

Integrative Analysis of miR-SNP–Associated Alterations in miRNA Expression and Regulatory Networks in Breast Cancer: A Systematic Review

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Abstract

Genetic variants located within mature miRNA-coding regions (miR-SNPs) have been implicated in breast cancer susceptibility; however, their regulatory effects on mature miRNA expression and downstream function remain incompletely characterized and inconsistently reported. In this study, we performed an integrative analysis of 3 miR-SNPs (rs11614913, rs2910164 and rs3746444) by combining evidence from population-based studies, TCGA transcriptomic data, and *in silico* analyses. A systematic literature search identified eligible population-based and cell-based studies examining rs11614913 (miR-196a), rs2910164 (miR-146a), or rs3746444 (miR-499a) in relation to mature miRNA expression. Meta-analyses were conducted under codominant, dominant, recessive, and over-dominant genetic models using standardized mean difference (SMD, Hedges' *g*) to accommodate heterogeneous expression metrics. Expression patterns of mature miRNAs were further examined using TCGA-BRCA miRNA-sequencing data, while miRNA–target interaction networks and binding energy changes (ΔG) were analyzed *in silico* to explore potential regulatory alterations. Population-based meta-analyses revealed genetic model-dependent associations, including a moderate association between rs11614913 and miR-196a-5p expression under the homozygote model (SMD = 0.49, 95% CI: 0.19 - 0.78, $p = 0.001$) and a small but significant association between rs2910164 and miR-146a-5p expression under the dominant model (SMD = 0.41, 95% CI: 0.13 - 0.69, $p = 0.004$), whereas evidence for rs3746444 was limited to single-study data. Cell-based experiments demonstrated strand-specific effects, with rs11614913 preferentially affecting miR-196a-5p expression and rs2910164 primarily influencing miR-146a-3p levels, highlighting context-dependent regulatory patterns. TCGA analyses showed significant upregulation of miR-146a-3p and miR-499a-3p in breast cancer tissues, while both miR-196a strands were upregulated; however, genotype-specific associations could not be assessed. *In silico* predictions suggested that these miR-SNPs may alter miRNA–target interaction networks involving cancer-related pathways. Collectively, this study provides preliminary and exploratory evidence that miR-SNPs are associated with strand- and genetic model-dependent variation in miRNA expression. Given the limited number of eligible studies and the lack of genotype-resolved tumor data, these findings should be interpreted with caution and are intended to provide a structured framework for future functional and clinical investigations.

Keywords: Breast cancer, miR-SNP, MicroRNA expression, rs2910164, rs11614913, rs3746444, Meta-analysis

Introduction

Breast cancer (BC) remains the most frequently diagnosed malignancy and a leading cause of cancer-

related mortality among women worldwide [1]. Despite substantial advances in early detection and targeted therapies, breast cancer exhibits marked molecular

heterogeneity, which contributes to variable clinical outcomes and therapeutic responses [2]. Understanding the genetic and epigenetic mechanisms underlying BC development and progression is therefore essential for improving risk stratification and identifying novel molecular targets [3].

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression at the post-transcriptional level by binding to complementary sequences within target messenger RNAs (mRNAs) [4]. Through this mechanism, miRNAs are involved in the regulation of key biological processes, including cell proliferation, apoptosis, differentiation, and immune responses [5]. Dysregulation of miRNA expression has been widely reported in BC and has been implicated in tumor initiation, progression, and metastasis [6]. Consequently, miRNAs have attracted considerable interest as potential biomarkers and therapeutic targets in BC [7,8].

Single-nucleotide polymorphisms located within miRNA genes, particularly within mature miRNA-coding regions (miR-SNPs), represent an important source of inter-individual variability in miRNA function [9]. Variants occurring within the seed region (nucleotides 2 - 8 from the 5' end of the mature miRNA) may directly disrupt target recognition by altering base-pairing with complementary sequences in target mRNAs, thereby leading to the loss or gain of target genes [10]. In contrast, miR-SNPs located outside the seed region may affect miRNA function through alternative mechanisms, including changes in miRNA secondary structure, strand stability, loading efficiency into the RNA-induced silencing complex (RISC), or the thermodynamics of miRNA-mRNA binding [11]. Through these mechanisms, both seed and non-seed miR-SNPs can reshape miRNA regulatory networks. Consequently, mature miRNA-coding miR-SNPs have been increasingly recognized as potential biomarkers of cancer susceptibility and modulators of oncogenic signaling pathways [9,11].

In our previous meta-analyses, rs11614913 located in the mature miR-196a-3p sequence, rs2910164 located in miR-146a-3p, and rs3746444 located in miR-499a-3p were identified as miRNA-coding SNPs associated with BC [12]. Population-based studies have reported associations between these variants and BC risk, prognosis, and treatment response across different

ethnicities [13,14]. However, evidence regarding their impact on miRNA expression remains inconsistent, with conflicting findings reported across studies and genetic models [15]. Moreover, it remains unclear whether these miR-SNPs exert consistent regulatory effects on miRNA expression or lead to broader alterations in downstream gene regulatory networks relevant to BC biology [16].

Although accumulating evidence supports the biological relevance of mature miRNA-coding miR-SNPs, their functional consequences have not been comprehensively characterized. Most previous investigations have primarily focused on genetic associations with disease risk [17], whereas studies addressing the effects of these variants on miRNA expression and regulatory function are limited and fragmented. In particular, integrative analyses that combine population-based evidence with transcriptomic data and functional evaluations are scarce, leaving an important gap in understanding how miR-SNP-associated sequence variations translate into measurable molecular alterations in BC.

Therefore, this study aimed to comprehensively evaluate the potential functional relevance of selected mature miRNA-coding variants (rs11614913, rs2910164 and rs3746444) in breast cancer by integrating evidence from expression-based meta-analyses and *in silico* analyses of miRNA-target interaction networks.

Materials and methods

Search strategy

A comprehensive literature search was conducted in PubMed, Crossref, Scopus, and Google Scholar from inception to December 8th, 2025. The search strategy focused on identifying studies reporting the effects of miR-SNPs on mature miRNA expression in breast cancer. The core search terms were: (microRNA OR miRNA) AND (polymorphism OR SNP OR variant) AND (expression OR level OR quantification OR fold change) AND (breast cancer OR breast carcinoma). In addition, individual SNP terms were included to ensure maximum retrieval: rs11614913 OR rs2910164 OR rs3746444. No restrictions on publication year were applied. This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-

Analyses (PRISMA) 2020 guidelines [18]. A formal PRISMA checklist is provided in **Table S1**. This review was not prospectively registered, which is acknowledged as a limitation; future updates should be registered in a comparable registry to enhance methodological transparency.

Eligibility criteria

Studies were included if they met the following criteria: (1) Investigated at least one of the 3 selected miR-SNPs. (2) Reported expression levels of the corresponding mature miRNA stratified by genotype. (3) Used human samples (breast tissue or blood) or human-derived breast cancer cell lines. (4) Provided extractable quantitative data (mean $\Delta\text{Ct} \pm \text{SD}$, fold-change, or relative expression). Articles were excluded if they met any of the following criteria: (1) Reviews, commentaries, and conference abstracts without primary data. (2) Studies lacking genotype-specific expression data. (3) Animal-only studies. (4) Functional studies without miRNA expression measurements.

Data extraction

Two reviewers independently extracted key information from each included study, including the authors, publication year, country, study design, and sample type. Data on the specific miR-SNP investigated, genotype groups, and corresponding sample sizes were also collected. Details on the methods used for miRNA quantification (RT-qPCR, microarray, or RNA-seq) and the reported expression values (mean $\Delta\text{Ct} \pm \text{SD}$, relative expression, or fold change) were recorded. Any discrepancies between reviewers were resolved through discussion and consensus.

Quality assessment

The methodological quality of included studies was evaluated using the Office of Health Assessment and Translation (OHAT) Risk of Bias (RoB) Tool developed by the National Toxicology Program (NTP). Six domains were assessed, with 3 considered key domains including selection bias, confounding, and detection bias. Each domain was rated as “definitely low” or “probably low” risk of bias, “probably high” or “definitely high” risk of bias [19]. Two reviewers independently assessed all studies, and any discrepancies were resolved through discussion and

consensus. In accordance with OHAT guidelines, an outcome-specific assessment was performed, and no overall numerical score was calculated. Studies were considered acceptable quality if all key OHAT domains were judged as definitely low or probably low risk of bias [20]. The judgments were summarized and visualized using a categorical heatmap, in which different colors represent different levels of risk of bias across domains and studies.

TCGA-based analysis of mature miRNA expression in breast cancer

To validate whether mature miRNAs harboring miR-SNPs exhibit aberrant expression patterns in breast cancer, mature miRNA expression data were retrieved from The Cancer Genome Atlas breast invasive carcinoma (TCGA-BRCA) cohort via the UCSC Xena browser (<https://xenabrowser.net>). Normalized miRNA-seq datasets generated using the Illumina HiSeq and Illumina Genome Analyzer (GA) platforms were used. Mature miRNAs corresponding to miR-146a-3p, miR-146a-5p, miR-196a-3p, miR-196a-5p, miR-499a-3p, and miR-499a-5p were identified based on their mature accessions (MIMAT0004608, MIMAT0000449, MIMAT0004562, MIMAT0000226, MIMAT0004772, and MIMAT0002870, respectively). Differential expression of these mature miRNAs between primary breast tumor and solid normal breast tissue samples was evaluated using an unpaired 2-tailed t-test. Statistical significance was defined as a p value < 0.05 .

miRNA-target interaction network construction

Putative target genes of miR-196a-3p, miR-146a-3p, and miR-499a-3p involved in the breast cancer pathway were identified using the multiMiR package in R (version 4.5.2), which integrates experimentally validated and computationally predicted miRNA-target interactions from multiple public databases [21].

