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Article

Landscape of Germline Pathogenic Variants in Luminal Breast Cancer from an Under-Represented Southeast Asian Populations

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Simple Summary

Luminal A and B breast cancers are usually considered to have better outcomes than other breast cancer subtypes, yet many patients still experience aggressive disease and recurrence that cannot be explained by tumor features alone. Inherited genetic changes passed down in families may play an important role in these differences, but data from Indonesian patients remain very limited. This study examined inherited genetic variants in women with luminal breast cancer treated at a national cancer center in Indonesia and explored how these variants relate to tumor characteristics and family history of cancer. A surprisingly high number of patients were found to carry clinically important inherited genetic alterations, particularly among those with mixed tumor histology and a family history of cancer. These findings highlight the need to integrate genetic testing into routine breast cancer care and may support the development of more precise risk assessment, surveillance, and treatment strategies in resource-limited settings.

Abstract

Germline pathogenic variants influence breast cancer risk and clinical behavior, yet data from Indonesian populations remain scarce. In this pilot cross-sectional study, 31 newly diagnosed Indonesian women with luminal A or luminal B breast cancer underwent germline testing using a 113-gene hereditary cancer panel, with variants classified according to ACMG criteria and correlated with clinicopathological features. Pathogenic or likely pathogenic variants were identified in 9 of 31 patients (29.0%), most frequently involving *BRCA2*, *PALB2*, and *RECQL4*. A significantly higher frequency of pathogenic/likely pathogenic variants was observed among patients with mixed invasive histology (3/3) compared with those with invasive carcinoma of no special type (6/27; $p = 0.019$), and a positive first-degree family history of breast cancer was also associated with pathogenic/likely pathogenic variant status ($p = 0.022$). This study provides the first description of germline pathogenic variants in Indonesian luminal breast cancer and suggests that mixed invasive histology and first-degree family cancer history may represent enrichment signals for hereditary predisposition, warranting validation in larger cohorts.

Keywords: germline mutation; luminal breast cancer; genetic profile; Indonesian population; DNA repair genes

1. Introduction

Breast cancer is still the most frequently diagnosed cancer in women around the world. In 2022, the Global Cancer Observatory (GLOBOCAN) reported more than two million new cases.[1] Among

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its molecular subtypes, luminal A and luminal B—defined by the presence of estrogen and/or progesterone receptor expression—comprise the majority of diagnoses and are traditionally associated with a more favorable biological and clinical profiles compared to their HER2-positive and triple-negative counterparts.[2,3] However, recent evidence highlights considerable heterogeneity in individuals with these subtypes as shown by variabilities in clinical presentations as well as histopathological architecture, suggesting underlying genomic alterations.[4]

This genomic alterations-derived variability is known to arise not only from somatic alterations but also from inherited germline variants, including pathogenic variants and variants of uncertain significance (VUS) in genes such as *BRCA1*, *BRCA2*, *PALB2*, and others involved in DNA repair pathways.[5] While tumors that carry pathogenic germline variants may phenotypically appear similar to the sporadic cases, they often differ in their molecular biology and clinical courses as they follow distinct molecular trajectories.[6,7] These distinctions are important because they can affect tumor behavior, inform the risk assessment, and steer treatment and surveillance strategies. This is especially true for patients with significant family histories or confirmed pathogenic germline variants.

Emerging evidence from research undertaken in East and Southeast Asia indicates marked heterogeneity in both the frequency and distribution of hereditary pathogenic variants among individuals with breast malignancies. A Japanese cohort reported that pathologic variants were found in 5.7% of cases overall, with the majority falling in the group of women aged before 40, at 15%. This rate significantly dropped to 3.2% in patients aged 80 and older. Moreover, *BRCA1* and *BRCA2* comprised about two-thirds of all pathogenic variants across various age groups. [8] In a Thai study, pathogenic germline variants were reported in 12.5% (8/64) of cases, comprising *BRCA1* (4.7%), *BRCA2* (6.3%), *ATM* (1.6%), and *PALB2* (1.6%), with one patient exhibiting concomitant variants in *BRCA2* and *ATM*.[9] Meanwhile, a Chinese study of 356 patients found deleterious germline variants in 21.6% of cases across a panel of 48 cancer-related genes, with *BRCA1/2* pathogenic variants accounting for the most (7.0%), followed by *RAD50* and *ATM* pathogenic variants at 1.4% each.[10]

Despite these associations being increasingly explored in East-Asian and Western populations, Indonesia remains underrepresented in germline variant profiling. The prevalence, spectrum, and clinical implications of pathogenic variants and VUS among Indonesian patients with luminal breast cancer subtypes remain largely unknown. This represents a significant barrier to implementing personalized cancer care, especially in a setting where stage at diagnosis remains advanced in most cases, and molecular testing is not routinely integrated into clinical workflows.

