Journal of Prevention, Diagnosis and Management of Human Diseases
Vol: 05, No. 01, Jan-June 2025
ISSN: 2799-1202, DOI: 10.55529/jpdmhd.51.20.31

Research Paper

Genetic variation in microRNA-423 and microRNA-137 genes among patients with breast cancer

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Article Info

Article History:
Received: 29 August 2024
Revised: 11 November 2024
Accepted: 17 November 2024
Published: 04 January 2025

Keywords:
Breast Cancer
Microrna-423
MIR 137 Gene VNTR
ARMS-PCR
Genetic Polymorphism

ABSTRACT

Aim MicroRNAs (miRNAs) are a family of non-coding RNAs that have been suggested as novel markers or therapeutic targets for breast cancer. In current study, we aimed to investigate the prevalence of microRNA-423 rs6505162C/T and the VNTR length of the MIR 137 gene (rs58335419) with regards to breast cancer susceptibility in Iraqi women. Methods: In this study, 190 individuals took part, out of which 110 were breast cancer patients and 80 were healthy controls. The amplification refractory mutation system PCR method (ARMS-PCR) was used to determine the polymorphism in the microRNA-423 (rs6505162) gene. While the VNTR length of the MIR 137 gene (rs58335419) was identified using PCR. The Graph Pad Prism 9 software was used to conduct the statistical analysis. Results: the allele frequency of T in the microRNA-423 rs6505162 was significantly associated with breast cancer (odds ratio [95% confidence interval] 2.333 [1.519-3.600], Risk factor [95% confidence interval]) 1.400 [1.184-1.655], $p < 0.0001$). On the other hand, all the allele frequencies in the MIR 137 gene (rs58335419) were not found to be associated with breast cancer. Conclusion: Based on the results, the study suggests that microRNA-423 rs6505162C/T could be useful markers for diagnosing breast cancer, whereas the MIR 137 gene (rs58335419) is not useful for diagnosing breast cancer.

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1. INTRODUCTION

Breast cancer is the most widespread cancer globally. We must act now and prioritize funding for research, screening, and treatment. According to recent global cancer statistics, there were approximately 2.26 million new cases of breast cancer in 2020 [1]. Breast cancer is the leading cause of cancer-related deaths in women worldwide. The Arab world accounts for 5.6% of the global population and has 2.4% of the total global incidence of new cancer cases [2]. Between 2000 and 2019, 72,022 cases of breast cancer were detected in women in Iraq [3].

Although heavily researched, ongoing debate surrounds the mechanisms involved in breast cancer development [4]. Epidemiological studies have indicated an increase in breast cancer incidence. Therefore, it is necessary to conduct multidirectional studies to identify associated risk factors for this type of cancer [5]. Various factors increase the risk of breast cancer such as gender, age, estrogen levels, family history, gene mutations, and unhealthy lifestyle choices [6].

About 50% of the genome's DNA can be transcribed into RNA, but only 2% of the RNA can be translated into proteins; the other 98% of RNA, known as ncRNAs, cannot be translated [7]. Non-coding RNAs can regulate epigenetics and gene expression by remodeling chromatin or controlling gene expression at the transcriptional or post-transcriptional level [8].

MicroRNAs are small, non-coding RNA molecules that range in size from 19 to 25 nucleotides and are highly conserved [9]. The miR-423 gene is a small noncoding RNA located on chromosome 17 within intron 1 of the nuclear speckle splicing regulatory protein NSRP1. NSRP1 is involved in alternative mRNA splicing [10], [11].

The pre-miRNA of miR-423 generates two mature transcripts, known as miR-423-3p and miR-423-5p. A C>A polymorphism, identified as rs6505162, is located 12 base pairs away from the 3' end of mature miR-423-3p. It is possible that miR-423 could have a role in cancer development [12]. The gene miR-137 is found on chromosome 1p21.3. It is a nonprotein-coding RNA (ncRNA) gene. Its document number is AK094607 [13]. The rs58335419 variant is located near the precursor sequence of miR-137 and consists of 15 nucleotides [14]. This region includes three variants: VNTRw which has 3 repeats (wild type), VNTR4 with 4 repeats, and VNTR5 with 5 repeats, which are relatively common [15].

