RESEARCH ARTICLE

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Evaluation of the Association between *LMTK3* Gene Polymorphism and Breast Cancer Risk in the Indian Population

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Abstract

Objective: The aim of this work was to elucidate the association of rs8108419 polymorphism in breast cancer patients in the Indian population. **Methods:** This was a pilot study involving sixty-four patients with confirmed breast cancer recruited from Mahatma Gandhi Cancer Hospital and Research Institute, Visakhapatnam and twenty-six healthy individuals were the volunteer blood donors from GITAM (Deemed to be University), Visakhapatnam, with no records of breast cancer history or familial lineage of breast cancer. Blood collected from the above individuals was used to extract genomic DNA, and the PCR-RFLP was performed to analyse all the samples. **Result:** There was no notable correlation between the genotypes of rs8108419 polymorphism and clinical characteristics like patient age, tumor stage and grade, tumor type, tumor size and distant metastasis. No correlation was observed between different subtypes of breast cancer and rs8108419 genotypes. The GG and GA genotypic frequencies were 90.6 and 9.3% in tumor cases and 92.3 and 8.3% in healthy controls, respectively. The *LMTK3* genotype GA was linked with a greater risk for the development of breast cancer (Odds ratio: 1.24; 95% confidence interval: 0.63-14.6; P>0.05) than the GG genotype (Odds ratio: 0.80; 95% confidence interval: 0.15-4.27; P>0.05). **Conclusion:** Overall, rs8108419 polymorphism was not associated with any clinicopathological factors in the above patients. However, the *LMTK3* GA genotype was correlated with an increased incidence of breast cancer development.

Keywords: *LMTK3*- Breast cancer- Polymorphism- Association studies

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Introduction

Breast cancer (BC) is currently the most often diagnosed cancer worldwide. It is the primary factor contributing to cancer-related mortality among women globally [1]. The World Health Organization (WHO) estimates that in 2022, 2.3 million women received a breast cancer diagnosis, and 670,000 people died from the disease globally. There are issues that must be resolved, such as expanding screening for breast tumors in high-risk groups, lowering the prevalence of breast cancer, and increasing the chances of survival [2]. Many multifactorial mechanisms, including genetic susceptibility and environmental variables, contribute to the complicated pathology of breast cancer [3]. Numerous genes and single-nucleotide polymorphisms (SNPs) relevant to breast cancer have been linked to the development and spread of the disease, according to genome-wide association studies [4-6].

SNPs are the most prevalent types of genetic variants found in the human genome. Gene SNPs have the ability to change the expression level of the gene product or the encoded protein structure [7, 8], which can alter disease susceptibility, carcinogenesis, cancer development and impact treatment resistance [9-12]. In addition to influencing the therapy and progression of the disease, certain genetic variations (e.g. polymorphisms) can predict an individual's predisposition to cancer [13].

Lemur Tail Kinase 3 (*LMTK3*), is found on chromosome 19 at 19q13.33. The gene codes for a serine-threonine kinase of 1489 amino acids comprising a transmembrane helical segment, a kinase domain and a large intrinsically disordered region, that expands to the end of the C-terminus [14]. *LMTK3* has been involved in a variety of cancers, including bladder [15], breast [16], colorectal [17, 18], gastric [19, 20], prostate [21], lung [22], ovarian [23], both as a valuable prognostic and predictive biomarker, as well as an essential part of numerous carcinogenic pathways. Elevated serum levels of *LMTK3*, associated with advanced disease stage, are reported in breast [24], thyroid [25], lung [22] and colorectal cancers [18]. Increased expression of *LMTK3* in tumor tissue, and high nuclear and cytoplasmic ratios are indicators of aggressive disease and poor clinical outcomes [24].

Two important polymorphisms have been identified in *LMTK3* gene that are linked to cancer, one at position

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rs8108419 (in intron 2) (Figure 1) and the other at position rs9989661 (in intron 15). The AA genotype of *LMTK3* rs8108419, or the CT or CC genotype of *LMTK3* rs9989661 is associated with aggressive breast cancer [24, 26]. *LMTK3* rs8108419 GA or GG, or *LMTK3* rs9989661 TT is associated with less aggressiveness of cancer in breast [24], gastric [19] and bladder cancer [15] patients. The distribution of these genotypes varies among different populations.

In this study, for the first time, we have examined the association between rs8108419 polymorphism in *LMTK3* gene and breast cancer in the Indian population. Additionally, the study also explored the possibility of the link between the gene polymorphism and the clinicopathological characteristics and subtypes of breast cancer.