Experimentally validated interactions curated in miRTarBase, TarBase, and miRecords were retained as high-confidence targets [22]. In parallel, computationally predicted interactions from miRDB, miRanda, DIANA-microT, and PicTar were included only when supported by at least 2 independent prediction algorithms, thereby minimizing false-positive predictions. These filtered targets were subsequently used for

downstream analyses. Interaction networks were visualized to illustrate the regulatory relationships between miRNAs and breast cancer-related genes.

To evaluate the potential impact of miR-SNPs on miRNA-target interactions, miRNA binding sites within target mRNAs were identified using TargetScan. The minimum free energy (MFE) of miRNA-mRNA duplex formation was subsequently calculated using IntaRNA [23]. Changes in binding energy (ΔG) were calculated as the difference between variant and reference MFE values. Positive ΔG values indicated reduced binding affinity, whereas negative ΔG values suggested enhanced miRNA-target interactions [24].

Statistical analysis

Meta-analyses were conducted to evaluate differences in miRNA expression levels between genotype groups under codominant, dominant, recessive, and over-dominant genetic models. Because the included studies reported miRNA expression using different quantitative metrics, including ΔCt , $2^{-\Delta Ct}$ values and fold change, standardized mean difference (SMD) was used as the summary effect size. The SMD enables pooling of continuous outcomes measured on different scales by standardizing the mean difference between comparison groups using the pooled standard deviation, as recommended by the Cochrane Handbook for Systematic Reviews of Interventions [25]. Expression values were directionally harmonized prior to analysis so that higher values uniformly indicated higher miRNA expression, with ΔCt measures inverted when applicable.

For each comparison, SMDs were calculated as Hedges' g , defined as the difference in mean miRNA expression between the comparison and reference genotype groups, standardized by the pooled standard deviation, with a correction for small-sample bias [26]. Pooled effect estimates are presented as SMDs with corresponding 95% confidence intervals (CIs). Positive SMD values indicate higher miRNA expression in the comparison genotype group, whereas negative SMD values indicate lower expression relative to the reference group. Statistical significance was defined as a 2-sided p value < 0.05 or when the 95% CI did not include 0 [27]. The magnitude of effect sizes was interpreted according to conventional criteria, with SMD values of approximately 0.2, 0.5, and 0.8

representing small, moderate, and large effects, respectively. Between-study heterogeneity was assessed using Cochran's Q test and quantified by the I^2 statistic. A fixed-effects model was applied when between-study heterogeneity was low ($I^2 < 50\%$), assuming a common true effect size across studies. Under this model, individual study estimates were pooled using inverse-variance weighting, with weights defined as weight $w_i = 1/SE_i^2$. The pooled effect size was calculated as $SMD_{FE} = (\sum w_i \cdot SMD_i) / (\sum w_i)$. When substantial heterogeneity was detected ($I^2 \geq 50\%$), a random-effects model based on the DerSimonian-Laird method was employed to account for between-study variability. In this model, the between-study variance (τ^2) was incorporated into the weighting scheme, such that the adjusted weights were defined as $w_i^* = 1 / (SE_i^2 + \tau^2)$, and the pooled effect estimate was calculated as $SMD_{RE} = (\sum w_i^* \cdot SMD_i) / (\sum w_i^*)$ [28]. To minimize false discovery resulting from multiple comparisons across 4 genetic models, a Bonferroni-corrected significance threshold of $p < 0.0125$ was applied [29]. For transparency, uncorrected p -values are also reported alongside the corrected threshold.

Sensitivity analyses were conducted to assess the robustness of the pooled estimates by sequentially omitting one study at a time (leave-one-out analysis) and recalculating the summary effect size. The stability of the overall results was evaluated by examining changes in the magnitude and statistical significance of the pooled SMDs following each omission. Publication bias was assessed using visual inspection of funnel plot asymmetry and Egger's regression test when a sufficient number of studies were available for a given comparison ($n \geq 3$). All meta-analyses were performed using R software (version 4.5.2) with the metafor package.

Results and discussion

Study selection

A total of 1,051 records were identified through database searching. After removing 140 duplicates, 911 records remained for title and abstract screening. Of these, 860 records were excluded because they were unrelated to miR-SNPs, did not report miRNA expression data, focused on diseases other than breast cancer, or were review articles or other non-original research. A total of 51 full-text articles were assessed for eligibility. Among these, 45 were excluded for reasons

including insufficient or non-quantitative miRNA expression data or lack of genotype-stratified expression results. Ultimately, 6 studies met the inclusion criteria and were included in the systematic review; those providing comparable quantitative data were

incorporated into the meta-analysis. The PRISMA flowchart is presented in **Figure 1**. All included studies were judged to have acceptable methodological quality based on the OHAT risk-of-bias assessment (**Figure S1**).

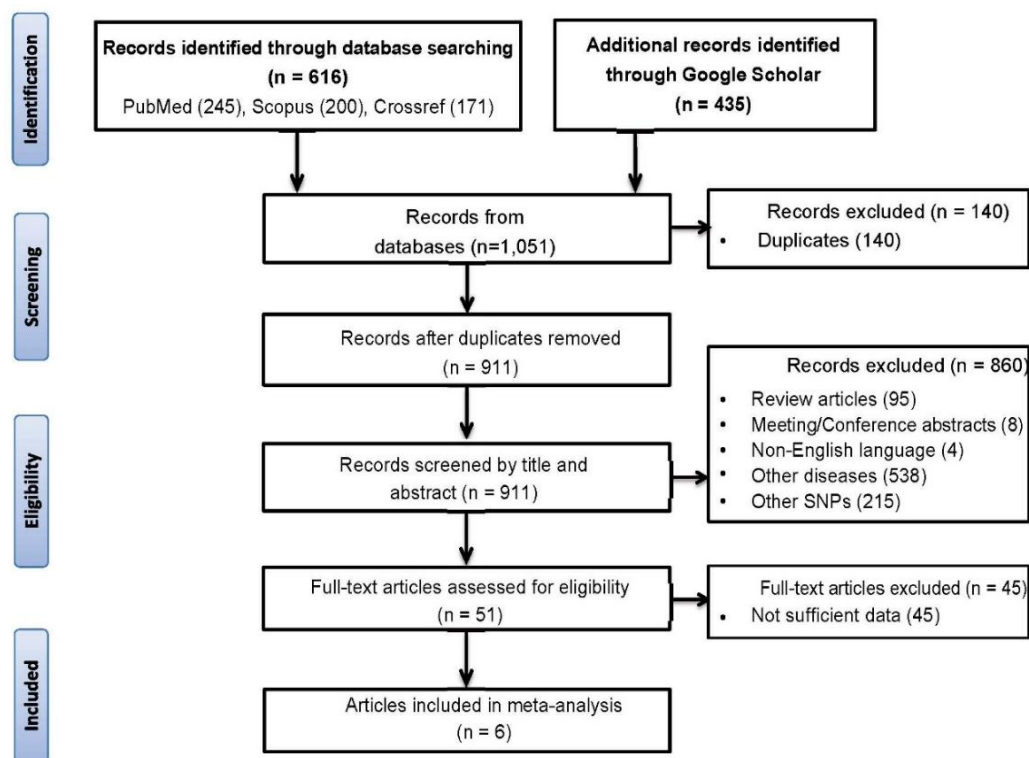


Figure 1 PRISMA flow diagram of study selection for the systematic review. The diagram summarizes the processes of literature identification, screening, eligibility assessment, and final inclusion of studies based on predefined criteria.

Main characteristics of the included studies

A total of 6 eligible studies published between 2008 and 2025 were included in the meta-analysis, collectively investigating 3 miR-SNPs (rs11614913 in miR-196a, rs2910164 in miR-146a and rs3746444 in miR-499a) and their associations with mature miRNA expression levels (**Table 1**). Among these, 4 studies evaluated rs11614913 (C/T), 3 examined rs2910164 (C/G), and one assessed rs3746444 (A/G). Genotyping was performed using validated platforms, including TaqMan assays, Sanger sequencing, and MassARRAY technology.

Mature miRNA expression levels were quantified primarily by SYBR Green-based or TaqMan-based real-time quantitative PCR. With respect to biological materials, 3 studies analyzed tumor tissue specimens, one utilized peripheral blood samples, and 2 were conducted in vitro using breast cancer cell lines (MCF-7 and MDA-MB-231). Sample sizes varied considerably across studies, ranging from small-scale cell-based experiments with 3 samples per genotype group to population-based investigations comprising up to 321 participants.

