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Research Article

rs 1514422 in hsa-miR-8060: Evidence for a novel protective variant against Breast cancer

Thanh Ngoc Thi Nguyen[1,2,3,*], Thuy Chung Thi Duong[2,3], Hue Thi Nguyen[2,3]

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ABSTRACT

MicroRNA (miRNA) polymorphisms can influence gene regulation and cancer susceptibility. A previous bioinformatics study suggested that the single nucleotide polymorphism rs1514422, located in the mature sequence of hsa-miR-8060, could alter miRNA-mRNA interactions, potentially influencing oncogenic regulation in breast cancer (BC). However, rs1514422 has not previously been the subject of experimental studies. This case–control study analyzed 100 DNA samples (50 BC cases, 50 controls) from Vietnamese women. Rs1514422 was genotyped as part of a panel of 101 SNPs in 100 mature miRNA coding genes. Statistical analyses, including chi-squared tests and logistic regression analyses, were conducted to evaluate genotype–phenotype associations. The results indicate that the GG genotype was significantly more frequent in BC cases (70%) than in controls (40%), while the GA genotype was more common in controls (56%) than in cases (26%). The A allele was associated with reduced BC risk (odds ratio (OR) = 0.38; $p = 0.0081$), while the GA genotype exhibited a protective effect in dominant (OR = 0.29; $p = 0.0024$) and overdominant models (OR = 0.28; $p = 0.0021$). These findings align with previous computational predictions, suggesting that the A allele may enhance the miRNA-mediated suppression of *KRAS*, thus reducing oncogenic activity. This study provides the first experimental evidence linking rs1514422 to breast cancer susceptibility, with Vietnam as the first population studied. The A allele and GA genotype appear to confer protective benefits, supporting prior bioinformatics predictions. Further research is needed to confirm its functional impact on *KRAS* regulation.

Key words: Breast cancer, rs1514422, microRNA, hsa-miR-8060, genetic susceptibility

[1]*Department of Physiology and Animal Biotechnology, Faculty of Biology and Biotechnology, University of Science, Ho Chi Minh City, Ho Chi Minh, Vietnam*

[2]*Human Genetic Laboratory, Faculty of Biology and Biotechnology, University of Science, Ho Chi Minh City, Ho Chi Minh, Vietnam*

[3]*Vietnam National University, Ho Chi Minh City, 268 Ly Thuong Kiet Street, District 10, Ho Chi Minh, Vietnam*

Correspondence

Thanh Ngoc Thi Nguyen, Department of Physiology and Animal Biotechnology, Faculty of Biology and Biotechnology, University of Science, Ho Chi Minh City, Ho Chi Minh, Vietnam

Human Genetic Laboratory, Faculty of Biology and Biotechnology, University of Science, Ho Chi Minh City, Ho Chi Minh, Vietnam

Vietnam National University, Ho Chi Minh City, 268 Ly Thuong Kiet Street, District 10, Ho Chi Minh, Vietnam

Email: nthue@hcmus.edu.vn

INTRODUCTION

Breast cancer (BC) is one of the most common cancers affecting women worldwide, with increasing incidence and mortality rates[1]. Advances in cancer genomics have revealed that microRNAs (miRNAs) are critical regulators of gene expression that influence tumor initiation, progression, and metastasis[2]. Even small changes in the binding affinity of miRNA can affect gene expression and disease susceptibility[3]. In particular, single nucleotide polymorphisms (SNPs) in miRNA sequences can significantly influence miRNA functionality by altering their ability to regulate target genes[4]. Consequently, the investigation of such SNPs can provide valuable insights into genetic susceptibility to BC as well as potential biomarkers for disease risk assessment[5].

