patient Demographics – Treatment

Treatment comparisons between groups are presented in Table 2. The proportion of patients who received neoadjuvant chemotherapy was significantly higher in those with detected PV or LPV compared to those without detected variants on WGS (48.8% vs. 23.4%, $p < 0.001$). Although not statistically significant, patients in the variant-detected group were less likely to receive adjuvant chemotherapy (18.6% vs. 35.9%, $p = 0.066$).

There were no significant differences in the types of breast or axillary surgeries performed between the two groups. However, a numerically higher proportion of patients in the detected group underwent axillary lymph node dissection (32.6% vs. 18.7%, $p = 0.097$).

Oncologic outcomes

The comparison of oncologic outcomes is presented in Table 3. The recurrence rate was higher in patients with PV or LPV detected by WGS (14.0%) compared to those without detected variants (7.5%), although this difference did not reach statistical significance ($p = 0.138$). Similarly, the incidence of metachronous contralateral breast cancer was higher in the detected group (9.3%) than in the non-detected group (4.2%), but this difference was also not statistically significant ($p = 0.120$). Rates of local recurrence, distant metastasis, and mortality were comparable between the two groups, with no statistically meaningful differences observed. Notably, there were no deaths among patients in the PV or LPV-detected group during the follow-up period, whereas three deaths (0.4%) occurred in the non-detected group ($p = 1.000$).

Discussion

In this study, WGS was performed on 871 *BRCA1/2* mutation-negative breast cancer patients, identifying PV or LPV in 43 patients (4.9%), with *PALB2*, *ATM*, and *TP53* being most frequently detected. The variant-detected group showed significantly younger age at diagnosis ($p = 0.025$), higher rates of advanced-stage disease ($p < 0.001$), greater proportions of premenopausal patients ($p = 0.029$), and higher neoadjuvant chemotherapy rates (48.8% vs. 23.4%, $p < 0.001$). These findings suggest that non-*BRCA* pathogenic variants may drive more aggressive tumor phenotypes. The intensive preoperative treatment in the detected group may reflect this aggressive presentation, and could potentially mitigate worse oncologic outcomes, consistent with the numerically higher but non-significant recurrence rate (14.0% vs. 7.5%, $p = 0.138$) and contralateral breast cancer rate (9.3% vs. 4.2%, $p = 0.120$) observed.

The Korean Hereditary Breast Cancer (KOHBRA) study emphasized individualized genetic testing criteria for Korean patients but did not include non-*BRCA* genes [30–32]. Our study addresses this gap using WGS, which, unlike conventional multigene panels constrained by predefined gene sets and coding regions, enables unbiased genome-wide detection of single nucleotide variants, insertions/deletions, structural variants, and copy number variants across both coding and non-coding regions. This

advantage was directly demonstrated in our cohort: among six patients previously negative for *BRCA1/2* mutations, WGS identified three involving exon deletions — a class of variant typically missed by conventional sequencing approaches. Furthermore, a Korean study of 700 *BRCA1/2*-negative patients using multigene panel testing found PV/LPV in 10.9%, with 7.4% in clinically actionable genes [16], suggesting that the slightly lower detection rate in our cohort (4.9%) may reflect the more conservative variant classification inherent to WGS-based analysis, rather than lower sensitivity.

Specific germline mutations were associated with distinct IHC subtypes, with important clinical implications. Variants in *BRCA1*, *PALB2*, *TP53*, *BARD1*, *MSH2*, *MLH1*, *RAD51C*, and *RAD51D* predominated in ER-negative tumors, consistent with their known association with TNBC [1, 4, 33–36], while *ATM* and *CHEK2* mutations were more frequent in ER-positive tumors. Notably, *PALB2* carriers exhibited a high rate of TNBC (33.3%), and *BARD1* and *MSH2* carriers were exclusively ER-negative. In contrast, *TP53* carriers showed 33.3% HER2 positivity, aligning with evidence linking *TP53* mutations to HER2 amplification. These genotype-phenotype correlations have direct clinical relevance: patients with TNBC or HER2-positive disease and strong hereditary risk features should be considered for WGS-based genetic testing, as their underlying germline variants may influence both treatment decisions and long-term surveillance strategies.