This study aimed to investigate the correlation between polymorphism in miR-423 rs6505162C/T and the VNTR length of the MIR 137 gene (rs58335419) and the risk of breast cancer among female Iraqi patients.

2. RELATED WORK

The Illumina OncoArray BeadChip, used in the recent GWAS on breast cancer, contained roughly 570,000 SNPs and was credited with ~11.8 million SNPs [1]. Gene expression and protein function are two biological processes VNTRs are known to affect [16]. The risk of developing several cancers, including breast cancer [17], is also mediated by these VNTRs (quantitative trait loci) [18]. MicroRNAs (miRNAs) are key epigenetic regulators in tumor development. They fall into two categories: oncogenic miRNAs (oncomiRs), which target tumor suppressor genes, and tumor suppressor miRNAs (TS miRNAs), which inhibit oncogene protein expression [19]. Previous study findings highlight miR-423 as a potential prognostic and therapeutic marker for metastatic breast cancer and imply that it plays a critical role in enhancing breast cancer cell invasion via the NF-κB signaling pathway [20]. According to earlier findings, the pre-miR-423 rs6505162 CC genotype SNP offers a reduced risk of breast cancer development [12].

[21] Found that the SNP rs6505162: C>A in pre-miR-423 affects how mature miRNA is expressed. This means that miR-423 could play a role in breast cancer development. Using a case-control study, previous studies found a strong link between rs6505162: C>A and breast cancer risk in the Chilean population [22]. Also, MicroRNA-423 (rs6505162) TT genotype and T allele are associated with increased metastasis and advanced breast cancer stages in Saudi Arabian patients [23]. Growing studies indicate that

miR-137 acts as a suppressor in tumor progression; however, the role of miR-137 in breast cancer remains unclear. A15-bp variable nucleotide tandem repeats that is only 5′ from the pre-miR-137 sequence modifies the way miR-137 is processed and functions in melanoma cell lines [24].

An increased copy number of VNTR in the MIR137 gene significantly elevates the risk of colon and gastric cancers, serving as a reliable marker for susceptibility to these diseases [25].

MiR-137 gene expression was significantly lower in multiple myeloma cell lines compared to normal plasma cells [26]. MiR-137 effectively inhibits the proliferation, migration, and invasion of colon cancer cell lines by directly negatively regulating the expression of TCF4 [27]. MiR-137 is downregulated in lung cancer [28].

3. METHODOLOGY

Population Study

The study was conducted at Tikrit University's Laboratory Center between 2022 and 2023. It involved 110 female patients diagnosed with breast cancer (BC) and 80 healthy females who served as a control group. The study's inclusion criteria included women with clinically diagnosed breast cancer as well as unrelated healthy women with no prior medical history of cancer. The Research Ethical Committee of the University of Tikrit approved the study, and all participants had to provide written consent before participating.

DNA Isolation and Genotyping of Mir-423 Rs6505162c/T and MIR 137 Rs58335419

The DNeasy Blood Kit from Qiagen in Germany was used for extracting genomic DNA from a blood sample. A sample was analyzed through a 1% agarose gel to ensure the quality of the DNA extracted. The amount of DNA extracted was determined using NanoDrop™ by Thermo Scientific in the USA.

The miR-423 rs6505162C/T polymorphism was genotyped through ARMS-PCR, using specific primers [29]. The amplification process was carried out under the following conditions: 94°C for 12 minutes, followed by 35 cycles of 94°C for 35 seconds, 62°C for 40 seconds, and 72°C for 40 seconds. The process was concluded with a final extension at 72°C for 10 minutes. The genotype for VNTR rs58335419 polymorphism on MIR 137 gene was determined through a PCR program. The PCR program included an initial denaturation at 94°C for 10 minutes, followed by 30 cycles of denaturation at 94°C for 1 minute, annealing at 62°C for 45 seconds, extension at 72°C for 45 seconds, and a final extension at 72°C for 10 minutes.

Afterward, the PCR products were separated using a 3% agarose gel with a voltage of 120 v for 30 minutes. Using a Gel Documentation system, we stained the gel with a safe stain method and then took photographs of the separated products. You can see the primer sequences of both miR-423 and MIR-137 genes in Table 1.