In this context, the present pilot study aimed to characterize the spectrum of germline variants detected by multigene panel testing in Indonesian women with luminal A and luminal B breast cancer, and to explore potential associations between pathogenic or likely pathogenic variants and baseline clinicopathological features. The findings are intended to provide hypothesis-generating data to inform larger validation studies and future development of tailored genetic risk assessment in this population.

2. Materials and Methods

This cross-sectional study was conducted at Dharmais National Cancer Center Hospital, Jakarta, Indonesia. Women aged ≥18 years with a recent diagnosis of luminal A or luminal B breast cancer were recruited. Subtyping was confirmed by immunohistochemical assessment performed at the same institution. Patients were eligible if they had not received any prior systemic therapy and did not have a diagnosis of primary cancer in any other organ. The diagnosis period spanned from January 2025 to May 2025.

Patients who consented to genetic testing underwent peripheral blood collection (5 mL) stored in EDTA-containing tubes. Genomic DNA was isolated from the buffy coat fraction using the QIAamp DNA Mini Kit (Qiagen, Germany), following the manufacturer's protocol. DNA quality and quantity were assessed spectrophotometrically to ensure suitability for downstream analysis.

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Samples that met quality thresholds were subjected to targeted sequencing using the TruSight Hereditary Cancer Panel (113 genes) (Illumina, USA).

Library preparation and target enrichment were carried out using the Illumina DNA Prep protocol. Sequencing was carried out using the Illumina NextSeq 550 platform. Primary sequencing data were processed through secondary and tertiary analyses using the DRAGEN Bio-IT Platform (Illumina), generating Variant Call Format (VCF) files. Variant annotation was conducted using the Variant Effect Predictor (VEP) tool from Ensembl. All identified variants were categorized according to the American College of Medical Genetics and Genomics (ACMG) standards based on clinical relevance.

Clinical and pathological data—including demographic characteristics, personal and family medical history (pedigree), hematological profiles, tumor stage at diagnosis, histopathological findings, and tumor grade—were collected via direct patient interviews and retrieved from the hospital's electronic medical record system.

2.1. Statistical Analysis

Statistical analyses were carried out using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). The characteristics of the cohort were summarized descriptively. Categorical data were reported as counts with corresponding percentages, while continuous data were summarized as mean values with their standard deviations. Bivariate analyses were performed to assess associations between germline variant status—categorized as "no finding or variant of uncertain significance (VUS)" versus "likely pathogenic or pathogenic"—and selected clinical and pathological variables. Pearson's Chi-Square test was applied for comparisons involving adequate sample sizes, while Fisher's exact test (two-sided) was used in cases with small expected cell counts. The clinical variables evaluated included age group (≤40 vs. >40 years), menopausal status, stage at diagnosis (early vs. advanced), molecular subtype, Ki67 proliferation index (<20% vs. ≥20%), histological type, histological grade, and first-degree relatives' history of breast cancer. Odds ratios (ORs) with 95% confidence intervals (CIs) were computed to assess the strength of associations. Statistical significance was defined as a p-value < 0.05.

3. Results

3.1. Patient Characteristics

Table 1 shows the demographic data of the total of 31 female patients with luminal-type breast cancer who were enrolled in this study. The mean age at diagnosis was 47.87 ± 9.52 years, with the majority (77.4%) aged over 40. Educational attainment was predominantly at the senior high school level or higher (80.6%). Most participants were multiparous (83.9%), and over half (54.8%) had a history of hormonal contraceptive use. Passive smoking exposure was reported by 22.6% of the patients.

Approximately two-thirds (64.5%) of the patients were premenopausal at the time of diagnosis. Obesity, based on Asia-Pacific BMI criteria, was common in 51.6% of cases. Notably, 74.2% of patients had advanced-stage disease (Stage IIIB or IV), highlighting a worrying delay in diagnosis.