Table 1 Characteristics of studies included in the systematic review and meta-analysis evaluating the association between miR-SNPs and mature miRNA expression in breast cancer.

Author (ref)	Country	MiR-SNP	Alleles (Ref/Alt)	Genotyping method	MiRNA	Expression profiling method	Sample type	Expression by genotype (mean $\Delta\text{Ct}/\text{FC} \pm \text{SD}$)			Genotype sample size (n)		
								Hom_Ref	Hom_Alt	Het	Hom_Ref	Hom_Alt	Het
Qi <i>et al.</i> [30]	China	rs11614913	C/T	TaqMan	miR-196a-5p	SYBR Green	Tumor tissue	0.52 $\pm$ 0.3	1.00 $\pm$ 0.10	0.76 $\pm$ 0.90	34	168	119
		rs2910164	C/G		miR-146a-5p	RT-qPCR		0.55 $\pm$ 0.03	1.00 $\pm$ 0.13	0.84 $\pm$ 0.08	43	146	132
Alshatwi, <i>et al.</i> [31]	Saudi Arabia	rs11614913	C/T	TaqMan	miR-196a-5p	SYBR Green	Blood	5.83 $\pm$ 0.77	3.89 $\pm$ 0.28	4.53 $\pm$ 0.75	24	26	42
	Arabia	rs2910164	C/G		miR-146a-5p	RT-qPCR		1.74 $\pm$ 0.07	0.59 $\pm$ 0.28	1.72 $\pm$ 0.06	29	26	35
		rs3746444	A/G		miR-499a-5p			5.12 $\pm$ 0.36	4.16 $\pm$ 0.30	4.66 $\pm$ 1.03	25	23	44
Zhao <i>et al.</i> [32]	China	rs11614913	C/T	Sanger sequencing	miR-196a-5p	Taqman RT-qPCR	Tumor tissue	3.21 $\pm$ 1.00	1.19 $\pm$ 0.24	2.76 $\pm$ 0.85	10	10	10
Hoffman <i>et al.</i> [33]	USA	rs11614913	C/T	MassARRAY	miR-196a-5p	SYBR Green	MCF-7 cells	9.30 $\pm$ 1.37	4.40 $\pm$ 0.67	NA	3	3	NA
					miR-196a-3p	RT-qPCR		3.10 $\pm$ 0.43	3.40 $\pm$ 0.07	NA	3	3	NA
Shen <i>et al.</i> [34]	USA	rs2910164	C/G	Sanger sequencing	miR-146a-5p	Taqman RT-qPCR	MCF-7 cells	1.58 $\pm$ 0.10	1.00 $\pm$ 0.01	NA	3	3	NA
Morales-González <i>et al.</i> [16]	Chile	rs2910164	C/G	Sanger sequencing	miR-146a-5p	Taqman RT-qPCR	MCF-7 cells	10.75 $\pm$ 0.33	11.02 $\pm$ 0.30	NA	3	3	NA
							MDA-MB-231 cells	3.01 $\pm$ 0.42	0.78 $\pm$ 0.36	NA	3	3	NA
					miR-146a-3p		MCF-7 cells	11.14 $\pm$ 0.53	4.37 $\pm$ 0.78	NA	3	3	NA
							MDA-MB-231 cells	9.88 $\pm$ 0.84	7.28 $\pm$ 0.19	NA	3	3	NA

NA, not applicable; Hom_Ref, reference homozygote (Ref/Ref); Hom_Alt, alternative homozygote (Alt/Alt); Het, heterozygote (Ref/Alt).

Association of SNP genotypes with miRNA expression

The investigated miR-SNPs are located within the mature 3p sequences of miR-196a, miR-146a, and miR-499a. However, because these variants reside in the 3p arm of the pre-miRNA hairpin, their potential impact is not necessarily restricted to the expression of the 3p strand. Alterations in the local hairpin structure or strand asymmetry may influence miRNA processing and strand selection, thereby affecting the relative abundance of the corresponding 5p strand, which represents the predominantly expressed form for these miRNAs. Accordingly, the associations between miR-SNP genotypes and expression levels of both strands were evaluated.

Across the included studies, the expression levels of mature miRNAs were compared among genotype groups of the investigated miR-SNPs using homozygote, heterozygote, dominant, recessive, and over-dominant genetic models, with the SMD used as the effect size.

To evaluate the association between the rs11614913 polymorphism and miR-196a-5p expression levels, a meta-analysis including 3 eligible studies [30-32] was conducted. Due to the low heterogeneity observed across studies (**Figure 2(a)**), fixed-effects models were applied for most genetic model analyses. The pooled analysis under the homozygote model (TT vs. CC) demonstrated a significant association between rs11614913 and miR-196a-5p expression, with a moderate effect size (SMD = 0.49, 95% CI: 0.19 - 0.78, $p = 0.001$). In contrast, no significant associations were detected under the heterozygote (CT vs. CC; $p = 0.19$), dominant (CT+TT vs. CC; $p = 0.11$), recessive (TT vs. CC+CT; $p = 0.21$), or over-dominant (CT vs. CC+TT; $p = 0.33$) models (**Figure 2(a)**).

In addition, the association between rs11614913 and the expression of miR-196a-3p and miR-196a-5p was further evaluated using data from one eligible cell-based study [33]. In MCF-7 cells, transfection with the T allele of rs11614913 resulted in a significantly lower expression level of miR-196a-5p compared with the C allele (SMD = -2.09, 95% CI: -4.08 to -0.10). Conversely, the T allele was associated with an increased expression of miR-196a-3p; however, this difference was not

statistically significant (SMD = 0.45, 95% CI: -1.17 to 2.07; $p = 0.59$) (**Figure 3**).

For rs2910164, the association between genotype and miR-146a-5p expression was assessed using data from 2 eligible studies [30,31]. Under the homozygote comparison (GG vs. CC), the pooled analysis revealed a moderate effect size; however, this association did not reach statistical significance (SMD = 0.68, 95% CI: -0.09 to 1.46, $p = 0.08$). In contrast, a statistically significant association was observed under the dominant genetic model (CG + GG vs. CC), indicating altered miR-146a-5p expression in carriers of the G allele compared with the CC genotype, with a small but significant effect size (SMD = 0.41, 95% CI: 0.13 - 0.69, $p = 0.004$). No significant associations were detected under the heterozygote (CG vs. CC; $p = 0.07$), recessive (GG vs. CC + CG; $p = 0.20$), or over-dominant (CG vs. CC + GG; $p = 0.29$) genetic models (**Figure 2(b)**).

Furthermore, functional evidence from 2 independent cell-based studies [16,34] was used to evaluate the effect of rs2910164 alleles on miR-146a strand expression. In breast cancer cells, transfection with the G allele was not significantly associated with changes in miR-146a-5p expression compared with the C allele (SMD = -1.53, 95% CI: -3.88 to 0.83; $p = 0.20$). For miR-146a-3p, a marked reduction in expression was observed in cells transfected with the G allele, with a large effect size (SMD = -3.05, 95% CI: -5.65 to -0.45; $p = 0.02$) (**Figure 3**).

Due to the limited number of available studies, only one study [31] was included in the analysis of the association between rs3746444 genotypes and miR-499a-5p expression. Under the homozygote genetic model, individuals carrying the GG genotype showed significantly higher miR-499a-5p expression compared with those carrying the AA genotype, with a moderate effect size and borderline nominal significance (SMD = 0.58, 95% CI: 0.00 - 1.15; $p = 0.05$). However, this association did not remain statistically significant after multiple-testing correction. No statistically significant associations were observed under the heterozygote (AG vs. AA), dominant (AG + GG vs. AA), recessive (GG vs. AA + AG), or over-dominant (AG vs. AA + GG) genetic models (all $p > 0.0125$) (**Figure 2(c)**). These findings suggest that any potential effect of

rs3746444 on miR-499a-5p expression may be limited to the homozygous GG genotype and should be interpreted cautiously given the lack of significance after multiple-testing correction.

Information on clinical characteristics, including disease stage and recurrence status, was not consistently reported across the included studies. Consequently, stratified analyses comparing miRNA expression between early-stage and recurrent breast cancer could not be performed.

Between-study heterogeneity varied across the analyzed miR-SNPs. Low heterogeneity was observed for rs11614913 in analyses of miR-196a-5p and miR-196a-3p expression ($I^2 < 50\%$), suggesting relatively consistent effect estimates across studies. For rs3746444 and miR-499a-5p

expression, heterogeneity could not be assessed because only a single eligible study was available. In contrast, substantial heterogeneity was detected in analyses involving rs2910164 and miR-146a-3p expression ($I^2 > 50\%$) under the homozygote, recessive, and over-dominant genetic models, as well as in cell-based analyses. However, only 2 eligible population-based studies were available for this comparison, precluding formal subgroup or meta-regression analyses. The observed heterogeneity may reflect differences in study populations, sample types, and experimental platforms in population-based studies, as well as variability in cellular context between different breast cancer cell lines used in functional experiments.