Table 1. Primer Sequence, PCR Band Size, and Sources

Gene			PCR Product	Source
miR-423 rs6505162C/T	FO	TTTTCCCGGATGGAAGCCCGAAGTTTGA	336 bp	[23]
	RO	TTTTGCGGCAACGTATACCCCAATTTCC		
	FI (T allele)	TGAGGCCCCTCAGTCTTGCTTCCCAA	228 bp	
	RI (C allele)	CAAGCGGGGAGAAACTCAAGCGCGAGG	160 bp	
MIR 137 VNTR rs58335419	F	5-CCCGAGGAAATG AAAAGAAC-3	396 bp 411 bp 426 bp 536 bp	[25]
	R	5- TTGGGCAGGAAGCAGCCGAG-3		

Statistical Analyses

We utilized the T-test to compare the demographic data of both the healthy and breast cancer groups. To determine the impact of predictor factors on the result, we conducted a regression analysis using computations of crude odds ratios (univariable), odds ratios (multivariable), and their 95% confidence intervals. The statistical analyses were performed using GraphPad Prism 9 software, and we considered a significance level of $P < .05$ as indicating statistical significance.

4. RESULTS AND DISCUSSION

Characteristics of the Study Population

The study included 110 cases of breast cancer and 80 healthy women as controls. Out of the 110 breast cancer patients, 34 (39.3%) were 40 years old or younger, and 76 (60.1%) were over 40. You can find a summary of the clinicopathological features of breast cancer cases in Table 2.

Table 2. Characteristics of Breast Cancer Patients: Clinical and Pathological Analysis

Parameters	Number	%
Breast cancer patient	110	57.89
Healthy control	80	42.11
Age group		
Age<40	34	39.9
Age >40	76	60.1
Stage Status		
Early (I & II)	62	56.36
Advanced (III & IV)	48	43. 64
Grading Status		
Early (T1 + T2)	68	61.2
Advanced (T2+T3)	42	38.8