Several studies have shown that polymorphisms in mature miRNAs can alter miRNA biogenesis, target recognition, and regulatory activity, thereby influencing cancer susceptibility. For example, the SNP rs2910164 in miR-146a may affect BC risk by dysregulating key oncogenic pathways involved in DNA repair and inflammation. Specifically, this variant reduces *BRCA1* expression, impairing DNA repair and leading to genomic instability, thus facilitating the progression of BC, particularly in triple-negative subtypes. In addition, rs2910164 disrupts the ability of miR-146a to regulate *TRAF6* and *IRAK1*, leading to the abnormal activation of the NF-κB signaling pathway, promoting inflammation, tumor initiation, and metastasis in BC[6,7]. Similarly, rs11614913 in miR-196a2 has been associated with increased miRNA expression and the suppression of targets like *ANXA1* and *HOX* genes. *ANXA1* regulates apoptosis and inflammatory responses; consequently, reduced *ANXA1* expression mediated by elevated miR-196a2 expression impairs apoptosis and promotes proliferation in BC cells. *HOX* genes regulate tissue development and cellular differentiation; altered *HOX* gene expression directly contributes to invasive and metastatic behaviors in BC[8,9]. Another well-characterized variant, rs3746444 in miR-499, has been reported to increase cancer risk by downregulating tumor suppressors such as *FOXO4*, *PDCD4*, and *SOX6*, which regulate cell cycle arrest, apoptosis, and the inhibition of metastasis. The loss of these func-

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tions significantly enhances BC cell survival, apoptosis evasion, and metastatic potential[10,11]. Collectively, these findings highlight the role of miRNA-related SNPs in BC susceptibility and provide context for evaluating novel variants such as rs1514422.

The SNP rs1514422, located at chromosome 3:96360020, is positioned within the mature sequence of hsa-miR-8060, an miRNA that is thought to function as a tumor suppressor[12]. Under normal conditions, hsa-miR-8060 regulates the *KRAS* oncogene, a key driver of multiple cancers, including BC[12]. Computational analysis has suggested that rs1514422 may alter miRNA-mRNA interactions by slightly increasing the binding affinity of miRNA to*KRAS* (ΔG = -0.2 kcal/mol) due to the alternative A allele[12]. This potential effect on *KRAS* regulation suggests that rs1514422 could influence BC sus- ceptibility, either through the enhanced repression of *KRAS* or the disruption of normal regulatory mechanisms[12].

Given that *KRAS* is frequently upregulated in BC (Log2FC = 0.31)[12], variations in its post- transcriptional regulation by hsa-miR-8060 could have important functional implications in cancer biology. However, rs1514422 has not been previously examined in experimental studies, and its association with BC risk remains unclear. This study represents the first experimental investigation into the rela- tionship between rs1514422 and BC by analyzing genotypic distributions and their association with BC risk. This study seeks to provide novel insights into the potential role of rs1514422 in BC susceptibility.

MATERIALS-METHODS

Study population and sample selection

This case–control study comprised 50 BC patients and 50 healthy controls. Case samples were selected based on clinical symptoms (e.g., breast lumps, axillary lymphadenopathy, pain, and nipple discharge), mammographic abnormalities, cytological findings, and the histopathological confirmation of BC. Most of the BC patients in this study consisted of early-stage cases (stages 0, I, and II; 81.6%), while the remaining cases were determined to be in the advanced stages of the disease (stages III and IV). Detailed staging was performed using the TNM classification system outlinedby the American Joint Committee on Cancer (AJCC). Controls had no clinical or imaging evidence of ma- lignancy at the time of collection. Sample collec- tion was approved by the Ethics Committee of the Ho Chi Minh City Oncology Hospital (Decision No. 177/ĐĐĐ-CĐT, 2014; extended No. 1271/BVUB-CĐT, 2022).

DNA sample preparation and genotyping

Genomic DNA was extracted from whole blood using the salt precipitation method. The quality and concentration of DNA were assessed using optical density (OD) at 260/280 nm and a Qubit fluorometer. Only samples meeting the quality criteria of DNA concentration $\geq$ 10 ng/μL and an OD260/OD280 ratio between 1.8–2.0 were included in the study. A minimum of 1 ng of DNA was required for sequencing library preparation.