Compared with major international studies (Supplementary Table S2), which predominantly employed predefined multigene panels and reported non-*BRCA* PV/LPV detection rates ranging from 2.89% to 10.9%, our WGS-based approach identified variants in 4.9% of patients. While the detection rate is comparable, our approach offers several key advantages over panel-based testing: first, WGS is not limited by a predefined gene set and can detect variants in any cancer susceptibility gene; second, it captures both coding and non-coding regions, including intronic splice-site alterations and structural variants that remain invisible to targeted panels; and third, it simultaneously enables assessment of homologous recombination deficiency and other genomic instability signatures. These advantages are particularly relevant in the context of precision oncology, where comprehensive germline information can guide not only surgical decisions but also systemic therapy selection. Furthermore, patients aged ≤ 40 years with ≥ 2 affected family members showed a markedly higher detection rate of 20.0% (OR = 5.10, p = 0.034), identifying a high-yield subgroup where WGS testing is most clinically warranted.

This study has several limitations. The relatively small size of the variant-detected subgroup (n = 43) limits gene-specific subgroup analyses, and the difference in follow-up duration between groups (64.6 ± 59.5 months in the detected group vs. 55.4 ± 40.4 months in the non-detected group) may not fully capture long-term oncologic outcomes. Future prospective studies with larger cohorts and standardized follow-up are warranted to validate these findings and further define the clinical utility of WGS in hereditary breast cancer risk assessment.

Conclusion

In conclusion, our study demonstrates that WGS, by enabling unbiased detection of pathogenic variants across both coding and non-coding regions beyond the constraints of predefined panels, identified clinically significant non-BRCA germline variants in 4.9% of BRCA1/2-negative breast cancer patients. These variants were significantly associated with advanced tumor stage, younger age at diagnosis, premenopausal status, and strong family history, and were accompanied by distinct genotype-phenotype correlations: PALB2, BARD1, and MSH2 variants were predominantly linked to triple-negative breast cancer, while TP53 mutations were associated with HER2-positive disease. Collectively, these findings support the clinical integration of WGS as a first-line germline testing strategy, particularly in patients with early-onset disease, advanced-stage tumors, or multiple affected family members, where conventional panel testing may inadequately capture the full spectrum of hereditary risk.

Abbreviations

WGS
whole-genome sequencing
PV
pathogenic variant
LPV
likely pathogenic variant
IRB
institutional review board
OR
odds ratio
CI
confidence interval
IQR
interquartile range
ACMG
American College of Medical Genetics
CNV
copy number variant
SV
structural variant
gnomAD
Genome Aggregation Database
KRGDB
Korean Reference Genome Database
ER
estrogen receptor
PR

progesterone receptor
HER2
human epidermal growth factor receptor 2
TNBC
triple-negative breast cancer
IHC
immunohistochemistry
ILC
invasive lobular carcinoma
IDC
invasive ductal carcinoma
DCIS
ductal carcinoma in situ
NAC
neoadjuvant chemotherapy
CTx
chemotherapy
BCS
breast conserving surgery
TM
total mastectomy
SLNB
sentinel lymph node biopsy
ALND
axillary lymph node dissection
BC
breast cancer.

Declarations

Competing Interests

JMR received research funding from AstraZeneca, Hanlim, Medtronic, BARD, and DCGen, outside the submitted work. All other authors declare no competing interests.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Samsung Medical Center, Seoul, South Korea (IRB No.: SMC 2020-10-042).

Informed consent was obtained from all participants as part of the National Project of Bio Big Data in South Korea.

Consent for Publication

Not applicable. This manuscript does not include any individual person's data in any form (e.g., individual images, videos, or identifiable case details).

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Author Contribution

J.M.R. and J.W.K. conceived and designed the study. Y.K. performed the overall data analysis and interpretation and wrote the manuscript. C.H. and J.W.K. performed whole-genome sequencing and genomic/bioinformatic analysis. M.K.K., W.K.P., S.K.L., B.J.C., J.Y., J.E.L., S.W.K., and S.J.N. contributed to patient recruitment, clinical data collection, and sample acquisition. J.M.R. supervised the overall study as the corresponding author, and J.W.K. supervised the genomic analysis as the corresponding author for the laboratory medicine component. All authors reviewed, critically revised, and approved the final manuscript.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request, subject to institutional review board approval.