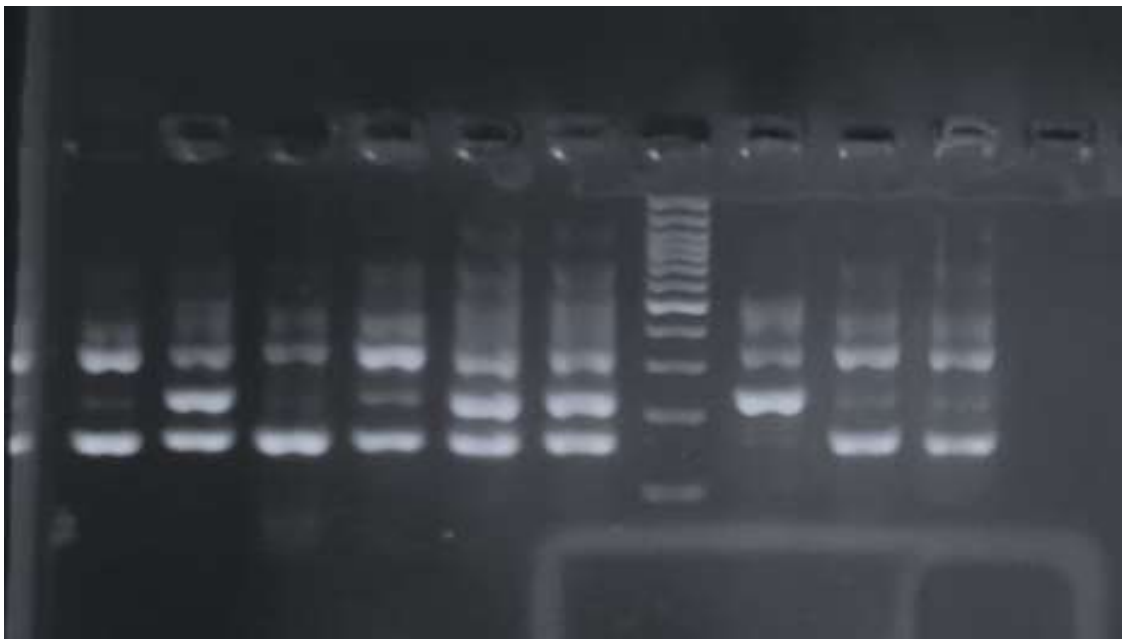


Figure 1. The PCR Products of the Mir-423 Rs6505162c/T Gene are Electrophoresis on an Agarose Gel (3%). M = Marker 100 Bp. Wells 1, 3, 8, and 9 Represent the CC Genotype. Well, 2, 4, 4 and 6 Represents the CT Genotype. Wells 7 Represent the TT Genotype

A total of 190 individuals were tested for their genotype using the polymerase chain reaction (PCR) method. To ensure the accuracy of the PCR, we analyzed the product on a 3% agarose gel. The study participants were found to have three distinct genotypes - CC, CT, and TT Figure 1. Based on the observed DNA bands, the genotypic frequencies and allelic frequencies were determined.

The of miR-423 rs6505162C/T analysis showed that genotypes CT [OR: 2.970 (95% CI: 1.630-6.534); RR: 1.629 (95% CI: 1.211-2.234); p = 0.001] and TT [OR: 3.548 (95% CI: 1.518-5.782); RR: 1.719 (95% CI: 1.229-2.387); p = 0.002] were significantly correlated with the risk of breast cancer statistically. In both the patient and control groups, the distribution and frequencies of the various miR-423 rs6505162C/T polymorphism genotypes are reported in Table 3.

Table 3. Allelic and Genotypic Distribution in Women Patients and Healthy with Statistical Analyses

Allele/genotype	Cases	Control	OR (95% CI)	Relative Risk (RR)	p-value
C /reference	115 (0.52 %)	115 (0.72 %)	1(ref.)		
T	105 (0.48 %)	45 (0.28 %)	2.333 (1.519-3.600)	1.400 (1.1841.655)	0.0001
Genotype					
CC	33	46	1(ref.)		
CT	49	23	2.970 (1.630 6.534)	1.629 (1.2112.234)	0.001
TT	28	11	3.548 (1.518 5.782)	1.719 (1.2292.387)	0.002

Figure 2 illustrates the distribution of miR-423 (rs6505162) genotypes among the patient group, based on the Clinicopathological Characteristics of Breast Cancer Patients. Figure 2 (A) displays the distribution based on Stage Status, which is categorized into Early (I & II) and Advanced (III & IV). On the other hand, Figure 2 (B) shows the distribution based on Grading Status, which is also classified into Early (T1 + T2) and Advanced (T2+T3).