The genotyping of rs1514422 was performed within a panel of 101 mature miR-SNPs identified in a previous study[12]. A total of 100 DNA samples were analyzed using next-generation sequencing (NGS) on the Ion Torrent platform.

Library preparation was conducted using a custom Ion AmpliSeq panel (Panel ID: IAD249282_236) designed using the Ion AmpliSeq Designer tool (Thermo Fisher Scientific). This panel was targeted at 101 SNPs (including rs1514422) located in mature miRNA sequences that had been previously implicated in BC. The panel was based on the human genome build hg38, with amplicon sizes of 125–175 bp. Primer pools were optimized for multiplex PCR amplification in a single reaction. Sequencing was conducted on the Ion S5 platform. Raw data were processed using Ion Torrent Suite v5.12, and variant calling was performed using the Variant Caller Plugin v5.12.0.4 with default parameters.

Statistical Analysis

The association between rs1514422 and BC risk was evaluated using statistical analysis. The Hardy-Weinberg equilibrium (HWE) in the control group was tested using the chi-squared test, while the genotype and allele frequencies of the cases and controls were compared using Pearson's Chi-square test (χ^2 test). Logistic regression was applied across allelic, dominant, recessive, overdominant, and codominant genetic models to evaluate these associations; odds ratios (ORs) and 95% confidence intervals (CIs) were also assessed. Statistical significance was set at $p < 0.05$, and all analyses were performed using R software version 4.1.3.

RESULTS

Genotypic and Allelic Association of rs1514422 with BC Risk

The analysis of rs1514422 genotype and allele frequencies revealed significant differences between the BC cases and controls (Table 1). Specifically, the GG genotype was significantly more prevalent in cases

(70%) compared to controls (40%), while the GA genotype was more common in controls (56%) than in cases (26%). The AA genotype was rare in both groups (4%), suggesting that homozygosity for the A allele may not significantly influence BC susceptibility. The chi-squared test also revealed a statistically significant difference in genotype distribution (p = 0.008).

P_{χ^2}: Chi-square P value for genotype and allele distribution; P_{HWE}: Hardy-Weinberg equilibrium P value (in controls).

Allelic frequency analysis further demonstrated that the G allele was more frequent in cases (83%) than in controls (68%), while the A allele was more common in controls (32%) than in cases (17%). The difference in allele distribution was statistically significant (p = 0.021), indicating the potentially protective role of the A allele against BC. HWE analysis in the control group (p = 0.06) confirmed that the genotype distribution followed expected genetic proportions, supporting the validity of the findings.

Genetic Model Analysis of rs1514422 and BC Susceptibility

Logistic regression analysis was conducted on multiple genetic models to further evaluate the association between rs1514422 and BC susceptibility (Table 2). The A allele consistently exhibited a protective effect across all models, particularly in individuals carrying the GA genotype. In the allelic model, the A allele was associated with a significantly reduced risk of BC (OR = 0.38; 95% CI = 0.18–0.8; p = 0.0081). The dominant model (GA + AA vs. GG) showed that individuals carrying at least one A allele had a 71% lower risk of BC compared to GG homozygotes (OR = 0.29; 95% CI = 0.12–0.65; p = 0.0024). This protective effect was also observed in the overdominant model (GA vs. GG + AA), suggesting a potential heterozygote advantage (OR = 0.28; 95% CI = 0.12–0.64; p = 0.0021). In the codominant model, the overall comparison among the three genotypes (GG, GA, and AA) yielded a statistically significant result (p = 0.008), suggesting that genotype plays a role in modulating disease susceptibility. No association was observed in the recessive model (AA vs. GG + GA; OR = 1.00; 95% CI = 0.14–7.39; p = 1.00); however, this result should be interpreted cautiously due to the low frequency of the AA genotype (4% of both groups) and wide CI.

OR: Odds Ratio; 95% CI: 95% Confidence Intervals; P: Logistic regression P value

Collectively, these findings reveal that the A allele plays a consistent and statistically significant protective role in BC susceptibility, especially in heterozygous individuals, supporting the hypothesis that rs1514422 may influence BC risk through miRNA-mediated regulatory mechanisms.