With regard to molecular subtypes, 48.4% had Luminal B HER2-positive tumors, 35.5% had Luminal B HER2-negative, and 16.1% had Luminal A subtype. A high Ki67 index (≥20%), suggestive of elevated tumor proliferative activity, was seen in 80.6% of cases. The predominant histological type was invasive breast carcinoma of no special type (NST), accounting for 87.1% of cases. Mixed histological patterns were observed in 9.7% of patients. More than half of the tumors (58.1%) were poorly differentiated (grade III), reflecting a more aggressive phenotype.

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Table 1. Patient Characteristics (n = 31).

Variable	Mean (SD)	n (%)
Age (year)	47.87 (9.52)	
≤ 40		7 (22.6)
>40		24 (77.4)
Education level		
No education		2 (6.5)
Primary school		3 (9.7)
Middle school		1 (3.2)
Senior high school		16 (51.6)
Diploma and above		9 (29)
History of Cigarette Smoking		
No history		24 (77.4)
Passive smoker		7 (22.6)
Age of Menarche	13.23 (1.89)	
Menopausal Status when the symptoms emerged		
Pre-menopause		20 (64.5)
Menopause		11 (35.5)
Parity		
Nulliparity		1 (3.2)
Primiparity		4 (12.9)
Multiparity		26 (83.9)
History of hormonal contraception usage		
No		14 (45.2)
Yes		17 (54.8)
History of first-degree family member(s) with breast cancer		
No		29 (93.5)
Yes		2 (6.5)
History of first-degree family member(s) with ovarian cancer		
No		31 (100)
Yes		0 (0)
BMI (Asia-Pacific population)	25.18 (4.99)	
Underweight		2 (6.5)
Normoweight		10 (32.3)
Overweight		3 (9.7)
Obese		16 (51.6)
Stage at diagnosis		
I		1 (3.2)
II		5 (16.1)
IIIA		2 (6.5)
IIIB		8 (25.8)
IV		15 (48.4)
Subtype		
Luminal A		5 (16.1)
Luminal B, HER2-negative		11 (35.5)
Luminal B, HER2-positive		15 (48.4)
Ki67 index	36.87 (23.16)	
Low (<20)		6 (19.4)
High (≥20)		25 (80.6)

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Histological type		
Invasive Breast Carcinoma, NST		27 (87.1)
Lobular Invasive Carcinoma		1 (3.2)
Mixed Invasive Carcinoma		3 (9.7)
Histological grade		
Well differentiated (grade I)		1 (3.2)
Moderately differentiated (grade II)		12 (38.7)
Poorly differentiated (grade III)		18 (58.1)
Hemoglobin level at diagnosis (g/dL)	11.87 (1.39)	
Leukocyte count (x 10^3 cells/μL)	8.31 (2.92)	
Platelet count (x 10^3 cells/μL)	314.32 (88.93)	
Germline-variant finding		
No finding		4 (12.9)
Variant of Uncertain Significance (VUS)		18 (58.1)
Likely-pathogenic		3 (9.7)
Pathogenic		6 (19.4)

SD: Standard Deviation; BMI: Body Mass Index; NST: No Special Type.

3.2. Germline Variant Profiles

Germline variants were detected in 87.1% (27/31) of the patients (Table 2). Among these, 18 patients (58.1%) harbored variants of uncertain significance (VUS), while three (9.7%) and six (19.4%) carried likely pathogenic and pathogenic variants, respectively. The most frequently encountered genes across the entire variant spectrum were *BARD1*, *POLE*, and *RECQL4*.

Notably, among the VUS, *BARD1* variants were observed in five different patients (16.1%), *POLE* in four patients, and *RECQL4* in three patients. These variants are not currently annotated in either ClinVar or gnomAD, suggesting they may represent population-specific polymorphisms or previously uncharacterized variants with uncertain clinical relevance.

Pathogenic and likely pathogenic variants were identified in seven distinct genes: *BRCA2*, *PALB2*, *RECQL4*, *NF1*, *CDKN2A*, *ERCC3*, *SPINK1*, and *MUTYH*. *BRCA2* and *RECQL4* were the most recurrent among these. Several patients exhibited multiple germline alterations, including combinations of pathogenic and VUS variants, highlighting the genetic complexity of breast carcinogenesis in this study.

Table 2. Germline Variant Profiles of the Patients.