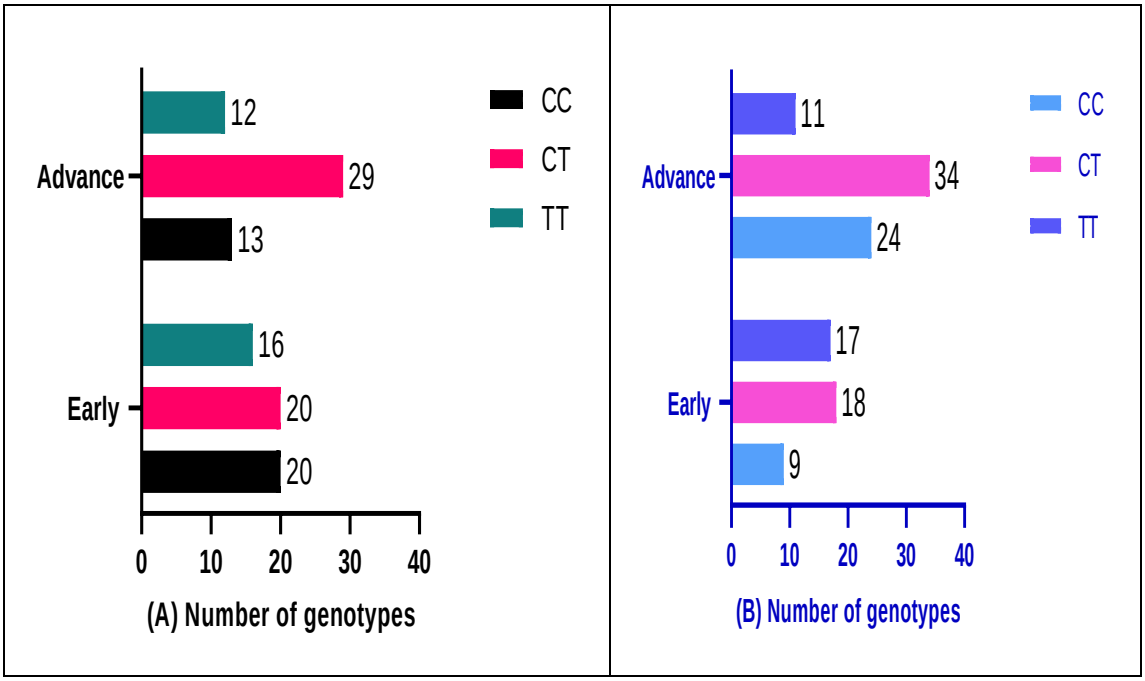


Figure 2. Mir-423 Rs6505162c/T Genotype Distribution by Stage (I & II as Early, III & IV as Advanced) in (A) and Grade (T1 + T2 as Early, T2 + T3 as Advanced) in (B)

The PCR product, which amplifies the DNA band for the allele with 3 repeats, has a length of 396 bp and increases by 15 bp for every additional repeat. The result was electrophoresed on a 3% agarose gel in order to evaluate the PCR's accuracy Figure 3. Genotype 3/3 produces two bands of 396 bp, genotype 4/4 produces two bands of 411 bp, genotype 5/5 produces two bands of 426 bp, and genotype 6/6 produces two bands of 536 bp. Two bands of 396 bp and 426 bp are found for genotype 3/5, two bands of 411 bp and 426 bp are found for genotype 4/5, and two bands of 426 bp and 536 bp are found for genotype 5/6. The distribution and frequencies of the various genotypes of the MIR 137 VNTR (rs58335419) found in the study population are shown in Table 4.