Materials and Methods

Ethical Confirmity

GITAM Institute of Medical Sciences and Research (GIMSR) Research Ethics Committee in Rushikonda, Visakhapatnam, Andhra Pradesh, India, accepted this study under protocol number GIMSR/Admn./Ethics/approval/IEC-4/2021. A form requesting informed consent was signed by each participant.

Study Population

This study includes sixty-four female patients (cases) diagnosed with breast cancer between the age of 22-68 years. As it was a pilot study to investigate the SNPs, sample size was limited to ninety (control and cases) (Figure 2). The patient samples were collected from Mahatma Gandhi Cancer Hospital & Research Institute (MGCHRI), MVP Colony, Visakhapatnam, Andhra Pradesh, India, between 2021 and 2022. Histopathological analysis confirmed the diagnosis of breast cancer, and each patient gave informed consent prior to blood collection. Additionally, demographic and clinical data about the patients, including age and family history of cancer, etc., were also documented. Twenty-six healthy and disease-free individuals (controls) were volunteer blood donors from GITAM (Deemed to be University), with no records of breast cancer history or familial lineage of breast cancer. Controls were age and gender matched with patients in a ratio of 1:2.4. The demographic and clinical characteristics of the patients, like tumor stage, tumor grade, tumor size, tumor type, IHC profile and distant metastasis, were presented in Table 1, and all the classification was based on AJCC 8th edition.

DNA Extraction

Whole blood was collected in EDTA-coated tubes in all the cases. A total of 2 ml blood was drawn and kept at 4°C until further use. Extraction of genomic DNA from whole blood was performed by digesting the cell pellet with proteinase K, extraction with phenol-chloroform-isoamyl alcohol (P:C:I) and precipitation with ethanol (70%). The extracted DNA was quantified using the DeNOVIX DS-11 spectrophotometer and stored at -20°C for further use. Detection of DNA was done by gel electrophoresis and observed under the gel documentation system (Vilber Fusion Solo S).

SNP Genotyping

The *LMTK3* rs8108419 polymorphism was determined by PCR-RFLP. A 20 µl volume comprising 100 ng of genomic DNA, *LMTK3* forward primer: 5'-ATTCCACCACTCCCTCCAG-3' and reverse primer: 5'-GACCCTGCAGTGCCTCAC-3' and PCR master mix (Takara Bio: Cat. No.# RR310A) was used for the amplification process. The conditions used for PCR were 5 m at 95˚C, followed by 30 cycles of 30 s at 95˚C, 30 s at 55˚C and 30 s at 72˚C, and 5 m at 72˚C. Five units of the BsrDI restriction enzyme from New England Biolabs, Inc. (Cat. No.# R0574S) were used to digest a 15 µl aliquot of the amplified product at 37°C for an hour. The undigested PCR product and the corresponding digest were run on a 4% agarose gel which was stained with ethidium bromide (EtBr) and examined using the Vilber Solo S gel documentation system. The complete BsrDI site (in the wild-type allele) generated 151 bp fragment after PCR. Following the G to A polymorphism, the 151 bp fragment is cleaved into 112 bp and 39 bp fragments upon digestion with BsrDI enzyme. PCR RFLP was performed to confirm genotypes in 90 randomly selected samples that include both patients and healthy individuals. The whole process was performed at MURTI-VB, GITAM (deemed to be University), Visakhapatnam and all samples were analysed simultaneously.

Statistical Analysis

The association between *LMTK3* rs8108419 polymorphism and risk of developing breast cancer was studied by odds ratio (OR). The matching criteria (age) for cases and controls were represented as mean ± SD. The Hardy-Weinberg equilibrium was tested using Pearson's chi-square. Logistic regression model was used to calculate odds ratio (OR), 95% confidence interval (95% CI) and associated P-values to determine breast cancer risk with the genotypes [28]. An odds ratio of >1.00 specified a positive risk association and vice versa. P-values less than 0.05 were considered statistically significant. All statistical analyses were performed using the MedCalc software (version 23.0.9, Ostend, Belgium).

Results

Demographic and Clinical Characteristics of Study Population

A total of 64 histopathologically confirmed females with breast tumor and 26 age and gender matched controls were recruited for this study. The average age (in years) of cases and controls was 47.98±9.58 and 45.3±11.17, respectively. The diagnostic parameters of patients and the age of controls are summed up in Table 1.