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Tables

Table 1. Patient demographics - clinicopathologic characteristics

Characteristics	detected	not detected	total	p-value
	(n = 43, 4.9%)	(n = 828, 95.1%)	(n = 871)	
Follow-up duration	64.6 ± 59.5	55.4 ± 40.4	55.9 ± 41.5	0.327
Age, mean	42.7 ± 8.0	46.0 ± 9.3	45.8 ± 9.3	0.025
Age				0.071
≤ 40yrs	20 (46.5%)	273 (33.0%)	293 (33.6%)	
> 40yrs	23 (53.5%)	555 (67.0%)	578 (66.4%)	
Family History				0.011
1 family member	11 (25.6%)	338 (40.8%)	349 (40.1%)	
≥ 2 family member	9 (20.9%)	72 (8.7%)	81 (9.3%)	
no	23 (53.5%)	418 (50.5%)	441 (50.6%)	
Histopathology				0.899
IDC	35 (82.4%)	643 (77.7%)	678 (77.8%)	
ILC	1 (2.3%)	36 (4.3%)	37 (4.2%)	
DCIS	4 (9.3%)	92 (11.1%)	96 (11.0%)	
others	3 (7.0%)	57 (6.9%)	60 (6.9%)	
Location				0.189
unilateral	36 (83.7%)	753 (90.9%)	789 (90.6%)	
bilateral	7 (16.3%)	75 (9.1%)	82 (9.4%)	
Stage				< 0.001
0- II	18 (41.9%)	597 (72.1%)	615 (70.6%)	
III- IV	4 (9.3%)	36 (4.3%)	40 (4.6%)	
yp	21 (48.8%)	190 (22.9%)	211 (24.2%)	
unknown	0 (0.0%)	5(0.6%)	5 (0.6%)	
menopausal status				0.029
post-	7 (16.3%)	252 (30.4%)	259 (29.7%)	
pre-	35 (81.4%)	573 (69.2%)	608 (69.8%)	

Abbreviation: ILC, invasive lobular carcinoma; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TNBC; triple negative breast cancer.

Characteristics	detected	not detected	total	p-value
	(n = 43, 4.9%)	(n = 828, 95.1%)	(n = 871)	
unknown	1 (2.3%)	3 (0.4%)	4 (0.5%)	
Nuclear grade				0.357
low	1 (2.3%)	75 (9.1%)	76 (8.7%)	
intermediate	26 (60.5%)	427 (51.6%)	453 (52.0%)	
high	13 (30.2%)	284 (34.3%)	297 (34.1%)	
unknown	3 (7.0%)	42 (5.1%)	45 (5.2%)	
ER				0.144
positive	28 (65.1%)	589 (71.1%)	617 (70.8%)	
negative	14 (32.6%)	236 (28.5%)	250 (28.7%)	
unknown	1 (2.3%)	3 (0.4%)	4 (0.5%)	
PR				0.132
positive	25 (58.1%)	540 (65.2%)	565 (64.9%)	
negative	17 (39.5%)	285 (34.4%)	302 (34.7%)	
unknown	1 (2.3%)	3 (0.4%)	4 (0.5%)	
HER2				0.132
positive	6 (14.0%)	143 (17.3%)	149 (17.1%)	
negative	32 (74.4%)	649 (78.4%)	681 (78.2%)	
SISH equivocal	0 (0.0%)	2 (0.2%)	2 (0.2%)	
unknown	5 (11.6%)	34 (4.1%)	39 (4.5%)	
Ki-67				0.125
≤ 20.0%	17 (39.5%)	363 (43.8%)	380 (43.6%)	
> 20.0%	19 (44.2%)	402 (48.6%)	421 (48.3%)	
unknown	7 (16.3%)	63 (7.6%)	70 (8.0%)	
subtype				0.715
luminal A	27 (62.8%)	509 (64.5%)	536 (61.5%)	

Abbreviation: ILC, invasive lobular carcinoma; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TNBC; triple negative breast cancer.

Characteristics	detected	not detected	total	p-value
	(n = 43, 4.9%)	(n = 828, 95.1%)	(n = 871)	
luminal B	2 (4.7%)	88 (10.6%)	90 (10.3%)	
HER2	4 (9.3%)	60 (7.2%)	64 (7.3%)	
TNBC	9 (20.9%)	161 (19.4%)	170 (19.5%)	
unknown	1 (2.3%)	10 (1.2%)	11 (1.3%)	

Abbreviation: ILC, invasive lobular carcinoma; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TNBC; triple negative breast cancer.

