RESEARCH ARTICLE

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Absence of Germline *BRCA1* and *BRCA2* Copy Number Variations Among Breast Cancer Patients in the Three Southern Border Provinces of Thailand

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Abstract

Objective: The objective of this study is to investigate germline CNVs in the *BRCA1* and *BRCA2* genes. **Materials and Methods:** Reanalysis of whole-exome sequencing (WES) data from 140 breast cancer (BC) patients originating from Thailand's three southern border provinces was performed using the Genome Analysis Toolkit Germline Copy Number Variant (GATK-gCNV) bioinformatics pipeline. CNVs identified as positive by this pipeline were further validated through multiplex ligation-dependent probe amplification (MLPA). **Results:** A total of 140 individuals were diagnosed with epithelial BC. Among them, 72.86% self-identified as Muslim-Thai, while 27.14% were Buddhist-Thai. The majority of cases (60.71%) were diagnosed at or before the age of 50 years. Notably, 20% of the patients presented with triple-negative breast cancer (TNBC). All enrolled patients underwent germline CNV analysis for the *BRCA1* and *BRCA2* genes. **Conclusion:** This study represents the first and largest investigation of germline CNVs in the *BRCA1* and *BRCA2* genes within this population. The absence of germline CNVs in both *BRCA1* and *BRCA2* suggests that routine screening for such alterations may be unwarranted in this specific population group.

Keywords: Breast cancer, *BRCA1, BRCA2*, Germline, Copy Number Variations

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Introduction

Breast cancer (BC) is the most prevalent malignancy among women globally and represents the leading cause of cancer-related mortality in this population [1]. In Thailand, BC is the most commonly diagnosed organ-specific malignancy among women, and its incidence is steadily increasing [2, 3]. Estimated projections suggest a continued rise in the incidence of BC in southern Thailand through the year 2030 [3]. Data from Naradhiwas Rajanagarindra Hospital in Narathiwat, one of the three southernmost provinces of Thailand, indicate that BC is frequently diagnosed at an advanced stage and is associated with poor survival outcomes [4].

Hereditary Breast and Ovarian Cancer (HBOC) syndrome is an autosomal dominant genetic disorder resulting from pathogenic mutations in the *BRCA1* or *BRCA2* genes. In addition to significantly elevating the risk of breast and ovarian cancers, HBOC syndrome is also associated with an increased susceptibility to several other malignancies [5]. BC patients and their first-degree relatives who carry germline pathogenic variants in the *BRCA1* or *BRCA2* genes may benefit from risk-reducing bilateral salpingo-oophorectomy, a surgical intervention that has been shown to significantly decrease the risk of developing ovarian cancer [6]. Bilateral risk-reducing mastectomy has been shown to substantially decrease the likelihood of developing BC in individuals carrying germline *BRCA* mutations [7].

The *BRCA1* gene is located on the long arm of chromosome 17 at cytogenetic band 17q21. It contains 22 coding exons and spans approximately 110 kilobases (kb) of genomic DNA. This gene encodes a protein composed of 1,863 amino acids, which plays a critical role in DNA repair and maintaining genomic stability. In contrast, the *BRCA2* gene is located at 13q12 on chromosome 13. It comprises 27 exons and spans roughly 84,761 base pairs, encoding a protein of 3,418 amino acids. Like *BRCA1*, *BRCA2* is essential for the homologous recombination repair pathway, contributing to the preservation of DNA integrity [8].

The three southernmost provinces of Thailand have a combined population of approximately two million people, of whom 83% identify as Muslim. This population differs markedly from the predominantly Buddhist population in central Thailand in terms of ethnicity, language, and

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religious beliefs [9]. The forensic analysis indicates that the populations exhibit heterozygosity at short tandem repeat (STR) loci, potentially due to cultural barriers that have limited recent genetic admixture among groups [10]. An exome sequencing study conducted on 151 unselected BC cases reveals that the spectrum of germline genetic mutations differs significantly from that observed in patients from central Thailand [11].

Germline copy number variations (CNVs) are structural alterations in the genome that are inherited and occur in the general population. These variations can influence phenotypic traits, potentially affecting gene function and expression [12]. Germline CNVs in the *BRCA1* and *BRCA2* genes are associated with HBOC syndrome, a genetic condition that significantly elevates the risk of developing various cancers [13]. A wide spectrum of CNVs in the *BRCA1* and *BRCA2* genes has been reported as pathogenic or likely pathogenic, as documented in the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar). There is a lack of data on CNVs in the *BRCA1* and *BRCA2* genes among populations in Thailand's three southernmost provinces, where the CNVs profiles may differ from those observed in other populations.