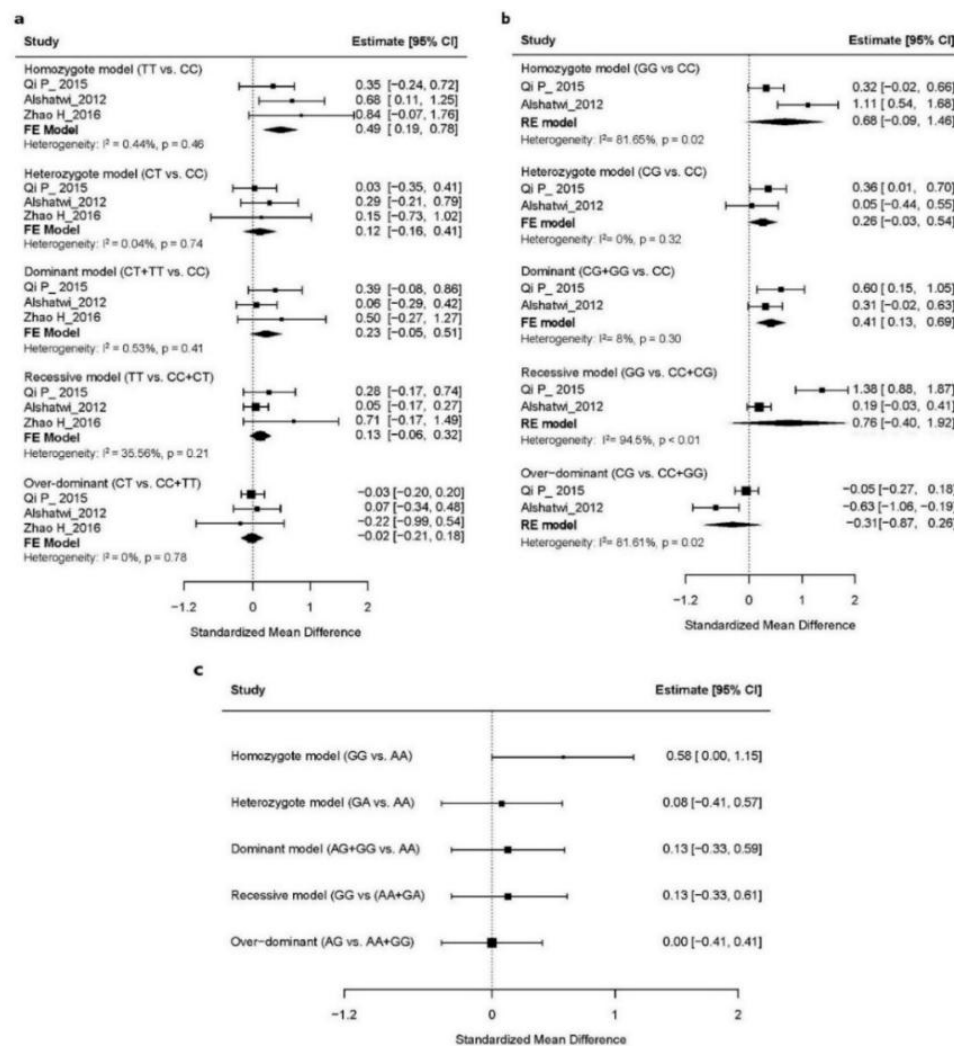


Figure 2 Forest plot illustrating the association between miR-SNPs and mature miRNA expression in population-based studies. (a) Association of rs11614913 genotypes with miR-196a-5p expression; (b) Association of rs2910164 genotypes with miR-146a-5p expression; (c) Association of rs3746444 genotypes with miR-499a-5p expression. Data are presented as standardized mean differences (SMD) with 95% confidence intervals (CI). Each study is represented by a square (size proportional to study weight), and the pooled effect is shown as a diamond.

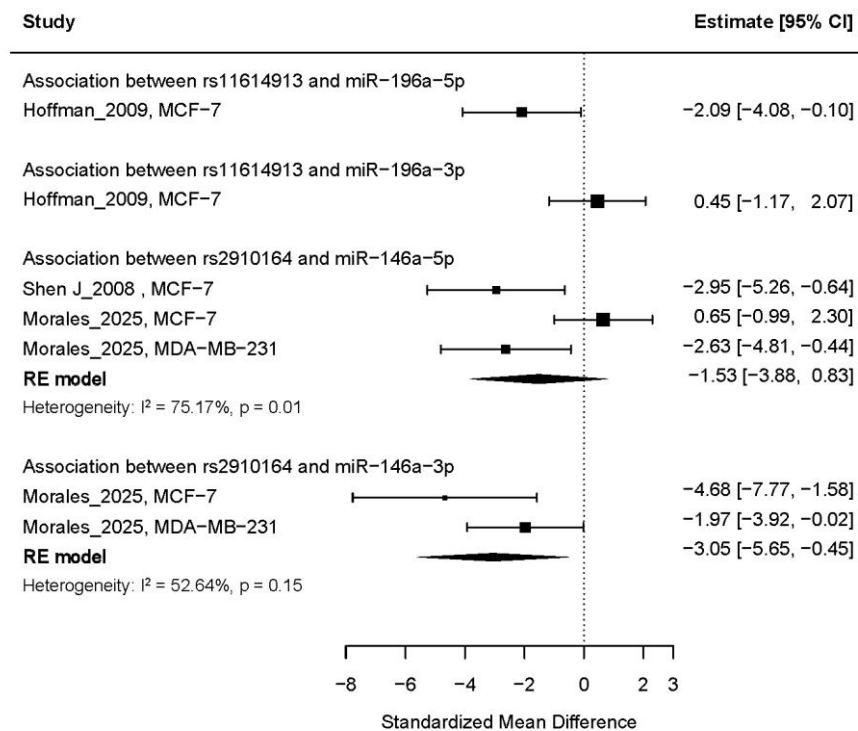


Figure 3 Forest plot illustrating the association between miR-SNPs and mature miRNA expression in cell-based studies. Data are presented as standardized mean differences (SMD) with 95% confidence intervals (CI). Each study is represented by a square (size proportional to study weight), and the pooled effect is shown as a diamond.

Publication bias and sensitivity analysis

Publication bias was assessed in analyses that included at least 3 independent studies, comprising the genetic models evaluating the association between rs11614913 and miR-196a-5p expression in population-based datasets, as well as the analysis of miR-146a-5p expression in cell-based experiments. Funnel plot asymmetry tests indicated no significant evidence of publication bias for the population-based analyses of miR-196a-5p across the homozygote ($p = 0.36$), heterozygote ($p = 0.77$), dominant ($p = 0.26$), recessive ($p = 0.09$), and over-dominant ($p = 0.94$) genetic models (**Figures S2(a) - S2(e)**).

In contrast, a significant publication bias was detected in the cell-based analysis of miR-146a-5p expression ($p = 0.003$; **Figure S2(f)**), suggesting that these findings should be interpreted with caution, particularly given the limited number of eligible studies and the heterogeneity of experimental conditions across cell line models.

Sensitivity analyses were performed to evaluate the robustness of the pooled estimates. Sequential omission of individual studies did not result in substantial changes in the overall effect

sizes for the association between rs11614913 and miR-196a-5p expression across all genetic models (**Figures S3(a) - S3(e)**), indicating that the meta-analytic results were stable and not driven by any single study.

Expression patterns of mature miRNAs harboring miR-SNPs in breast cancer

The expression levels of mature miRNAs harboring miR-SNPs, including miR-146a-3p/5p, miR-196a-3p/5p, and miR-499a-3p/5p, were evaluated using data from The Cancer Genome Atlas (TCGA). MiR-146a-3p expression was significantly higher in breast cancer tissues than in normal controls ($p < 0.002$), whereas no significant difference was observed for miR-146a-5p ($p = 0.52$; **Figure 4(a)**). Similarly, both miR-196a-3p and miR-196a-5p showed markedly increased expression levels in breast cancer samples compared with controls (both $p < 0.0001$; **Figure 4(b)**). In contrast, miR-499a-3p exhibited a modest but statistically significant upregulation in breast cancer tissues ($p = 0.04$), while miR-499a-5p expression did not differ significantly between tumor and normal groups ($p = 0.77$; **Figure 4(c)**).

All 3 analyzed miR-SNPs are located within the mature 3p sequences. In the TCGA dataset, expression differences were predominantly observed for the corresponding 3p miRNAs. The TCGA-BRCA dataset does not provide genotype-resolved information for these variants, nor does it include

stratification by early-stage versus recurrent disease; therefore, the results presented here reflect overall comparisons between tumor and normal tissues without stratification by SNP genotype or disease stage.