Patient's Code	Main Finding	Gene(s)	Nucleotide Change	Amino Acid Change	Other findings	
					Gene	Classification
BR01	VUS	MEN1				
BR02	VUS	DICER1, NF2				
BR03	Pathogenic	CDKN2A	c.159G>C	p.Met53Ile	BLM, MUTYH	VUS
BR04	VUS	BARD1, PDGFRA, TERT, XRCC2				
BR05	Likely-Pathogenic	ERCC3	c.1730del	p.Lys577AsnfsTer34	XPC	VUS
BR06	Pathogenic	BRCA2	c.262_263del	p.Leu88AlafsTer12	EPCAM	VUS
BR07	VUS	ATM, TERT				
BR08	VUS	PTCH1				
BR09	Likely-Pathogenic	RECQL4	c.2881del	p.His961Thrfs*83	FANCE	VUS
	Pathogenic	SPINK1	c.101A>G	p.Asn34Ser		
BR10	VUS	PALB2, SMARCA4				

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BR11	Likely-Pathogenic	RECQL4	c.1342C>T	p.Pro448Ser	BRCA2, RAD51	
BR12	No Finding					
BR13	VUS	KIF1B				
BR14	No Finding					
BR15	VUS	BRD10, POLE, TCHHL1				
BR16	VUS	KIF1B, POLE, RAD50				
BR17	No Finding					
BR18	VUS	BARD1, BRIP1, FANCI, HOXB13, POLE				
BR19	VUS	BARD1				
BR20	No Finding					
BR21	VUS	NTHL1				
BR22	VUS	FANCE, FANCI				
BR23	VUS	RECQL4				
BR24	Likely-Pathogenic	NF1	c.3817A>G	p.Thr1273Ala	CTAGE1, RB1	VUS
BR25	VUS	BARD1, MSH3				
BR26	Pathogenic	PALB2	c.1168dup	p.Ser390PhefsTer11	CTRC	VUS
BR27	Pathogenic	BRCA2	c.8639_8640del	p.Thr2880AsnfsTer26	BARD1, MSH3, SMARCA4	
BR28	VUS	SLX4				
BR29	VUS	TSC2, ATM, CHEK2, SDHA				
BR30	Pathogenic	MUTYH	c.383G>A	p.Trp128Ter		
BR31	VUS	RAD51D				

VUS: Variant of Uncertain Significance.

3.3. Association Between Germline Variants and Clinical Variables

Bivariate analysis (Table 3) revealed several clinically significant associations. A notable correlation was identified between the existence of pathogenic or likely pathogenic variants and a family record of breast cancer in relatives of the first degree ($p = 0.022$, Chi-square; $p = 0.077$, Fisher's exact), with an odds ratio of 15.0 (95% CI: 1.1–204.5).

Histological type was also significantly associated with variant classification ($p = 0.019$). All patients with mixed-type invasive carcinoma harbored pathogenic or likely pathogenic variants, compared to only 22.3% of those with NST histology. These findings suggest a possible connection between histological differences and underlying germline pathogenicity.

No significant associations were found between variant classification and age, menopausal status, tumor stage, molecular subtype, Ki67 index, or tumor grade (all $p > 0.05$).

Table 3. Bivariate Analysis of the Association Between Germline Variant Findings and Clinical Variables.

Variable	**Germline-Variant Finding**		**OR (95% CI)**	**p***	**p****
	No Finding and VUS (%)	**Likely- and Pathogenic (%)**			
Age					
Young age (≤ 40)	5 (71.4)	2 (28.6)	1.03 (0.16–6.62)	0.976	1.000
>40	17 (70.8)	7 (29.2)	ref		

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History of first-degree family member(s) with breast cancer					
No	22 (75.8)	7 (24.2)	ref		
Yes	0	2 (100)	15.0 (1.1–204.5)[1]	0.022	0.077
Stage at diagnosis					
Early stage (I-IIIA)	6 (75)	2 (25)	1.31 (0.21–8.18)	0.771	1.000
Advanced stage (IIIB-IV)	16 (69.5)	7 (30.5)	ref		
Subtype					
Luminal A	2 (40)	3 (60)	0.20 (0.03–1.49)	0.096	0.131
Luminal B	20 (76.9)	6 (23.1)	ref		
Ki67 index					
Low	3 (50)	3 (50)	0.32 (0.05–1.99)	0.208	0.320
High	19 (76)	6 (24)	ref		
Histological type					
Invasive Breast Carcinoma, NST	21 (77.7)	6 (22.3)	ref		
Lobular Invasive Carcinoma	1 (100)	0	1.10 (0.04–30.4)	0.019	0.019
Mixed Invasive Carcinoma	0	3 (100)	23.15 (1.05–506.3)		
Histopathological grade					
Well differentiated (grade I)	1 (100)	0	ref		
Moderately differentiated (grade II)	6 (50)	6 (50)	3.0 (0.10–89.4)	0.133	0.133
Poorly differentiated (grade III)	15 (83.3)	3 (16.7)	0.68 (0.02–20.5)		