In this study, germline whole-exome sequencing (WES) data were utilized to characterize CNVs in the *BRCA1* and *BRCA2* genes among individuals with unselected BC from the population in Thailand's deep southern region.

Materials and Methods

Population

We identified 140 WES datasets from the high-capacity memory system at the Translational Medicine Research Center, Medical Research and Innovation Institute Building, Faculty of Medicine, Prince of Songkla University. All patients had histologically confirmed diagnoses of epithelial BC or ductal carcinoma in situ (DCIS), obtained from four general and regional hospitals in Thailand's three southernmost provinces. Our previous data published in the Journal of Personalized Medicine (2023) reported germline mutations involving small insertions, deletions, and base substitutions [11].

Whole Exome Sequencing (WES)

A volume of 10 milliliters of peripheral blood was collected from each patient and immediately stored in ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes for subsequent analysis. Genomic DNA was isolated from the buffy coat using the High-Pure PCR Template Preparation Kit (Roche, Berlin, Germany). DNA quality and concentration were evaluated with a Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA) and a NanoDrop spectrophotometer (Thermo Scientific, Waltham, MA, USA). Exome regions were enriched using the Agilent SureSelect XT V6 kit. Sequencing was performed on the Illumina NextSeq 550 platform (Illumina, San Diego, CA, USA), utilizing paired-end reads with a length of 150 base pairs. The mean sequencing depth reached approximately 200X, yielding around 9 gigabytes of data per sample.

Bioinformatics Analysis

First, FASTQ file format was used to assess the quality of the WES data. Only high-quality datasets proceeded to downstream analysis, following the GATK Best Practices pipeline recommended by the Broad Institute. Sequence reads will be aligned to the GRCh38 reference genome using BWA-MEM. The alignment sequence file is processed using MarkDuplicatesSpark to identify and mark duplicate sequencing reads, thereby minimizing biases introduced by polymerase chain reaction (PCR) amplification during downstream genomic analyses. Principal Component Analysis (PCA) is employed to cluster samples based on their underlying variance, enabling the differentiation between distinct types of library preparation methods. Genome Analysis Toolkit Germline Copy Number Variant (GATK-gCNV) is a state-of-the-art algorithm widely recognized as a benchmark tool for detecting CNVs in WES data. It is specifically designed to identify CNVs within exonic regions with high accuracy and resolution. The CollectReadCounts tool is utilized on the sample dataset to quantify the sequencing depth across each defined exonic interval, thereby providing a detailed measure of coverage distribution throughout the targeted genomic regions. The DetermineGermlineContigPloidy tool is utilized to infer the baseline ploidy state of genomic contigs, providing a foundational estimate for subsequent copy number variation analyses. IntervalListTools is utilized to partition a filtered interval list into smaller, more manageable subsets, thereby improving the efficiency and scalability of downstream genomic analyses. The GermlineCNVCaller is utilized to detect CNVs in each individual sample. The PostprocessGermlineCNVCalls function will be employed to convert the output from the Germline CNV Caller into a VCF file and generate denoised copy ratio values. The analysis was conducted in a stepwise and systematic manner. CNVs are categorized according to the guidelines established by the American College of Medical Genetics and Genomics (ACMG) [14]. Only those classified as pathogenic or likely pathogenic will be considered.

Positive findings from the analysis should be confirmed using Multiplex Ligation-Dependent Probe Amplification (MLPA).

Results

A total of 140 publicly available FASTQ files were included in the study, corresponding to female patients diagnosed with DCIS or epithelial BC, ranging in age from 23 to 79 years (mean age = 48.21 ± 11.01 years). Detailed patient characteristics are summarized in Table 1. Of the 140 BC patients included in the analysis, 85 individuals (60.71%) received their diagnosis at or before the age of 50, while the remaining 55 patients (39.29%) were diagnosed after the age of 50. BC staging was determined according to the criteria established in the 7th edition of the American Joint Committee on Cancer (AJCC) staging system. Among the 140 patients assessed, 5 individuals (3.57%) were diagnosed with DCIS of the breast. Of the