DISCUSSION

This study represents the first experimental investigation into the relationship between rs1514422, a SNP located within the mature sequence of hsa-miR-8060, and BC susceptibility. Prior computational analyses predicted that this SNP may influence the binding affinity between hsa-miR-8060 and its oncogenic target *KRAS*, a gene frequently upregulated in BC [12, 13]. Specifically, the A allele of rs1514422 was associated with a slight increase in predicted binding affinity (ΔG = –0.2 kcal/mol), which was linked to the possi- ble enhancement of miRNA-mediated *KRAS* suppres- sion [12].

Our results revealed a non-random genotype distribution, with the GA genotype notably underrepresented among BC patients. This finding, which was supported across multiple genetic models (including dominant and overdominant), indicates a potential protective effect of the A allele, particularly in the heterozygous state. Although the AA genotype was rare and its role could not be assessed with statistical certainty, the observed trends support a biological model in which rs1514422 modulates oncogene regulation. These associations suggest that the A allele enhances the suppressive capacity of miR-8060 against *KRAS*. Given that *KRAS* expression is moderately upregu- lated in BC (Log2FC = 0.31) and contributes to key oncogenic processes such as proliferation and apopto- sis evasion, increased miRNA affinity could mitigate its impact [12].

Although the difference in ΔG between the alleles (–18.5 vs. –18.3 kcal/mol) is relatively modest [12], these subtle changes may still influence miRNA–mRNA interactions, particularly within highly regulated oncogenic pathways like *KRAS* [4,14]. Specifically, *KRAS* functions as a key signal transducer, and even mi- nor fluctuations in its regulation can result in signif- icant biological consequences [15].

Nevertheless, our conclusions remain predictive and statistical in na- ture. Functional validation is essential to confirm whether this SNP affects *KRAS* regulation in a bio- logically meaningful way. In particular, experimen- tal approaches such as luciferase reporter assays [16] or CRISPR-Cas9-mediated allele editing [17] could help clarify the impact of rs1514422 on miRNA binding ef- ficiency and *KRAS* expression levels.

The association of rs1514422 is consistent with previously reported findings for other SNPs located in mature miRNA sequences. For example, rs2910164 in miR-146a has been shown to modulate BC risk

Table 1: Genotypic and allelic distribution of rs1514422 in breast cancer cases and controls

Group (Total sample)	GG (%)	GA (%)	AA (%)	P_{χ^2}	G (%)	A (%)	P_{χ^2}	PHWE
Case (50)	70	26	4	0.008	83	17	0.021	
Control (50)	40	56	4		68	32		0.06

Table 2: Association of rs1514422 with breast cancer risk across different genetic models

Genetic model		OR	95% CI	P
Allelic	A vs. G	0.38	0.18 - 0.8	0.0081
Dominant	(GA + AA) vs. GG	0.29	0.12 - 0.65	0.0024
Recessive	AA vs. (GG + GA)	1	0.14 - 7.39	1
Overdominant	GA vs. (GG + AA)	0.28	0.12 - 0.64	0.0021
Codominant	GA vs. GG	0.27	0.11 - 0.63	0.008
	AA vs. GG	0.57	0.07 - 4.37	

by regulating miRNA expression and targeting key oncogenes such as *BRCA1*, *TRAF6*, and *IRAK1*, all of which influence NF-κB signaling and tumor progression[6,7]. A meta-analysis of 17 studies found that individuals with the CC genotype possessed significantly increased BC risk (p = 0.0019)[18]. Similarly, rs11614913 in miR-196a2 may promote tumor progression by enhancing miRNA expression and suppressing key targets such as *ANXA1* and *HOX* genes, thereby reducing apoptosis and facilitating proliferation and metastasis in BC[8,9,19,20]. Notably, rs11614913 exhibits population-specific effects, with the C allele linked to increased BC risk in Asians, while findings in Caucasians remain inconclusive[10,20–24]. Another variant, rs3746444 in miR-499, has also been implicated in multiple cancers, including BC. While the C allele has been associated with higher BC risk in Caucasian populations, it may have a protective role in some Asian cohorts[24,25]. Mechanistically, rs3746444 enhances miR-499 expression and downregulates tumor suppressors such as *FOXO4*, *PDCD4*, and *SOX6*, contributing to apoptosis resistance and metastasis[10,11,26–28].