*Pearson Chi-Square; **Fisher's exact test, 2-sided; [1] Odds ratio calculated using continuity correction due to a zero cell count. OR: Odds Ratio; CI: Confidence Intervals.

4. Discussion

This study contributes to the germline variant landscape of luminal subtype breast cancer in the underrepresented Indonesian population. Of the 31 patients included in this study, 87.1% of the subjects carried detectable variants, including those with pathogenic, likely-pathogenic, and VUS. This finding is disproportionately very high, compared to the similar study conducted by Biancolella et al. for the 51 subjects from Burkina Faso, showing that only 24% of the subjects carried pathogenic variants, VUS, and novel undescribed variants.[11] With 66,271 new cases per year reported with a mortality rate of 22,598 cases in Indonesia itself,[1] this should raise concern for more precise risk stratification in the target population when they first present to the healthcare facility, as it would benefit both the patients and clinicians in providing more comprehensive information, particularly regarding treatment strategies. As also noted by a previous British study, cancer genetics should be progressively integrated into the practice of general practitioners, breast surgeons, oncologists, and nurses with regard to ethical matters.[12]

A notable finding revealed a statistically significant association between histological type and variant status (p = 0.019), with all cases of mixed invasive carcinoma harboring likely pathogenic or pathogenic variants. This study emphasizes the necessity of incorporating genetic testing into clinical

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practice, serving as a fundamental element for future risk modeling and stratification in newly diagnosed patients, as well as a crucial instrument for informing treatment strategies, despite prior research indicating that mixed invasive carcinomas do not consistently exhibit a poorer biological profile compared to invasive carcinoma of no special type (NST).[13-15].

4.1. Pathogenic and Likely-Pathogenic Variants and Their Clinical Correlations

This study also highlights an important finding where 100% of the subjects with mixed invasive carcinoma subtype carry either pathological or likely-pathological variants, including *RECQL4*, *NF1*, and *MUTYH*–alongside additional VUS such as *BRCA2*, *RAD51*, *CTAGE1*, and *RB1*. These variants have been proven to play a role in the pathogenesis of breast cancer in several mechanisms, including dysfunction in homologous recombination (HR) and base excision repair (BER), as well as regulation failure in the RAS/MAPK signaling pathway. Previous clinical research showed that elevated *RECQL4* expression correlates with more aggressive cancer types[16], while breast tumors associated with *NF1* typically have a worse prognosis and are frequently expressing negativitiees for estrogen receptor (ER) and progesterone receptor (PR). Women with pathogenic *NF1* germline variants exhibit a markedly elevated risk of breast cancer—up to fivefold before to age 50, and roughly 3.5 times higher overall.[17] Tumors in individuals with a monoallelic *MUTYH* pathogenic germline variants exhibited significantly larger sizes, higher histologic grades, and more high-risk biomarker characteristics (including HER2-positivity and triple-negative subtype) compared to breast cancer patients with other susceptibility genes, excluding *BRCA1*.[18]