Table 1. Demographic and Clinical Characteristics of the Patient Population

Study Characteristic	No. (N=140)	%
Age at diagnosis (years)		
Mean ± SD	48.21 ± 11.01	
Median	47	
Max	79	
Min	23	
Range		
≤ 50	85	60.71
> 50	55	39.29
Stage at diagnosis		
DCIS	5	3.57
Stage I	16	11.43
Stage II	44	31.43
Stage III	50	35.71
Stage IV	25	17.86
Pathological group		
Invasive ductal carcinoma (IDC)	123	87.86
Invasive mammary carcinoma	5	3.57
Ductal carcinoma in situ (DCIS)	5	3.57
Others	7	5
Histopathological Subtypes		
Luminal A	54	38.57
Luminal B	31	22.14
HER2-enriched	27	19.29
Triple-negative breast cancer (TNBC)	28	20
Religion		
Muslim-Thai	102	72.86
Buddhist-Thai	38	27.14

140 patients evaluated, 25 (17.86%) were diagnosed with BC at an advanced stage (Stage IV). The distribution of earlier stages was as follows: Stage I in 16 patients (11.43%), Stage II in 44 patients (31.43%), and Stage III in 50 patients (35.71%).

Invasive ductal carcinoma (IDC) represented the predominant pathological subtype, accounting for 123 out of 140 cases (87.86%), while the remaining cases comprised other histological types. Among the 140 patients analyzed, triple-negative breast cancer (TNBC) was identified in 28 cases (20.0%), and the *HER2*-enriched subtype was observed in 27 cases (19.29%). The majority of patients (60.71%) were classified as having the luminal subtype.

The majority of patients identified as Muslim-Thai, comprising 102 out of 140 individuals (72.86%), while the remaining 27.14% were Buddhist-Thai.

CNV analysis was performed for all patients using WES data processed through a bioinformatics pipeline; notably, no CNVs were detected in any of the 140 cases.

Discussion

A deleterious germline mutation in the *BRCA1* or *BRCA2* gene constitutes an autosomal dominant genetic alteration and is a well-established etiological factor in HBOC syndrome [15]. Individuals who carry a germline mutation in the *BRCA* genes exhibit a significantly elevated lifetime risk of developing cancer, with an estimated 60% risk for BC and a 15–60% risk for tubo-ovarian cancers. Risk-reducing bilateral mastectomy and bilateral salpingo-oophorectomy are effective prophylactic interventions that substantially lower the incidence of these malignancies [16]. Poly (ADP-ribose) polymerase (PARP) inhibitors have been shown to significantly improve survival outcomes in patients with BC associated with *BRCA* germline mutations [17]. Platinum-based chemotherapy regimens have demonstrated enhanced therapeutic efficacy in the treatment of *HER2*-negative BC among patients harboring germline *BRCA* mutations [18]. Germline *BRCA* testing offers significant clinical benefits for both BC patients and their at-risk relatives by informing treatment decisions, guiding risk-reducing strategies, and enabling cascade genetic screening. In Thailand, the Universal Coverage public health insurance scheme provides coverage for *BRCA* germline testing in BC patients who meet high-risk criteria.

Table 2. Prevalence of Copy Number Variants in the *BRCA1* and *BRCA2* Genes as Reported in a Prior Study Conducted in a Distinct Population.

Population	Method	Sample size	CNVs (%)	References
Our study	NGS	140	0(0.00)	
Thailand	MLPA	100	1(1)	[29]
Thailand	NGS	4041	9(0.22)	[30]
Tunisia	MLPA	36	2(5.56)	[33]
Prague	MLPA	521	14(2.67)	[34]
Turkey	MLPA	1540	52(3.68)	[35]
Colombia	MLPA	400	0(0.00)	[27]
Argentina	MLPA	85	10(11.76)	[31]
Denmark	MLPA	617	3(0.47)	[36]
Korea	MLPA	306	3(0.89)	[37]
Tanzania	NGS + MLPA	100	0(0.00)	[28]
Finland	Microarray + MLPA	1137	1(0.09)	[38]

The National Comprehensive Cancer Network (NCCN) Guidelines, Version 3.2025, recommend genetic testing for high-penetrance BC susceptibility genes based on specific clinical criteria. These include a personal history of BC diagnosed at age 50 or younger, the presence of TNBC, or a personal history of BC accompanied by a close blood relative with a relevant cancer diagnosis. The American Society of Breast Surgeons recommends that genetic testing be offered to all individuals diagnosed with BC, regardless of age, family history, or other risk factors [19]. This guidance reflects a growing recognition of the clinical utility of genetic information in informing treatment decisions, assessing future cancer risk, and guiding surveillance strategies. Thailand's Universal Coverage public health insurance program currently provides financial support for *BRCA1* and *BRCA2* genetic