Table 2
Patient demographics – Treatment

Characteristics	detected	not detected	total	p-value
	(n = 43, 4.9%)	(n = 828, 95.1%)	(n = 871)	
NAC				< 0.001
yes	21 (48.8%)	194 (23.4%)	215 (24.7%)	
no	22 (51.2%)	634 (76.6%)	656 (75.3%)	
adjuvant CTx				0.066
yes	8 (18.6%)	297 (35.9%)	305 (35.0%)	
no	35 (81.4%)	530 (64.0%)	565 (64.9%)	
unknown	0 (0.0%)	1 (0.1%)	1 (0.1%)	
Breast surgery				0.511
BCS	24 (55.8%)	517 (62.4%)	541 (62.1%)	
TM	19 (44.2%)	303 (36.6%)	322 (37.0%)	
unknown	0 (0.0%)	8 (1.0%)	8 (0.9%)	
Axillary surgery				0.097
SLNB	28 (65.1%)	602 (72.7%)	630 (72.3%)	
ALND	14 (32.6%)	155 (18.7%)	169 (19.4%)	
no axillary surgery	1 (2.3%)	64 (7.7%)	65 (7.5%)	
unknown	0 (0.0%)	7 (0.8%)	7 (0.8%)	

Abbreviation: NAC, neoadjuvant chemotherapy; CTx, chemotherapy; BCS, breast conserving surgery; TM, total mastectomy; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

Table 3
Oncologic Outcomes

Characteristics	detected (n = 43, 4.9%)	not detected (n = 828, 95.1%)	total (n = 871)	p-value
Recurrence				0.138
yes	6 (14.0%)	62 (7.5%)	68 (7.8%)	
no	37 (86.0%)	766 (92.5%)	803 (92.2%)	
Local Recurrence				1.000
yes	1 (2.3%)	23 (2.8%)	24 (2.8%)	
no	42 (97.7%)	805 (97.2%)	847 (97.2%)	
Metachronous contralateral BC				0.120
yes	4 (9.3%)	35 (4.2%)	39 (4.5%)	
no	39 (90.7%)	793 (95.8%)	832 (95.5%)	
Distant Metastasis				0.429
yes	1 (2.3%)	10 (1.2%)	11 (1.3%)	
no	42 (97.7%)	818 (98.8%)	860 (98.7%)	
Expire				1.000
yes	0 (0.0%)	3 (0.4%)	3 (0.3%)	
no	43 (100.0%)	825 (99.6%)	868 (99.7%)	
Abbreviation: BC, Breast Cancer				