SNP rs8108419 Genotyping

A total of 64 breast cancer samples and 26 healthy control samples were subjected to rs8108419 (G>A) genotyping (Figure 3). In all the samples, a 151 bp fragment was observed after *LMTK3* amplification

Table 1. Distribution of Selected Demographic and Pathophysiologic Variables among the Study Population

	Cases n = 64 (%)	Controls n = 26 (%)
Age		
Less than 50	38 (59.3)	15 (57.6)
More than 50	26 (40.6)	11 (42.3)
Tumor stage		
Early (0, I and II)	33 (51.5)	-
Late (III and IV)	31 (48.4)	-
Tumor grade		
Grade 2	30 (46.8)	-
Grade 3 and more	34 (53.1)	-
Tumor size		
Less than 2 cm	10 (15.6)	-
More than 2 cm	54 (84.3)	-
Tumor type		
IDC, NOS	58 (90.6)	-
Others	6 (9.3)	-
ER/PR expression		
positive	18 (28.1)	-
negative	46 (71.8)	-
HER2 expression		
positive	21 (32.8)	-
negative	43 (67.1)	-
TNBC subtype	25 (39.0)	-
Distant metastasis		
Positive	21 (32.8)	-
Negative	43 (67.1)	-

Table 2. Association between Genotypes of *LMTK3* rs8108419 Polymorphism and Clinicopathological Characteristics

	GG n = 58 (%)	GA n = 6 (%)
Age		
Less than 50	34 (58.6)	4 (66.6)
More than 50	24 (41.3)	2 (33.3)
Tumor stage		
Early (0, I and II)	29 (50.0)	4 (66.6)
Late (III and IV)	29 (50.0)	2 (33.3)
Tumor grade		
Grade 2	27 (46.5)	3 (50.0)
Grade 3 and more	31 (53.4)	3 (50.0)
Tumor size		
Less than 2 cm	9 (15.5)	1 (16.6)
More than 2 cm	49 (84.4)	5 (83.3)
Tumor type		
IDC, NOS	53 (91.3)	5 (83.3)
Others	5 (8.62)	1 (16.6)
ER/PR expression		
Positive	15 (25.8)	3 (50.0)
Negative	43 (74.1)	3 (50.0)
HER2 expression		
Positive	20 (34.4)	1 (16.6)
Negative	38 (65.5)	5 (83.3)
TNBC subtype		
Positive	23 (39.6)	2 (33.3)
Distant metastasis		
Positive	20 (34.4)	1 (16.6)
Negative	38 (65.5)	5 (83.3)

with specific primers mentioned above. In six patient samples, the 151 bp fragment was digested by Bsrd1 to yield 112bp and 39bp fragments, indicating a G>A polymorphism in these samples. In other cancer patient samples and healthy samples, no digestion of the PCR product with Bsrd1 was detected. The final success rate of *LMTK3* rs8108419 genotyping in this cohort is 100%. There was no notable correlation between the genotypes of rs8108419 polymorphism and clinical characteristics like patient age, tumor stage and grade, tumor type, tumor size and distant metastasis (Table 2). The relationship between rs8108419 genotypes and breast cancer subtypes-hormone positive, *HER2* amplified, and triple-negative subtypes- was also investigated. No correlation was observed between different subtypes of breast cancer and rs8108419 genotypes.

Allelic and Genotypic Frequencies of rs8108419 Polymorphism

The allelic and genotype frequencies of the *LMTK3* rs8108419 polymorphism in association with the clinicopathological parameters of breast cancer patients are listed in Table 3. The distribution of the *LMTK3* rs8108419 alleles and genotypes in all the groups was in equilibrium according to Hardy-Weinberg (P>0.05). The GG and GA genotypic frequencies were 90.6 and 9.3% in tumor cases and 92.3 and 8.3% in healthy controls, respectively. The *LMTK3* genotype GA was linked with