testing exclusively for BC patients who are classified as high-risk for HBOC syndrome [20]. This policy reflects a targeted approach aimed at optimizing resource allocation by focusing on individuals with the greatest likelihood of harboring pathogenic variants associated with hereditary cancer predisposition. In our study, 98 out of 140 patients (70%) met the established criteria for genetic testing, based on a diagnosis of BC at age 50 or younger and/or the presence of TNBC. A study conducted among Korean women with TNBC identified germline *BRCA* mutations in 171 out of 534 participants, representing a prevalence of 32% [21]. In a cohort of 802 German patients diagnosed with TNBC, 127 individuals (15.8%) were identified as carriers of pathogenic *BRCA* mutations [22].

To date, over 2,900 pathogenic variants of the *BRCA1* gene and more than 3,400 pathogenic variants of the *BRCA2* gene have been documented. The distribution and frequency of these genetic alterations vary across different populations, often influenced by geographic or cultural isolation, where one or more ancestors carried the mutated gene, leading to the establishment of population-specific or founder mutations [5]. A systematic review demonstrated that the prevalence of *BRCA* mutations exhibits substantial variability across different clinical and demographic subgroups, as well as between countries. This heterogeneity reflects the influence of diverse genetic backgrounds, population structures, and healthcare practices on mutation detection and reporting [23]. The majority of available *BRCA* variant data originates from European populations, with distinct *BRCA* mutation spectra observed across different ethnic and regional groups. This diversity underscores the influence of genetic background and population-specific factors on the distribution of *BRCA* alterations [24].

CNVs are a class of structural genomic variations characterized by deletions or duplications of large DNA segments, resulting in a variable number of copies of specific genomic regions relative to a reference genome [25]. CNVs in the *BRCA1* and *BRCA2* genes exhibit patterns consistent with those observed for pathogenic single nucleotide variants (SNVs) and insertions/deletions (indels) associated with cancer [26]. Our analysis of 140 individual BC cases did not identify any CNVs in the *BRCA1* or *BRCA2* genes, as determined through bioinformatic evaluation of WES data. A study conducted in Colombia similarly reported a 0% detection rate of CNVs, corroborating our findings [27]. Data from Tanzania also did not identify any CNVs in a study of 100 BC patients [28]. Table 2 presents a comparative analysis of *BRCA1*/*BRCA2* CNVs across different populations. Our study focused on a population from the Three Southern Border Provinces of Thailand, predominantly composed of Thai Muslims, whose ethnic background differs significantly from that of the central Thai population. In this cohort, no CNVs were detected in the *BRCA1* or *BRCA2* genes. This contrasts with reported CNV frequencies of 1% and 0.22% in central Thai populations [29, 30]. Due to demographic differences, Argentina reported a CNV detection rate of 11.76%, which differs significantly from that observed in our study population [31]. Overall, the detection rate of *BRCA1*/2 CNVs ranges from approximately 0% to 12%, depending on the selection criteria and the ethnic composition of the studied population.

A primary limitation of our study is the detection of CNVs using GATK-gCNV from WES data, which is not considered the gold standard for CNV analysis and may therefore result in false-negative findings. However, GATK-gCNV demonstrates a recall rate of 95% for CNV detection from WES data when the CNVs span more than two exons, as measured by the ratio of true positives to the sum of true positives and false negatives [32]. The study is limited by a small sample size, and the inclusion of BC patients was not based on specific criteria for hereditary cancer syndromes. This study represents a preliminary investigation into CNVs in the context of HBOC syndrome. We recommend that future research expand the analysis to include additional susceptibility genes and employ validated gold-standard methodologies, particularly in breast cancer patients exhibiting a high clinical risk for hereditary cancer syndromes.

In conclusion, in the present study, we conducted an analysis of a cohort comprising 140 BC patients originating from Thailand's three southern border provinces an area marked by unique ethnic and genetic diversity relative to the country's central regions. To the best of our knowledge, this investigation represents the first and most extensive effort to examine germline CNVs in the *BRCA1* and *BRCA2* genes among individuals from this specific demographic group. Importantly, our analysis did not identify any germline CNVs in either gene. These results imply that routine screening for germline CNVs in *BRCA1* and *BRCA2* may have limited clinical utility within this population and may not be necessary as part of standard genetic testing protocols in this regional context.

Author Contribution Statement

All authors made equal contributions to the conception, design, execution, and preparation of this study.

Acknowledgements

Ethical Declaration

The study protocol received ethical approval from the Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University (REC.68-176-10-3). The research was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

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