Genetic alterations and copy number gains of the *RECQL4* gene—which encodes a helicase essential for DNA replication and repair—have been linked to breast cancer through several oncogenic mechanisms. *RECQL4* plays a key role in homologous recombination (HR) and base excision repair (BER), and its dysfunction compromises the repair of double-strand breaks and oxidative DNA damage. A missense germline variant, such as the Proline-to-Serine substitution at position 448 identified in this study, may disrupt the structural integrity of the helicase domain or hinder its interaction with other DNA repair proteins. This alteration contributes to genomic instability and an elevated mutation burden. In addition to point mutations, some breast tumors exhibit *RECQL4* copy number gains and overexpression. This dysregulation promotes accelerated S-phase progression, promotes DNA replication, and drives uncontrolled cell proliferation by upregulating genes involved in the cell cycle and mitosis.[19,20] Moreover, *RECQL4* dysregulation affects hormone receptor–positive breast cancers by interfering with cell cycle checkpoints and disrupting estrogen receptor–associated gene expression.[21] From a therapeutic perspective, these findings are in line with those reported by Liu et al. (2024), which demonstrated that pathogenic *RECQL4* germline variants – particularly when co-occurring with alterations in *BRCA2* and *PALB2*—may enhance tumor susceptibility to targeted therapies, including PARP inhibitors.[22] The *BRCA2* variant identified in this study is currently classified as a VUS and necessitates further validation to assess its clinical relevance. Additionally, the potential co-segregation of *RECQL4* and *BRCA2* germline variants within the family warrants further investigation, particularly given the patient's reported family history of breast cancer involving an affected elder sister (Figure 1).

Another notable finding is a single-nucleotide variant in the *NF1* gene (c.3817A>G; p.Thr1273Ala). *NF1* is a tumor suppressor gene known for its importance in predicting outcomes in various malignancies, including breast cancer. Alterations in *NF1* have been linked to worse survival rates in breast cancer patients. Moreover, individuals with germline *NF1* pathogenic variants exhibit an elevated lifetime risk of acquiring numerous cancers, including those of the breast, ovary, liver, lung, bone, thyroid, and gastrointestinal tract.[23] Neurofibromin, encoded by the *NF1* gene, acts as a GTPase-activating protein that inhibits the RAS signaling pathway, which encompasses HRAS, NRAS, and KRAS. The absence of neurofibromin results in persistent RAS activation, promoting cancer progression. Mouse models of chromosomal instability have demonstrated that *NF1* deletions are prevalent in mammary adenocarcinomas, underscoring *NF1*'s role as an essential tumor suppressor and a key factor in breast cancer formation. These results emphasize the cancer-

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promoting effects of disrupted RAS/MAPK signaling after *NF1* loss.[24] *NF1* is classified as a moderate-penetrance gene,[25,26] with cancer risk estimates comparable to those associated with pathogenic variants in *ATM*, *CHEK2*, and *NBN*. The National Comprehensive Cancer Network (NCCN) guidelines recommend annual mammography starting at age 30 and suggest considering contrast-enhanced breast MRI between ages 30 and 50 for individuals carrying pathogenic *NF1* germline variants.[27] Through a similar biological context, this study identified a likely pathogenic *NF1* germline variant co-occurring with an *RB1* germline variant of uncertain significance (VUS). *RB1* is a tumor suppressor gene, the inactivation of which results in a defect of G1/S checkpoint control, although the synergistic impact of *NF1* and *RB1* as a VUS in this case should be further investigated.

A pathogenic germline variant in the *MUTYH* gene was also identified in this study. *MUTYH* encodes a DNA glycosylase involved in the BER pathway,[28] which prevents G:C to T:A transversions caused by oxidative DNA damage. Specifically, oxidative stress can lead to the formation of 8-oxo-7,8-dihydro-2-deoxyguanosine (8-oxoG), which results in adenine mispairs during DNA replication; failure to correct this error via *MUTYH*-mediated repair results in G:C to T:A transversions.[29] In this study, a nonsense pathogenic germline variant (c.383G>A; p.Trp128Ter) was detected in the subject with a family history of colorectal cancer in her elder sister and thyroid cancer in her father (Figure 2). Biallelic pathogenic variants in *MUTYH* are well-established causes of *MUTYH*-associated polyposis (MAP), an autosomal recessive disorder that elevates the risk of colorectal cancer. The family history observed in this case warrants further investigation into the potential contribution of *MUTYH* pathogenic germline variants to both breast and colorectal cancer risk in closely related individuals. This finding aligns with prior studies showing that this particular variant has been prevalent among Dutch patients with adenomatous polyposis, accounting for approximately 75% of *MUTYH* pathogenic variants.[30] Notably, this variant has also been reported in Egyptian families with a history of familial breast cancer, as well as in Dutch families with co-occurring breast and colorectal cancers.[31,32] Thus, this study's findings may contribute to the growing evidence supporting the involvement of *MUTYH* pathogenic germline variants in breast cancer susceptibility and may inform future risk assessment strategies and therapeutic development.