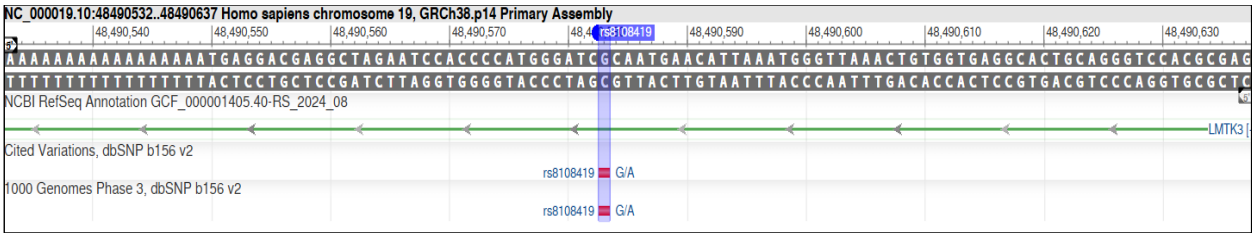

Figure 1. Human *LMTK3* Polymorphism (rs8108419) on Chromosome 19 [27]

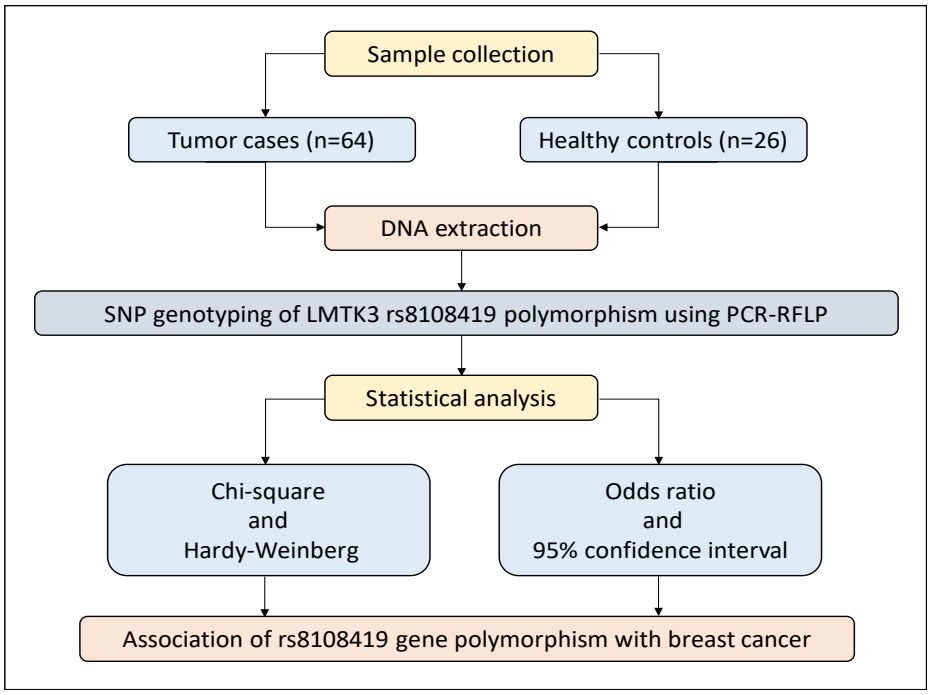

Figure 2. Flowchart of a Study on the Relationship between rs8108419 Polymorphism and Breast Cancer Risk

Table 3. Distribution of *LMTK3* rs8108419 Polymorphism

rs8108419	Healthy Controls n = 26 (%)	Tumor Cases n = 64 (%)	P-value	OR (95% CI)
Allele				
G	50 (96.1)	122 (95.3)	NS	0.81 (0.15-4.16)
A	2 (3.8)	6 (4.6)		1.22 (0.24-6.29)
Genotype				
GG	24 (92.3)	58 (90.6)	NS	0.80 (0.15-4.27)
GA	2 (8.3)	6 (9.3)		1.24 (0.23-6.59)

OR, odds ratio; CI, confidence interval; NS, not significant

a greater risk for the development of breast cancer (Odds ratio: 1.24; 95% confidence interval: 0.63-14.6; P>0.05) when compared with the genotype GG (Odds ratio: 0.80; 95% confidence interval: 0.15-4.27; P>0.05) (Table 3).