Figures

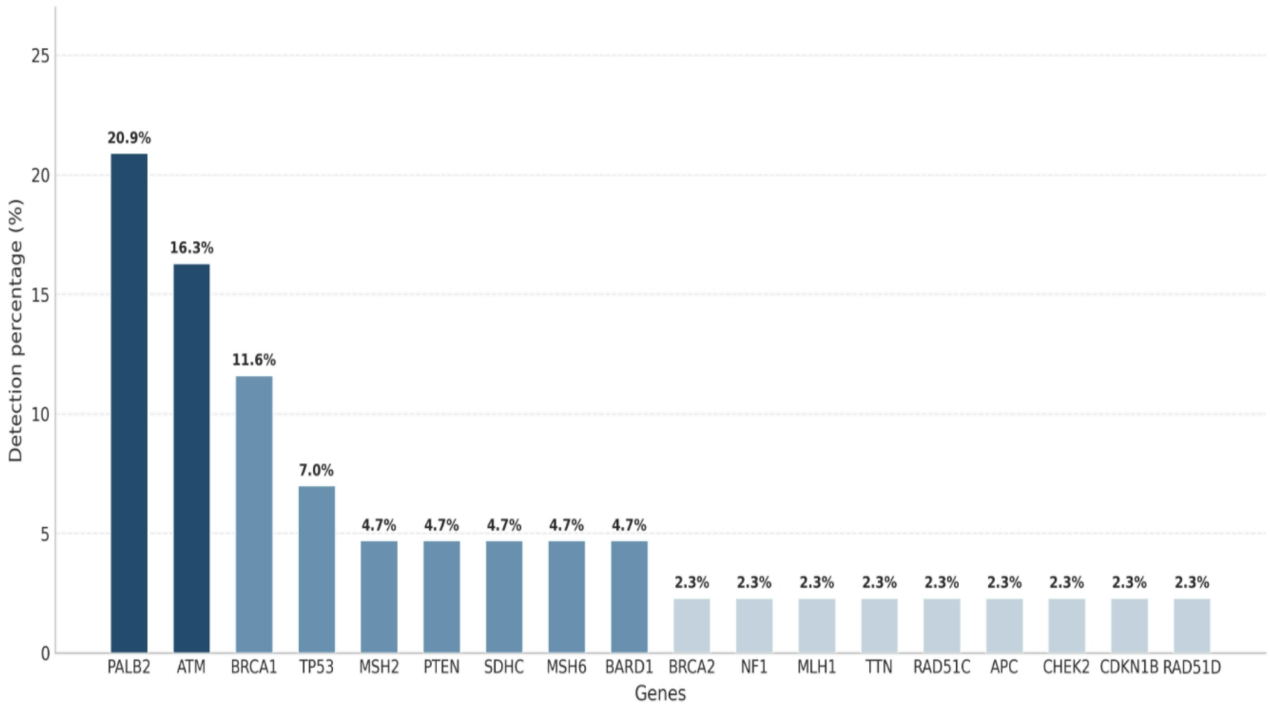


Figure 1

Distribution of pathogenic or likely pathogenic variants genes

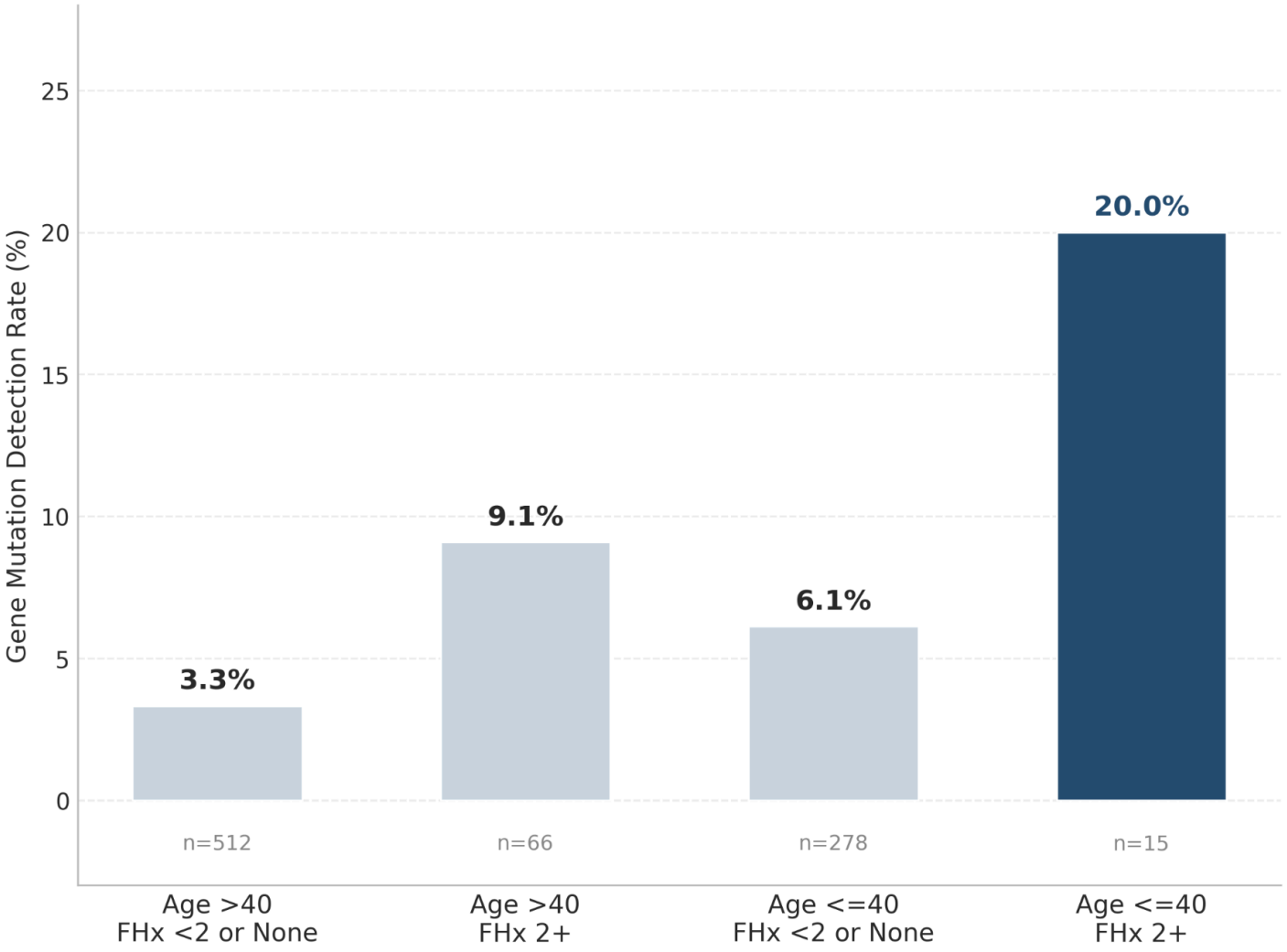


Figure 2

Detection Rate by Age and Family History Group. This subgroup analysis is exploratory in nature; formal testing of the age-by-family history interaction term did not reach statistical significance (OR=1.32, p=0.745). FHx, family history..

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.docx