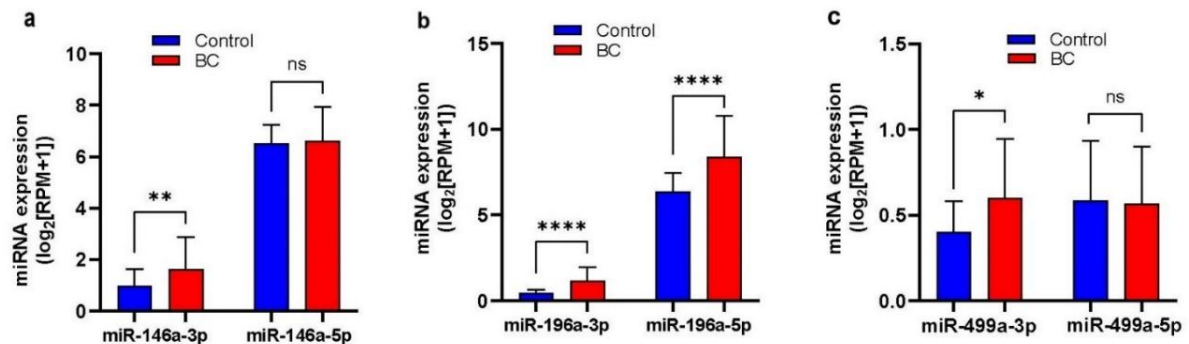


Figure 4 Expression levels of mature miR-146a-3p/5p, miR-196a-3p/5p, and miR-499a-3p/5p in breast cancer and control samples. (a) miR-146a-3p and miR-146a-5p; (b) miR-196a-3p and miR-196a-5p; (c) miR-499a-3p and miR-499a-5p. Data are shown as mean $\pm$ SD. Statistical comparisons were performed using an unpaired 2-tailed t-test. Statistical significance is indicated as $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, and $****p < 0.0001$; ns, not significant.

Effects of miR-SNPs on miRNA–target interactions in breast cancer

To explore the potential of miR-146a-3p, miR-196a-3p, and miR-499a-3p in BC, miRNA–target interaction networks were constructed using multiple databases, including miRecords, TarBase, miRTarBase, miRDB, miRanda, DIANA-microT, and PicTar. The complete list of predicted and validated target genes is provided in **Table S2**.

miR-146a-3p was predicted to target EGFR, BCL2, ERBB2, PTEN, FZD4, RAF1, and TCF7, whereas miR-196a-3p targeted BRAF, JAG1, MAPK3, and NCOA3. In addition, miR-499a-3p was associated with GRB2, DLL1, TCF7L2, MAPK1, MAP2K1, and JAK2, genes involved in key breast cancer–related signaling pathways. These results suggest that miR-SNP–associated miRNAs may regulate multiple oncogenic and tumor suppressor genes in BC. (**Figure 5**).

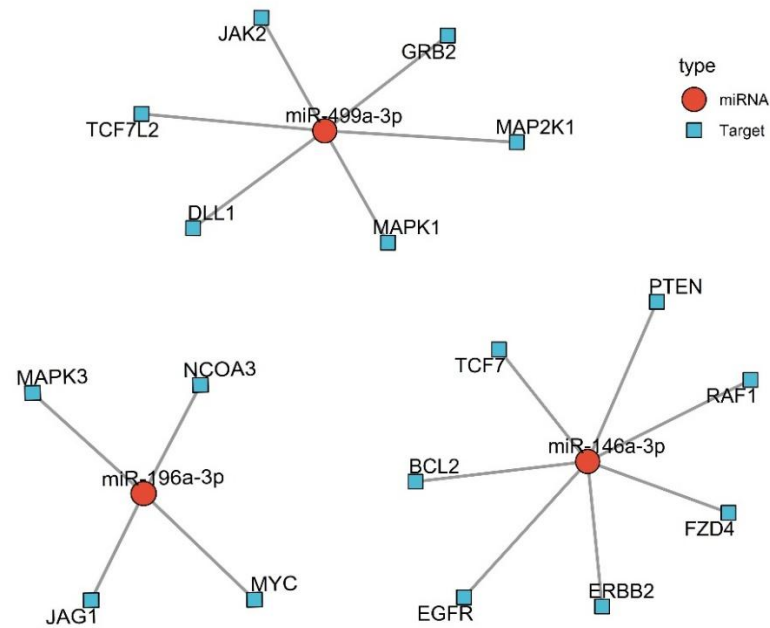


Figure 5 Network interactions between miR-146a-3p, miR-196a-3p, and miR-499a-3p with their predicted target genes in breast cancer. Red circular nodes represent miRNAs, whereas blue square nodes denote predicted target genes. Edges indicate predicted miRNA–mRNA interactions derived from established miRNA target prediction databases.

To further assess the functional impact of miR-SNP-associated miRNAs, changes in miRNA–target binding stability were estimated using ΔG and minimum free energy (MFE) for each interaction (Table 2). For rs2910164 in miR-146a-3p, the variant allele resulted in a loss of predicted interactions with several oncogenic targets, including EGFR, ERBB2, FZD4, RAF1, and TCF7. In contrast, enhanced binding stability was observed for PTEN ($\Delta G = -2.16$), while a reduced interaction was predicted for BCL2 ($\Delta G = 3.05$). For

rs11614913 in miR-196a-3p, the variant allele was associated with loss of interactions with MAPK3 and MYC, whereas increased binding stability was predicted for NCOA3 and JAG1 ($\Delta G = -2.37$ and -2.48 , respectively). Similarly, for rs3746444 in miR-499a-3p, the variant allele led to reduced binding stability with multiple targets involved in key signaling pathways, including DLL1, GRB2, MAP2K1, MAPK1, TCF7L2, and JAK2 (ΔG range: 1.06 - 1.07)

Table 2 *In silico* prediction of miR-SNP effects on miRNA–target binding stability.

SNP	miRNA	Sequence of miRNA		Target	Database	Mean MFE		ΔG (Alt – Ref)
		Ref.	Alt			Ref.	Alt	
rs2910164	hsa-miR-146a-3p	CCUCUG	CCUGUG	BCL2	TarBase	-3.91	-0.86	3.05
		AAAUUC	AAAUUC	EGFR	miRTarBase	-6.77	NI	NA
		AGUUCU	AGUUCU	ERBB2	miRTarBase	-7.44	NI	NA
		UCAG	UCAG	PTEN	miRTarBase; miRanda	-3.04	-5.2	-2.16
				FZD4	DIANA-microT; miRDB; PicTar	-9.64	NI	NA
				RAF1	DIANA-microT; miRanda	-10.16	NI	NA

SNP	miRNA	Sequence of miRNA		Target	Database	Mean MFE		ΔG (Alt – Ref)
		Ref.	Alt			Ref.	Alt	
				TCF7	DIANA-microT; PicTar	–11.32	NI	NA
rs116	hsa-miR-	CGGCAA	CGGCAA	MAPK3	TarBase	–0.66	NI	NA
1491	196a-3p	CAAGAA	CAAGAA	NCOA3	TarBase	–8.66	–11.03	–2.37
3		ACUGCC	ACUGUC	MYC	TarBase	–6.86	NI	NA
		UGAG	UGAG	JAG1	miRanda; miRDB	–12.27	–14.75	–2.48
rs374	hsa-miR-	AACAUC	AACGUC	GRB2	TarBase	–5.3	–4.23	1.07
6444	499a-3p	ACAGCA	ACAGCA	MAP2K1	TarBase	–6.94	–5.87	1.07
		AGUCUG	AGUCUG	MAPK1	TarBase	–10.5	–9.44	1.06
		UGCU	UGCU	DLL1	DIANA-microT; miRanda; miRDB	–7.34	–6.28	1.06
				TCF7L2	DIANA-microT; miRanda; miRDB; PicTar	–7.34	–6.28	1.06
				JAK2	DIANA-microT; miRanda	–7.06	–5.99	1.07

Ref, reference allele; Alt, alternative allele; MFE, minimum free energy; ΔG , difference in binding energy between alternative and reference alleles; NI, no interaction; NA, not applicable.

Discussion

MiRNAs play a central role in post-transcriptional regulation of gene expression, and dysregulation of miRNA expression or function has been implicated in a wide range of diseases, including breast cancer [6]. Genetic variations within miRNA genes, particularly those located in mature miRNA sequences, may influence both the biogenesis of mature miRNAs and their interactions with target mRNAs, thereby contributing to breast cancer development [9]. Among these, rs11614913 in the mature miR-196a coding region, rs2910164 in the mature miR-146a coding region, and rs3746444 in the mature miR-499a coding region are among the most extensively investigated miR-SNPs in breast cancer [35–40]. Although numerous population-based studies have reported associations between these miR-SNPs and breast cancer risk, evidence regarding their effects on mature miRNA expression and underlying molecular mechanisms remains inconsistent. In the present study, we comprehensively evaluated the functional consequences of these miR-SNPs by integrating population-based evidence with *in silico* analyses of miRNA–target interactions.

Precursors (mir-196a2, mir-146a, and mir-499a) are each processed into 2 mature strands, designated as the 5p and 3p miRNAs, through the canonical miRNA biogenesis pathway [41]. During strand selection, the 5p strand (miR-196a-5p, miR-146a-5p, and miR-499a-5p, respectively) is generally the predominant form incorporated into the RNA-induced silencing complex (RISC), whereas the 3p strand is usually expressed at lower levels [33,42]. Notably, rs11614913, rs2910164, and rs3746444 are all located within the mature sequences of the less abundant 3p strands of miR-196a, miR-146a, and miR-499a, respectively [16, 33, 43]. Variants occurring within mature miRNA sequences may disrupt hairpin structure stability, alter strand selection efficiency, or modify miRNA–mRNA binding affinity, thereby affecting both the abundance and regulatory capacity of mature miRNAs toward their downstream target genes.