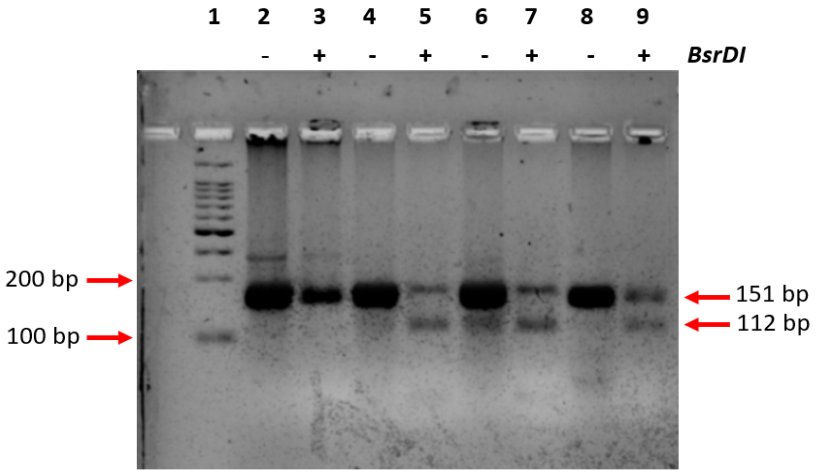

Figure 3. The PCR-RFLP Evaluation of the rs8108419 Polymorphism. A representative image of the healthy (lanes 2-3) and breast cancer patient samples (lanes 4-9) run on ethidium bromide-stained electrophoresed agarose gel: 100 bp ladder (lane 1); genotypes – GG (lanes 2-4,6,8 – 151 bp) and GA (lanes 5,7,9 – 112 bp) based on the digestion of the PCR product with BsrDI enzyme

Discussion

LMTK3 was detected in breast and gastric cancers as a reliable biomarker in these cancers [16, 19]. *LMTK3* has been reported to perform diverse functions ranging from cell signalling, gene regulation, trafficking and oncogenesis [14]. Alterations in the *LMTK3* gene, such as mutations or polymorphisms, are linked to several disease conditions, including cancers. *LMTK3* polymorphisms rs8108419 and rs9989661 are associated with breast cancer in European patients [16] and gastric cancer in the Japanese population and the US population [19]. In this study, we have explored for the first time, *LMTK3* rs8108419 polymorphism and its correlation with breast cancer in the Indian population. This is a single-center study with 64 breast cancer patients and 26 age matched controls in which germline polymorphism of rs8108419 was investigated. No significant correlation was observed between the rs8108419 GA polymorphism and clinicopathological features of breast cancer patients like tumor stage, grade, patient age, tumor type, tumor size and distant metastasis.

The abundance of *LMTK3* and its polymorphisms was substantially connected with tumor phenotype, disease-free survival (DFS) and overall survival (OS) of patients in previous studies [16, 24]. Wakatsuki et al. found that *LMTK3* polymorphisms rs9989661 and rs8108419 were strongly linked with overall survival, disease-free survival, and time to recurrence in gastric cancer. *LMTK3* rs9989661 was linked with disease-free survival (DFS) and overall survival (OS) in Japanese males and time to recurrence in US females. On the other hand, *LMTK3* rs8108419 was associated with overall survival in Japanese females and in US males [19]. Asano et al. reported that no correlation was found between *LMTK3* germline polymorphisms rs9989661 and rs8108419 and breast cancer outcomes in Japanese patients, contrary to what was observed by Giamas group in European breast cancer patients [16]. This could be due to ethnic differences among different populations [26]. Our study is limited by the number of collected samples, in which long-term follow-up was not feasible, to ascertain the disease-free survival or overall survival rates. Also, the variations in the polymorphism associations with cancer progression and high-grade tumors could be attributed to the physiology and ethnic/regional genetic changes of patients, as observed in the gastric cancer study [19].

In conclusion, in the present study, we found that *LMTK3* gene polymorphism rs8108419 has no association with patient clinicopathological parameters like age, stage and grade, tumor type, tumor size and distant metastasis. Our data also showed that rs8108419 doesn't have any correlation with different subtypes of breast cancer in the above population. In contrast to the genotype GG (Odds ratio: 0.80; 95% confidence interval: 0.15-4.27; P>0.05), the *LMTK3* GA genotype was linked to a greater incidence of breast cancer development (Odds ratio: 1.24; 95% confidence interval: 0.63-14.6; P>0.05). An effective association between *LMTK3* and cancer progression in the Indian population can be further determined by measuring the *LMTK3* protein levels in the tumor tissue, which can then be used as a prognostic marker along with the rs8108419 polymorphism.

Author Contribution Statement

SVG conceptualised the idea, SCG and GBY performed the experiments, SCG collected the data and drafted the manuscript, SVG reviewed and finalised the manuscript.

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General

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Ethical Declaration

GITAM Institute of Medical Sciences and Research (GIMSR) Research Ethics Committee in Rushikonda, Visakhapatnam, Andhra Pradesh, India, accepted this study under protocol number GIMSR/Admn./Ethics/approval/IEC-4/2021.

Conflict of Interest

None.

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