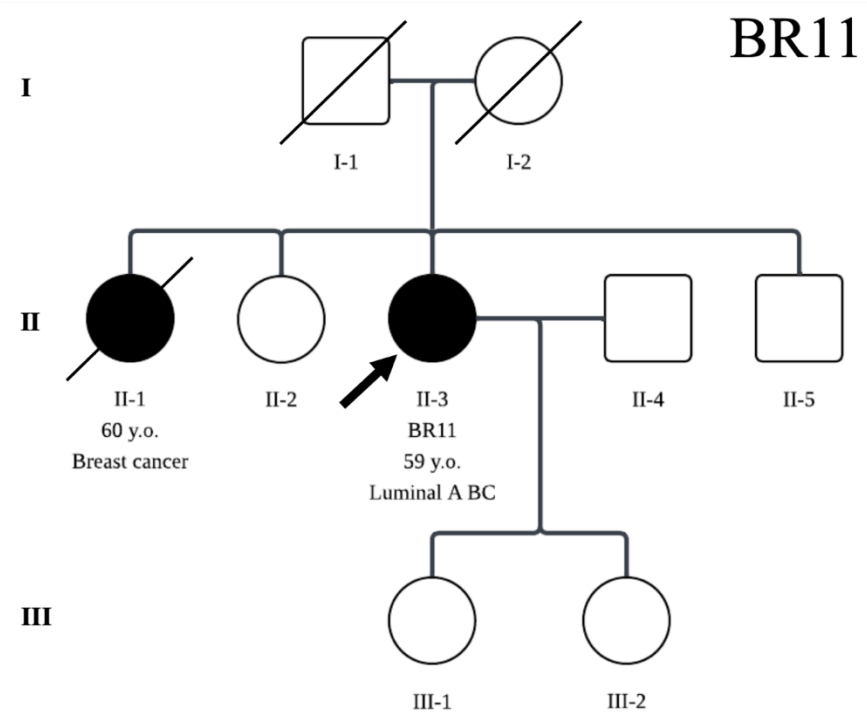

Figure 1. Family pedigree of the patient with the *RECQL4* (c.1342C>T; p.Pro448Ser) missense variant. The proband was diagnosed with luminal A breast cancer at 59 years of age, while her elder sister was diagnosed

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with breast cancer at 60 years of age. Symbols denote the proband (arrow), males (squares), females (circles), individuals affected by cancer (black-filled symbols), and deceased individuals (diagonal strikethrough).

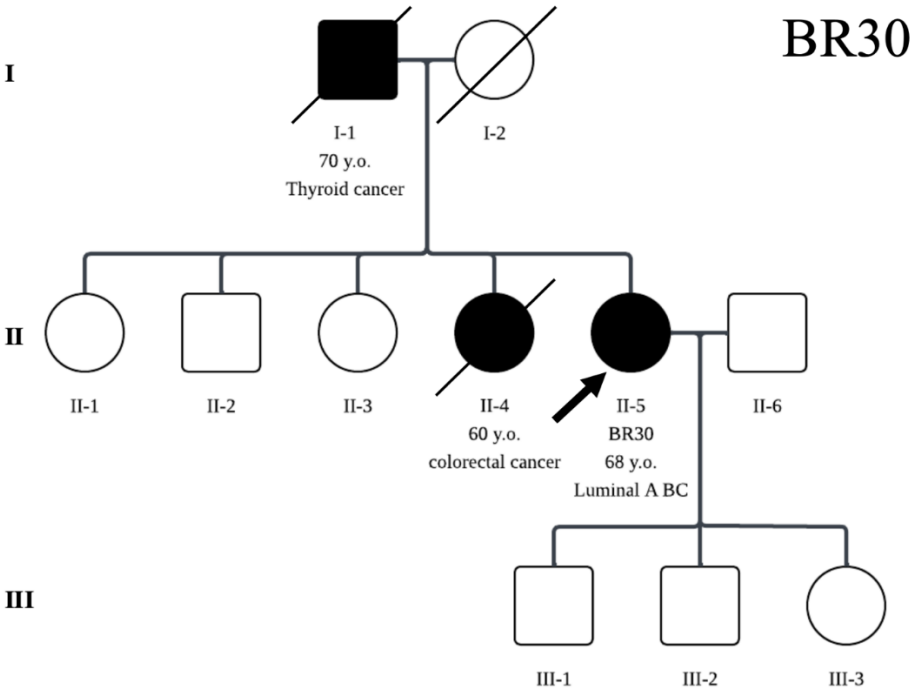

Figure 2. Family pedigree of the patient with the *MUTYH* (c.383G>A; p.Trp128Ter) nonsense variant. The proband was diagnosed with luminal A breast cancer at the age of 68. Her family history includes an elder sister diagnosed with colorectal cancer at age 60 and a father diagnosed with thyroid cancer at age 70. Both affected relatives are deceased at the time of reporting. Symbols denote the proband (arrow), males (squares), females (circles), individuals affected by cancer (black-filled symbols), and deceased individuals (diagonal strikethrough).