By integrating evidence from population-based meta-analyses and cell-based experiments, our findings indicate that the regulatory effects of miR-SNPs on mature miRNA expression are highly SNP-specific, genetic model-dependent, and context-dependent, with clear differences between *in vivo* population data and *in vitro* cellular models, as well

as between miRNA strands. Rather than introducing novel susceptibility loci, the primary contribution of this work lies in systematically delineating the strand-specific regulatory effects of miR-SNPs on mature miRNA expression, an aspect that has not been systematically evaluated in previous meta-analyses.

For rs11614913, population-based analyses showed a significant association with miR-196a-5p expression exclusively under the homozygote model (TT vs. CC), with a moderate effect size (SMD = 0.49, 95% CI: 0.19 - 0.78, $p = 0.001$), whereas no significant associations were observed under other genetic models. This finding is consistent with, but does not definitively establish, a potential dosage-related effect in which 2 copies of the T allele are required to exert a measurable influence on miR-196a-5p expression *in vivo*. Consistently, cell-based experiments demonstrated that the T allele markedly reduced miR-196a-5p expression, while no significant effect was observed for miR-196a-3p. Despite the SNP being located within the 3p sequence, these findings suggest that its regulatory impact may preferentially involve the 5p strand, possibly through effects on strand selection or post-transcriptional processing during miRNA biogenesis.

In contrast, rs2910164 exhibited a different regulatory pattern. Population-based analysis identified a significant association with miR-146a-5p expression under the dominant model (CG + GG vs. CC; SMD = 0.41, 95% CI: 0.13 - 0.69, $p = 0.004$), indicating that a single G allele may be sufficient to modulate expression at the population level. However, cell-based studies revealed a pronounced reduction in miR-146a-3p expression following transfection with the G allele, with no significant effect on miR-146a-5p. Given that rs2910164 resides within the stem region of pre-miR-146a, this discrepancy may reflect altered hairpin stability or processing efficiency, which could differentially affect strand maturation under *in vitro* conditions. The divergence between population and cellular contexts may stem from differences in experimental design, the presence of compensatory regulatory mechanisms *in vivo*, or experimental system-specific effects.

For rs3746444, only a single population-based study was available, showing higher miR-499a-5p expression in GG carriers (SMD = 0.58, 95% CI: 0.00 - 1.15, $p = 0.05$). However, given the lack of significance after multiple-testing correction and the absence of replication, the observed association remains inconclusive and warrants further investigation.

Analysis of TCGA miRNA-seq data provided context for the biological relevance of these miR-SNP-associated miRNAs in breast cancer at the population level. MiR-146a-3p and miR-499a-3p showed significant upregulation in tumor tissues compared with normal controls, whereas their 5p counterparts were not differentially expressed. Conversely, both miR-196a-3p and miR-196a-5p were markedly elevated in breast cancer samples. These findings indicate that miRNA dysregulation in breast cancer is strand-specific and locus-dependent. It should be noted, however, that TCGA-BRCA datasets do not provide genotype information for the specific miR-SNPs analyzed in this study. Therefore, the results reflect the overall expression landscape of these miRNAs in breast cancer tissues rather than genotype-specific regulatory effects. These data serve as a reference framework to contextualize miRNA behavior in tumors and may inform the design of future studies integrating matched genotype and expression data to directly assess genetic influences on miRNA regulation.

Network and binding energy analyses further suggested that miR-SNPs may influence miRNA function by altering miRNA–target interactions. Specifically, rs2910164 in miR-146a-3p was associated with predicted loss of interactions with several oncogenic signaling components, including EGFR, ERBB2, FZD4, RAF1, and TCF7, while showing enhanced interaction with PTEN, a key tumor suppressor involved in cell cycle regulation and apoptosis. This pattern raises the hypothesis that rs2910164 may differentially affect interactions with oncogenic and tumor-suppressive targets in a context-dependent manner, though whether these predicted changes translate into measurable differences in target gene expression *in vivo* remains to be determined experimentally. Similarly, rs11614913 was predicted to affect interactions with multiple components of the MAPK signaling

cascade, including MAPK3, BRAF, JAG1, and NCOA3, highlighting a potential mechanism through which this variant may modulate proliferation- and differentiation-related pathways. In addition, rs3746444 was associated with decreased predicting binding to several signaling adaptors and kinases implicated in breast cancer-related pathways, including DLL1, GRB2, MAP2K1, MAPK1, TCF7L2, and JAK2, suggesting a broad impact on growth factor and transcriptional signaling networks. Collectively, these *in silico* analyses are hypothesis-generating and suggest that miR-SNPs may exert pleiotropic effects across multiple cancer-relevant pathways; however, they should not be interpreted as evidence of established functional mechanisms. Experimental validation using luciferase reporter assays, site-directed mutagenesis, and functional rescue experiments in appropriate cell models will be essential to determine whether these predicted interaction changes translate into biologically meaningful effects.

Several limitations of this study should be acknowledged. First, the number of eligible population-based studies was limited for certain miR-SNPs, and some analyses were based on single-study evidence, which substantially reduces statistical power and limits the generalizability of the conclusions. Future studies with larger cohorts are needed to confirm these findings. Second, substantial between-study heterogeneity was observed for rs2910164, likely reflecting differences in population characteristics, sample types, and experimental platforms. Third, this study integrates evidence from population-based analyses and cell line-based experiments, which differ fundamentally in biological context and experimental design; accordingly, cross-context interpretations should be made with caution. Fourth, TCGA data lack genotype-specific information, preventing direct evaluation of how miR-SNP genotypes influence miRNA expression in tumor tissues, rendering the observed expression differences exploratory rather than causal. Fifth, miRNA–target interactions were computationally predicted using *in silico* tools based on ΔG and sequence complementarity. These findings require experimental validation through luciferase reporter assays, RNA

immunoprecipitation, or CRISPR-based functional studies in relevant cell and animal models. Finally, the discrepancies between population-based and cell-based findings underscore the complexity of miR-SNP regulation and highlight the need for mechanistic studies to elucidate the biological factors underlying these context-dependent effects. Taken together, the present findings should be considered exploratory and hypothesis-generating rather than definitive, and the conclusions have been framed accordingly.

Conclusions

This study integrates meta-analytical evidence, TCGA-based expression analyses, and *in silico* predictions to explore the potential regulatory relevance of miR-SNPs in breast cancer. The findings suggest that rs11614913, rs2910164, and rs3746444 are associated with genetic model-dependent and strand-specific variations in miRNA expression, indicating that sequence variation within miRNA genes may influence miRNA maturation and regulatory capacity. Importantly, these findings should be interpreted as hypothesis-generating, given the limited number of eligible studies and the exploratory nature of the analyses. Nevertheless, this integrative framework provides a basis for prioritizing miR-SNPs for future functional and mechanistic investigations in breast cancer. Further well-designed experimental and clinical studies are required to validate the biological relevance and translational implications of these miR-SNPs.

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Declaration of generative AI in scientific writing

We acknowledge the use of ChatGPT (OpenAI) to assist in improving the English language and readability of the manuscript. No content generation or data interpretation was performed by AI. The authors take full responsibility for the content and conclusions of this work.

CRedit author statement

Thuy Thi Chung Duong: Conceptualization, Data curation, Investigation, Methodology, Software, Writing -original draft. **Thanh Thi Ngoc Nguyen:** Conceptualization, Methodology, Data curation, Software, Supervision, Writing - review & editing. **Nga Thi Nguyen:** Conceptualization, Investigation, Methodology, Visualization, Writing - review & editing. **Luan Huu Huynh:** Conceptualization, Investigation, Methodology, Software, Writing - review & editing. **Hang Thi Thu Do:** Conceptualization, Investigation, Formal analysis, Software, Writing -review & editing. **Hue Thi Nguyen:** Conceptualization, Methodology, Data curation, Software, Resource, Validation, Project administration, Writing - review & editing.

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Supplementary Material

Integrative analysis of miR-SNP–associated alterations in miRNA expression and regulatory networks in breast cancer: A systematic review

Table S1 PRISMA 2020 checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title (Page 1)
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract (Page 2)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction (Page 3)
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction (Page 4)
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Materials and methods (Page 4)
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Materials and methods (Page 4)
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Materials and methods (Page 4)
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Materials and methods (Page 4)
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Materials and methods (Page 4)
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Materials and methods (Page 4)

Section and Topic	Item #	Checklist item	Location where item is reported
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Materials and methods (Page 4)
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Materials and methods (Pages 4-5)
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Materials and methods (Page 6)
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Materials and methods (Page 4)
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Materials and methods (Page 6)
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Materials and methods (Page 6)
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Materials and methods (Page 6)
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Materials and methods (Page 6)
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Materials and methods (Page 6)
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Materials and methods (Page 5)
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results (Pages 7-8)
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Results (Pages 7-8)
Study characteristics	17	Cite each included study and present its characteristics.	Results (Pages 8-9); Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results (Pages 7); Figure. S1