Collectively, these studies demonstrate that SNPs in mature miRNA sequences can influence cancer susceptibility by altering miRNA expression or affecting target binding efficiency. Although rs1514422 had not previously been examined experimentally, its location and predicted impact on miRNA–*KRAS* interactions suggest a similar functional paradigm. The consistent pattern in these interactions, in which certain alleles influence cancer risk by altering miRNA activity, provides strong support for the findings of this study and highlights the need for a broader investigation into miRNA-SNP interactions in diverse populations.

Nevertheless, several limitations of this study must be acknowledged. The low frequency of the AA genotype limits our ability to assess its independent contribution to BC risk through statistical analysis. In addition, the relatively small sample size of the full cohort (n = 100) limits the statistical significance and generalizability of our findings. Furthermore, the study cohort consisted exclusively of Vietnamese women, which may limit the generalizability of our results. Future studies with larger, multi-ethnic populations and integrated functional assays will be essential to clarify the biological relevance of rs1514422 and validate its potential as a biomarker for BC susceptibility.

Future investigations should also explore the relationship between rs1514422 and other cancers characterized by abnormal *KRAS* regulation, such as colorectal, pancreatic, and lung cancers, to assess its broader potential as a biomarker across *KRAS*-driven malignancies.

CONCLUSIONS

This study provides the first experimental evidence linking rs1514422 in hsa-miR-8060 to BC susceptibility. The A allele was significantly associated with reduced BC risk, indicative of a potentially protective role against the disease. These findings suggest that rs1514422 could be a potential biomarker for BC risk assessment. Further research, including functional assays and validation in larger, more ethnically diverse populations, is needed to confirm these findings.

ABBREVIATIONS

AA, GA, GG: Genotypes (homozygote AA, heterozygote GA, homozygote GG)
AJCC: American Joint Committee on Cancer
BC: Breast cancer
bp: Base pair
BRCA1: Breast cancer type 1 susceptibility protein
CI: Confidence interval
Chi-squared (χ^2): Chi-squared statistic/test
CRISPR-Cas9: Clustered Regularly Interspaced Short Palindromic Repeats–CRISPR associated protein 9
Delta G (ΔG): Change in Gibbs free energy
DNA: Deoxyribonucleic acid
ER: Estrogen receptor
FOXO4: Forkhead box O4
HER2: Human epidermal growth factor receptor 2
hg38: Human Genome Reference build GRCh38
HWE: Hardy–Weinberg equilibrium
IRAK1: Interleukin-1 receptor–associated kinase 1
KRAS: Kirsten rat sarcoma viral oncogene homolog
Log2FC: Log2 fold change
miR: MicroRNA (gene symbol prefix, e.g., miR-146a)
miRNA: MicroRNA
NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells
NGS: Next-generation sequencing
OD (OD260/OD280): Optical density at 260/280 nm
OR: Odds ratio
PCR: Polymerase chain reaction
PDCD4: Programmed cell death protein 4
PHWE: P-value for Hardy–Weinberg equilibrium
PR: Progesterone receptor
R: R statistical software
SOX6: SRY-box transcription factor 6
TNM: Tumor–Node–Metastasis (staging system)
TRAF6: TNF receptor–associated factor 6

COMPETING INTERESTS

The author(s) declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Thanh Nguyen Thi Ngoc: Conceptualization, Software, Data curation, Visualization, Writing- Original draft preparation. Thuy Duong Thi Chung: Methodology, Investigation, Reviewing and Editing. Hue Nguyen Thi: Supervision, Reviewing and Editing, Final approval.

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