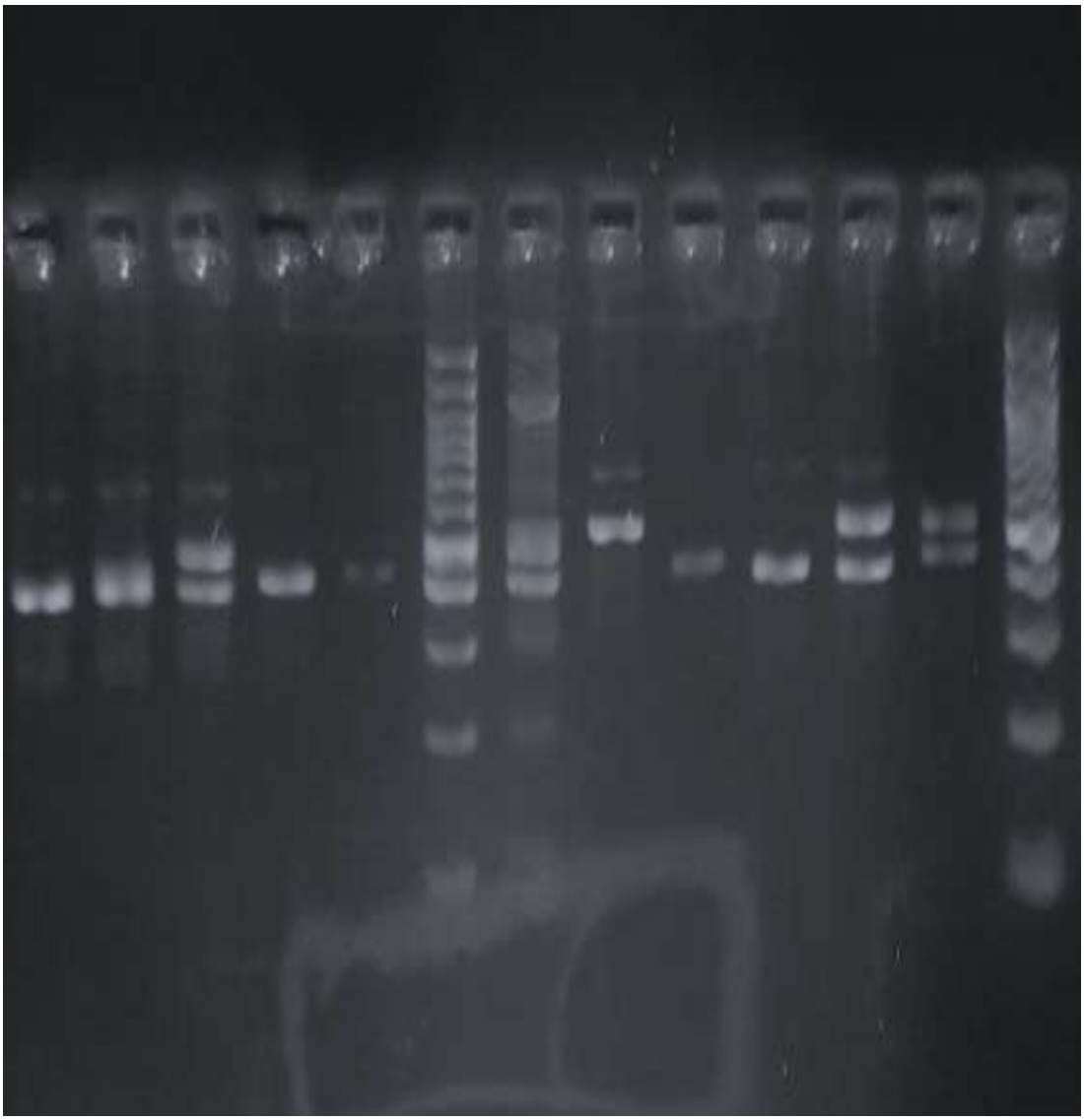


Figure 3. The PCR Products of the MIR 137 VNTR Rs58335419 Gene are Electrophoresis on an Agarose Gel (2%). M = Marker 100 Bp. Wells 1, 2, and 4 Represent the 3/3 Genotype. Well, 3 Represents the 3/5 Genotype. Well, 5 Represents the 4/4 Genotype. Wells 6 and 10 Represent the 4/5 Genotype. Well, 7 Represents the 6/6 Genotype Wells 8 and 9 Represent the 5/5 Genotype. Well, 11 Represents the 5/6 Genotype

The analysis of VNTR rs58335419 on the MIR 137 plate revealed that the genotypes 3/3, 4/4, 5/5, 6/6, 3/5, 4/5, and 5/6 were not statistically associated with breast cancer development. Table 4 shows the frequency distribution of VNTR rs58335419 genotypes in the study population.

Table 4. Allelic and Genotypic Distribution of MIR 137 VNTR Rs58335419 Gene in Women Patients and Healthy with Statistical Analyses

Allele	Cases	Control	OR (95% CI)	Relative Risk (RR) (95% CI)	P-value
3 /reference	74	44	1(ref.)		
4	41	45	1.846 (1.040 to 3.189)	1.315 (1.023 to 1.729)	0.0325
5	76	47	1.040 (0.6116 to 1.774)	1.015 (0.8317 to 1.238)	0.8825
6	29	24	1.392 (0.7386 to 2.735)	1.146 (0.8823 to 1.555)	0.3232
Genotype					
3/3	31	18	1(ref.)		
4/4	11	14	2.192 (0.8181 to 5.433)	1.438 (0.9240 to 2.458)	0.1136
5/5	17	6	0.6078 (0.1945 to 1.905)	0.8559 (0.6258 to 1.238)	0.3715
6/6	9	7	1.340 (0.4439 to 4.508)	1.125 (0.7442 to 1.971)	0.6165
3/5	12	8	1.148 (0.3653 to 3.171)	1.054 (0.7249 to 1.700)	0.7995
4/5	19	17	1.541 (0.6278 to 3.860)	1.199 (0.8354 to 1.791)	0.3317
5/6	11	10	1.566 (0.5744 to 4.208)	1.208 (0.8017 to 2.026)	0.3943

In the study, MIR 137 VNTR rs58335419 genotypes were analyzed among breast cancer patients based on clinicopathological characteristics. Figure 4 presents the genotype distribution among patients, categorized by stage status (Early: I & II, Advanced: III & IV) in (A) and by grading status (Early: T1 + T2, Advanced: T2 + T3) in (B).