Section and Topic	Item #	Checklist item	Location where item is reported
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results (Forest plots, Figures 2–3)
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results (Pages 7)
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results (Forest plots, Figures 2–3)
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results (Page 11)
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Results (Pages 11–12); Figure S3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results (Pages 11–12); Figure S2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion (Pages 18–20)
	23b	Discuss any limitations of the evidence included in the review.	Discussion (Page 20)
	23c	Discuss any limitations of the review processes used.	Discussion (Page 20)
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion (Page 20)
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Materials and methods (Page 4)
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Materials and methods (Page 4)
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not reported
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Acknowledgements (Page 21)
Competing	26	Declare any competing interests of review authors.	Consent to publish

Section and Topic	Item #	Checklist item	Location where item is reported
interests			file
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not reported

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

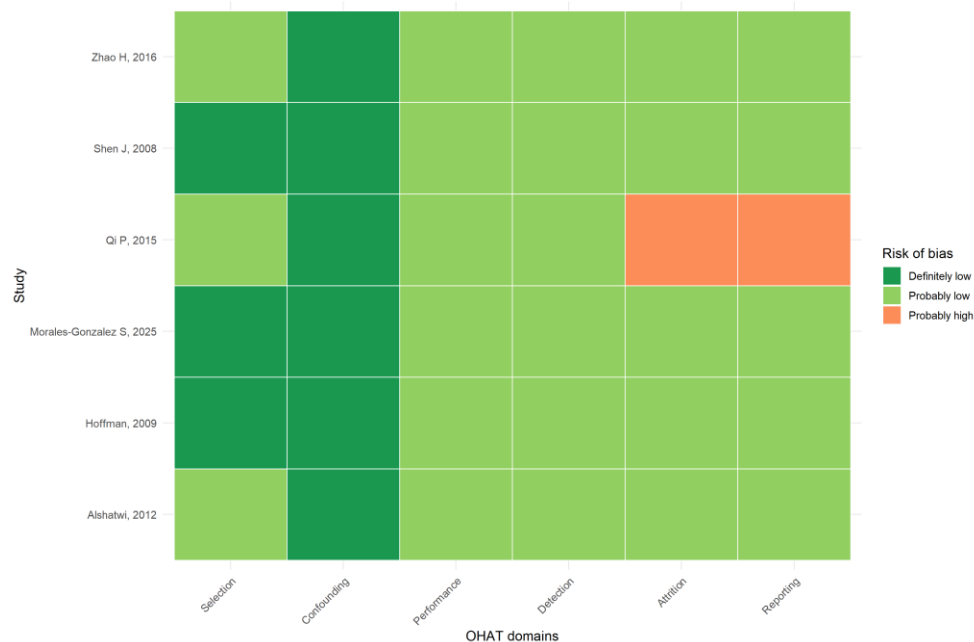


Figure S1 OHAT risk-of-bias assessment of included studies. This figure presents the risk-of-bias assessment of all studies included in the systematic review, evaluated using the Office of Health Assessment and Translation (OHAT) framework. Each row represents an individual study, and each column corresponds to a specific OHAT bias domain, including selection bias, confounding, performance bias, detection bias, attrition bias, and reporting bias. Risk-of-bias judgments are color-coded as green (definitely low risk), light green (probably low risk), and orange (probably high risk), allowing for a visual comparison of methodological quality across studies and domains.

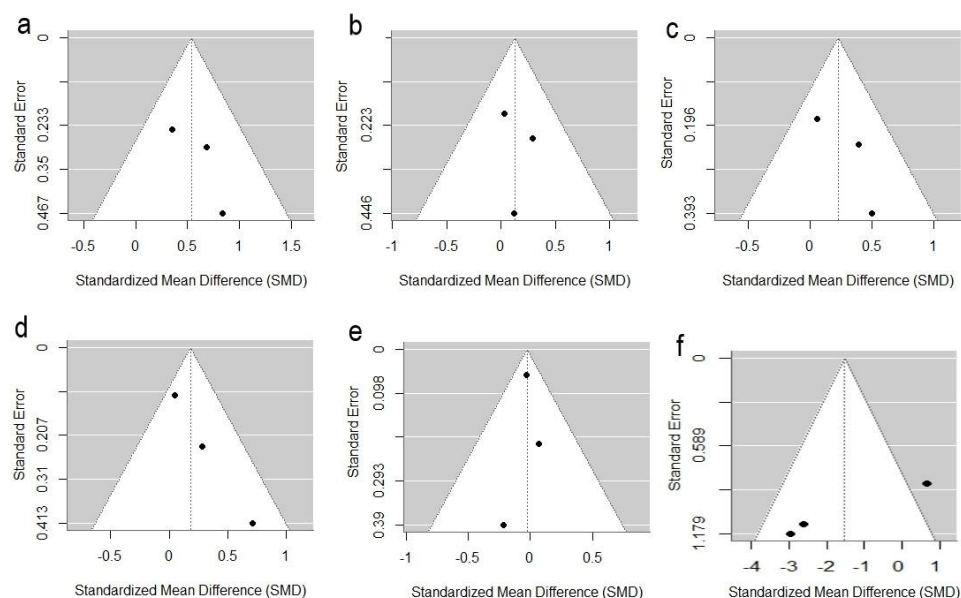


Figure S2 Funnel plots for assessment of small-study effects in the meta-analyses; (a–e) present funnel plots for the association between rs11614913 and miR-196a-5p under different genetic models, including the homozygous (a), heterozygous (b), dominant (c), recessive (d), and over-dominant (e) models. (f) shows the funnel plot for the association between rs2910164 and miR-146a-5p expression in breast cancer cell line–based studies.

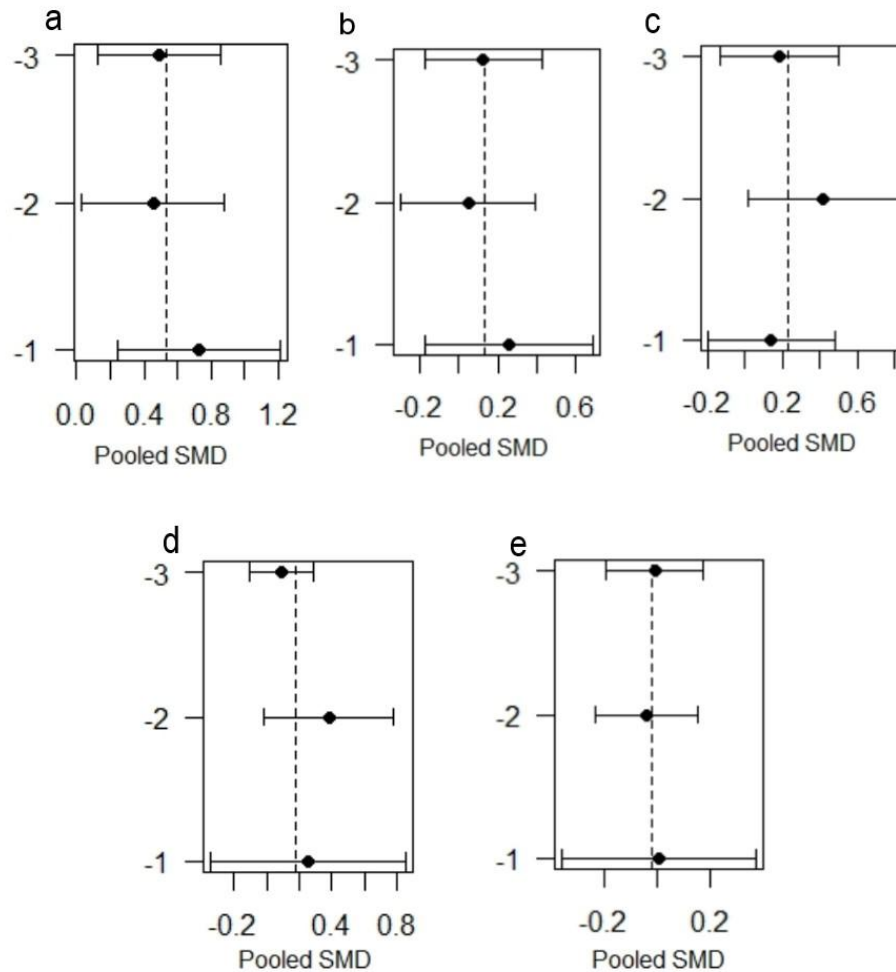


Figure S3 Leave-one-out sensitivity analysis of the meta-analyses; (a–e) show the results of leave-one-out sensitivity analyses for the association between rs11614913 and miR-196a-5p under different genetic models, including the homozygous (a), heterozygous (b), dominant (c), recessive (d), and over-dominant (e) models. In each panel, pooled standardized mean differences (SMDs) and their 95% confidence intervals were recalculated after sequential exclusion of one study at a time. The labels -1, -2, and -3 indicate analyses excluding the studies by Qi P. (2015), Alshatwi (2012), and Zhao H. (2016), respectively.

Table S2 Complete list of predicted and validated target genes.