4.2. Family History and Variant Status

Although the association between family history of breast cancer and the presence of pathogenic germline variants did not reach statistical significance by Fisher's exact test ($p = 0.077$), it was found to be significant using Chi-Square analysis ($p = 0.022$). This discrepancy shows the study's limited statistical power. However, it matches wider observations that pathogenic germline variants often cluster in families with a history of cancer.[33] Furthermore, this study corroborates previous findings, as two of the three patients with mixed histology types, harboring likely pathogenic and pathogenic variants, all had a family history of cancer in their first-degree relatives (Figures 1 and 2).

4.3. Implications for Histopathological Interpretation

These results also emphasize that mixed histological types—traditionally considered ambiguous or rare—may be phenotypic markers of underlying hereditary pathogenic variants, particularly in DNA repair and cell-cycle regulation genes. The statistically significant enrichment of pathogenic/likely-pathogenic germline variants in mixed histology tumors provides a strong rationale for histopathology-directed genetic testing, which could optimize resource allocation in low-to-middle-income countries.

4.4. Study Strengths and Limitations

This study also underscores that mixed histological subtype—often regarded as uncommon or diagnostically ambiguous—may serve as phenotypic indicators of underlying hereditary pathogenic

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variants, particularly in DNA repair and cell cycle regulation genes. The statistical significance of pathogenic and likely pathogenic variants in tumors with mixed histology supports the implementation of histopathology-guided genetic testing. Such an approach may be particularly valuable for optimizing genetic testing strategies and resource utilization in low- and middle-income settings.

5. Conclusions

This pilot study provides the first description of germline pathogenic and likely pathogenic variants in Indonesian women with luminal A and luminal B breast cancer. Approximately one-third of patients were found to carry clinically relevant germline variants, most frequently involving *BRCA2*, *PALB2*, and *RECQL4*. Exploratory analyses suggest potential enrichment of pathogenic variants among patients with mixed invasive histology and those with a positive first-degree family history of breast cancer.

These findings should be interpreted as hypothesis-generating and require validation in larger prospective cohorts. Nevertheless, the results highlight the genetic heterogeneity of luminal breast cancer in this under-represented population and provide an initial foundation for future population-adapted genetic risk assessment and screening strategies in Indonesia.

Supplementary Materials: The datasets produced and/or examined in this study are not openly accessible owing to the sensitive genomic information involved and the need to protect participant confidentiality. However, the data may be obtained from the corresponding author upon reasonable request and following the necessary institutional clearances.

Author Contributions: **NS** contributed to the conceptualization, collected the data, validation, supervision, resource provision, writing of the original draft, project administration, and funding acquisition; **YHP** contributed to the conceptualization, methodology, collected the data, formal analysis, investigation, data curation, visualization, and writing of the original draft; **FS** was involved in the methodology, formal analysis, investigation, data curation, and visualization; **RK** participated in the conceptualization, collected the data, validation, supervision, resource provision, and review and editing of the manuscript.

All authors have reviewed and approved the final manuscript, confirm adherence to the authorship criteria specified, and assert that the manuscript constitutes honest and original work.

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Institutional Review Board Statement: The study protocol received approval from the Medical Research Ethics Committee at Dharmais National Cancer Center Hospital, Jakarta, Indonesia (Approval No. 305/KEPK/IX/2023). Written informed consent was obtained from every participant prior to enrolment. The study procedures adhered to the ethical standards set forth in the Declaration of Helsinki.

Informed Consent Statement: Written consent for publication of anonymised data was obtained from all participants.

Data Availability Statement: In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study. Please refer to suggested Data Availability Statements in section “MDPI Research Data Policies” at https://www.mdpi.com/ethics. If the study did not report any data, you might add “Not applicable” here.

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