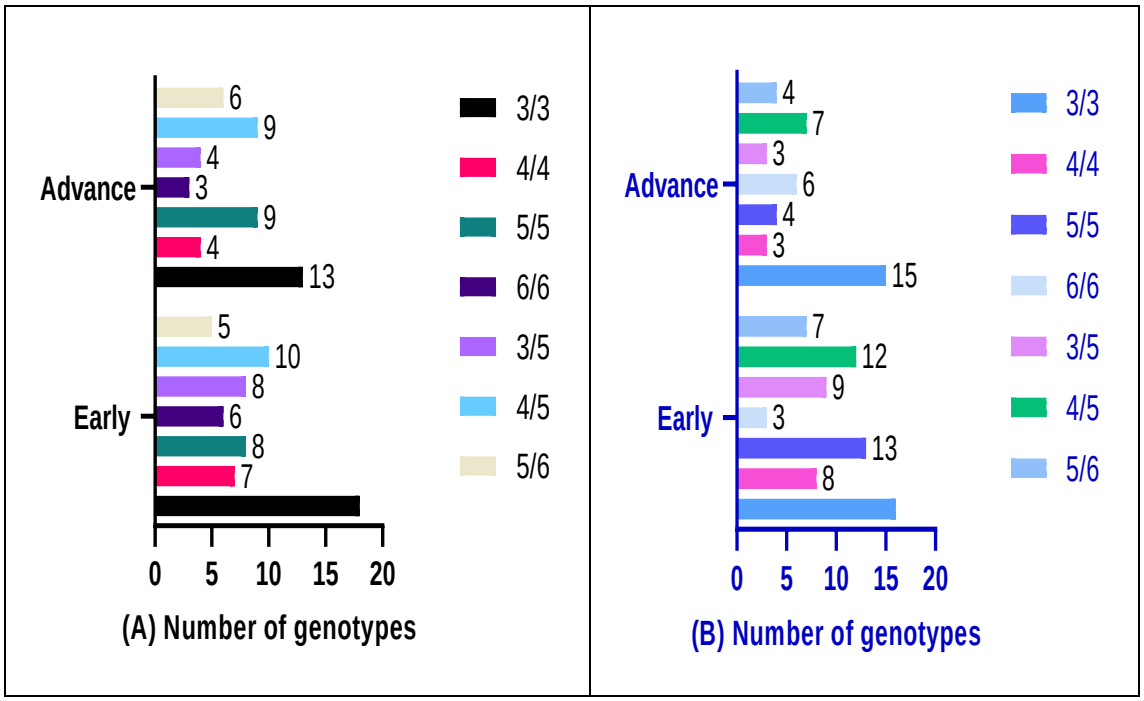


Figure 4. VNTR Rs58335419 Genotype Distribution by Stage (I & II as Early, III & IV as Advanced) in (A) and Grade (T1 + T2 as Early, T2 + T3 as Advanced) in (B).

Discussion

MicroRNAs (miRNAs) are small RNA molecules that regulate gene expression. They are found in various cancers, including breast cancer. However, the role of miRNAs in breast cancer oncogenesis is not

yet fully understood [30]. SNPs within miRNAs can impact transcription, processing, or target recognition, causing cancer [31].

The present study aimed to investigate the potential link between two miRNA variants - microRNA-423 and microRNA-137 - and the occurrence of breast cancer in a sample of the Iraqi population. Additionally, the purpose of the research was to investigate the correlation between these genetic variants and disease outcomes. It is worth noting that since the complementary sequence required for target gene recognition is relatively short, each miRNA can potentially target tens to hundreds of transcripts [32].

The study found a significant link between an increased risk of BC and the T allele of miR-423 rs6505162C/T (OR = 2.333, 95% CI: 1.519-3.600; RR= 1.4, 95% CI: 1.184-1.655 p = 0.0001). Based on a meta-analysis of miR-423 polymorphisms and cancer prognoses, rs6505162 is a prognostic marker across all common human cancers [33].

Recent studies and bioinformatics investigations suggest that rs6505162 may influence the expression of miR-423 [28]. It is necessary to conduct experiments to evaluate the impact of the rs6505162 SNP on the function of miR-423. Currently, [29] is the only research that has investigated the relationship between the SNP rs6505162:C>A and the process of metastasis in breast cancer patients. The results showed that the rs6505162 allele A is significantly associated ($p < 0.009$) with the occurrence of metastasis in Saudi Arabian breast cancer patients. This suggests that this allele is closely linked with the progression of the disease and the status of distant metastasis [29].

Among Egyptians, previous research has suggested that the miR-423 rs polymorphism could be a potential risk factor for breast cancer development [34]. The rs6505162 allele A is substantially linked to familial breast cancer risk in individuals with a strong family history, according to a study on breast cancer in South American women [35].

It was observed in the current study that there is no statistically significant correlation between the risk of breast cancer and 12 different genotypes of MIR 137 VNTR rs58335419. However, multiple other studies have reported that miR-137 plays a crucial role in inhibiting the growth and progression of tumors, either directly or indirectly [36]. The promoter region adjacent to the pre-miR-137 sequence contains a variable number tandem repeat (VNTR) domain [37].

The VNTR genotype modified reporter gene activity directed by this promoter, which contrasts early studies suggesting miR-137 as a medicinal biomarker for BC individuals [36]. Early analysis of MIR137 VNTR showed significant repeat distribution differences between BRCA-positive and BRCA-negative patients. The study also found significant differences in repeat distribution between BRCA1 and BRCA2 germline mutation carriers using clump statistical analysis [38].

In general, genetic variations have a direct or indirect impact on the susceptibility to breast cancer, which may be related to the type of the disease, whether it is monogenic or polygenic. However, there are other factors to consider such as sample size, study population, age, and the presence of other diseases associated with breast cancer. Despite these factors, the underlying mechanisms that link genetic variations to breast cancer susceptibility remain unclear [39].

5. CONCLUSION

According to this study, alleles with more than three repeats in the microRNA-423 rs6505162 are significantly associated with a higher chance of breast cancer. Although there were no statistically significant associations found between alleles in the miRNA-137 gene VNTR (rs58335419) and breast cancer risk, these findings could potentially aid in the development of a biomarker for breast cancer screening.

Acknowledgments

The author sincerely acknowledges the support and guidance provided by the Department of Paramedical Sciences, Radiology, Netherlands, in carrying out this study. Special thanks are extended to

the clinical radiology team for their valuable input on imaging protocols and patient care standards. The author is also grateful to the researchers and professionals whose studies and references have contributed to this work.

Funding Information

No specific grant from any funding agency in the public, commercial, or not-for-profit sectors was received for this research. The study was carried out as part of academic and clinical practice activities.

Author Contributions Statement

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Nahidah Kzar Madhloom	✓	✓	✓	✓	✓	✓		✓		✓	✓	✓	✓	

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

Conflict of Interest Statement

The author declares no conflicts of interest related to the preparation, content, or publication of this manuscript.

Informed Consent

The study did not involve direct experimentation on human subjects or animals. All data and imaging protocols mentioned are based on standard clinical practices and published guidelines. Patient privacy and confidentiality were strictly maintained, with no personal identifiers included in the study.

Data Availability

The data supporting this research are derived from standard imaging protocols and clinical practice references. Any additional details regarding imaging parameters, phases of abdominal CT scans, or study-related materials can be made available by the corresponding author upon reasonable request.

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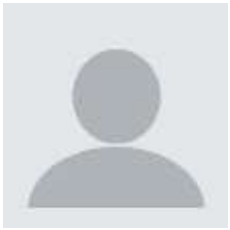
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How to Cite: Nahidah Kzar Madhloom. (2025). Genetic variation in microRNA-423 and microRNA-137 genes among patients with breast cancer, Journal of Prevention, Diagnosis and Management of Human Diseases (JPDMHD), 5(1), 20-31. https://doi.org/10.55529/jpdmhd.51.20.31

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