Database	Mature_mirna_acc	Mature_mirna_id	Target_symbol	Target_entrez	Target_ensembl	Experiment	Support_type	Pubmed_id	Type	Score	Disease_drug	Paper_pubmed ID
tarbase	MIMAT0004608	hsa-miR-146a-3p	BCL2	596	ENSG00000171791	PAR-CLIP	negative	22291592	validated	NA	NA	NA
diana_microt	MIMAT0004608	hsa-miR-146a-3p	BRCA1	672	ENSG00000012048	NA	NA	NA	predicted	0.956	NA	NA
diana_microt	MIMAT0004608	hsa-miR-146a-3p	BRCA1	672	ENSG00000012048	NA	NA	NA	predicted	0.956	NA	NA
miranda	MIMAT0004608	hsa-miR-146a-3p	CDKN1B	1027	ENSG00000111276	NA	NA	NA	predicted	-0.9646	NA	NA
mirtarbase	MIMAT0004608	hsa-miR-146a-3p	EGFR	1956	ENSG00000146648	Microarray//ELISA		31727077	validated	NA	NA	NA
mirtarbase	MIMAT0004608	hsa-miR-146a-3p	ERBB2	2064	ENSG00000141736	HITS-CLIP//westernblotting//qrt-per		24906430	validated	NA	NA	NA
mirtarbase	MIMAT0004608	hsa-miR-146a-3p	ERBB2	2064	ENSG00000141736	HITS-CLIP//westernblotting//qrt-per		33447879	validated	NA	NA	NA
mirtarbase	MIMAT0004608	hsa-miR-146a-3p	ERBB2	2064	ENSG00000141736	HITS-CLIP	Functional MTI (Weak)	24906430	validated	NA	NA	NA
diana_microt	MIMAT0004608	hsa-miR-146a-3p	ERBB2	2064	ENSG00000141736	NA	NA	NA	predicted	0.736	NA	NA
pictar	MIMAT0004608	hsa-miR-146a-3p	ERBB4	2066	ENSG00000178568	NA	NA	NA	predicted	28.0255	NA	NA
diana_microt	MIMAT0004608	hsa-miR-146a-3p	FZD4	8322	ENSG00000174804	NA	NA	NA	predicted	0.87	NA	NA
mirdb	MIMAT0004608	hsa-miR-146a-3p	FZD4	8322	ENSG00000174804	NA	NA	NA	predicted	90.53846773	NA	NA
pictar	MIMAT0004608	hsa-miR-146a-3p	FZD4	8322	ENSG00000174804	NA	NA	NA	predicted	33.5543	NA	NA
miranda	MIMAT0004608	hsa-miR-146a-3p	GATA3	2625	ENSG00000107485	NA	NA	NA	predicted	-0.8446	NA	NA
diana_microt	MIMAT0004608	hsa-miR-146a-3p	MAPK1	5594	ENSG00000100030	NA	NA	NA	predicted	0.761	NA	NA
diana_microt	MIMAT0004608	hsa-miR-146a-3p	MAPK1	5594	ENSG00000100030	NA	NA	NA	predicted	0.761	NA	NA
diana_microt	MIMAT0004608	hsa-miR-146a-3p	NCOA3	8202	ENSG00000124151	NA	NA	NA	predicted	0.705	NA	NA
diana_microt	MIMAT0004608	hsa-miR-146a-3p	NCOA3	8202	ENSG00000124151	NA	NA	NA	predicted	0.705	NA	NA
diana_microt	MIMAT0004608	hsa-miR-146a-3p	PGR	5241	ENSG00000082175	NA	NA	NA	predicted	0.888	NA	NA
diana_microt	MIMAT0004608	hsa-miR-146a-3p	PGR	5241	ENSG00000082175	NA	NA	NA	predicted	0.888	NA	NA
mirtarbase	MIMAT0004608	hsa-miR-146a-3p	PTEN	5728	ENSG00000284792	Immunohistochemistry (IHC)//qRT-PCR//Western blotting		31915154	validated	NA	NA	NA
miranda	MIMAT0004608	hsa-miR-146a-3p	PTEN	5728	ENSG00000171862	NA	NA	NA	predicted	-1.0173	NA	NA
miranda	MIMAT0004608	hsa-miR-146a-3p	PTEN	5728	ENSG00000171862	NA	NA	NA	predicted	-1.0173	NA	NA
diana_microt	MIMAT0004608	hsa-miR-146a-3p	RAF1	5894	ENSG00000132155	NA	NA	NA	predicted	0.91	NA	NA
miranda	MIMAT0004608	hsa-miR-146a-3p	RAF1	5894	ENSG00000132155	NA	NA	NA	predicted	-0.8104	NA	NA
miranda	MIMAT0004608	hsa-miR-146a-3p	RAF1	5894	ENSG00000132155	NA	NA	NA	predicted	-0.8104	NA	NA
miranda	MIMAT0004608	hsa-miR-146a-3p	RB1	5925	ENSG00000139687	NA	NA	NA	predicted	-0.8236	NA	NA
miranda	MIMAT0004608	hsa-miR-146a-3p	RB1	5925	ENSG00000139687	NA	NA	NA	predicted	-0.8236	NA	NA
diana_microt	MIMAT0004608	hsa-miR-146a-3p	TCF7	6932	ENSG00000081059	NA	NA	NA	predicted	0.747	NA	NA
diana_microt	MIMAT0004608	hsa-miR-146a-3p	TCF7	6932	ENSG00000081059	NA	NA	NA	predicted	0.747	NA	NA
pictar	MIMAT0004608	hsa-miR-146a-3p	TCF7	6932	ENSG00000081059	NA	NA	NA	predicted	18.5934	NA	NA

Database	Mature_mirna_acc	Mature_mirna_id	Target_symbol	Target_entrez	Target_ensembl	Experiment	Support_type	Pubmed_id	Type	Score	Disease_drug	Paper_pubmed ID
pictar	MIMAT0004608	hsa-miR-146a-3p	TCF7	6932	ENSG000000081059	NA	NA	NA	predicted	18.5378	NA	NA
mirdb	MIMAT0004562	hsa-miR-196a-3p	BRAF	673	ENSG000000157764	NA	NA	NA	predicted	85.4873	NA	NA
miranda	MIMAT0004562	hsa-miR-196a-3p	CDK2	1017	ENSG000000123374	NA	NA	NA	predicted	-0.8255	NA	NA
diana_microt	MIMAT0004562	hsa-miR-196a-3p	CREB1	1385	ENSG000000118260	NA	NA	NA	predicted	0.707	NA	NA
diana_microt	MIMAT0004562	hsa-miR-196a-3p	CREB1	1385	ENSG000000118260	NA	NA	NA	predicted	0.707	NA	NA
miranda	MIMAT0004562	hsa-miR-196a-3p	JAG1	182	ENSG000000101384	NA	NA	NA	predicted	-1.0675	NA	NA
mirdb	MIMAT0004562	hsa-miR-196a-3p	JAG1	182	ENSG000000101384	NA	NA	NA	predicted	90.60084	NA	NA
miranda	MIMAT0004562	hsa-miR-196a-3p	KIT	3815	ENSG000000157404	NA	NA	NA	predicted	-0.861	NA	NA
miranda	MIMAT0004562	hsa-miR-196a-3p	KIT	3815	ENSG000000157404	NA	NA	NA	predicted	-0.861	NA	NA
tarbase	MIMAT0004562	hsa-miR-196a-3p	MAPK3	5595	ENSG000000102882	PAR-CLIP	negative	23592263	validated	NA	NA	NA
tarbase	MIMAT0004562	hsa-miR-196a-3p	MYC	4609	ENSG000000136997	HITS-CLIP	negative	24906430	validated	NA	NA	NA
tarbase	MIMAT0004562	hsa-miR-196a-3p	NCOA3	8202	ENSG000000124151	HITS-CLIP	negative	24906430	validated	NA	NA	NA
diana_microt	MIMAT0004562	hsa-miR-196a-3p	RAF1	5894	ENSG000000132155	NA	NA	NA	predicted	0.734	NA	NA
miranda	MIMAT0004562	hsa-miR-196a-3p	RELA	5970	ENSG000000173039	NA	NA	NA	predicted	-1.0339	NA	NA
miranda	MIMAT0004562	hsa-miR-196a-3p	RELA	5970	ENSG000000173039	NA	NA	NA	predicted	-1.1188	NA	NA
miranda	MIMAT0004562	hsa-miR-196a-3p	RELA	5970	ENSG000000173039	NA	NA	NA	predicted	-1.1714	NA	NA
diana_microt	MIMAT0004562	hsa-miR-196a-3p	WNT2B	7482	ENSG000000134245	NA	NA	NA	predicted	0.709	NA	NA
diana_microt	MIMAT0004772	hsa-miR-499a-3p	CREB1	1385	ENSG000000118260	NA	NA	NA	predicted	0.823	NA	NA
diana_microt	MIMAT0004772	hsa-miR-499a-3p	CREB1	1385	ENSG000000118260	NA	NA	NA	predicted	0.823	NA	NA
diana_microt	MIMAT0004772	hsa-miR-499a-3p	DLL1	28514	ENSG000000198719	NA	NA	NA	predicted	0.855	NA	NA
miranda	MIMAT0004772	hsa-miR-499a-3p	DLL1	28514	ENSG000000198719	NA	NA	NA	predicted	-1.2825	NA	NA
mirdb	MIMAT0004772	hsa-miR-499a-3p	DLL1	28514	ENSG000000198719	NA	NA	NA	predicted	83.9974	NA	NA
mirdb	MIMAT0004772	hsa-miR-499a-3p	DLL1	28514	ENSG000000275555	NA	NA	NA	predicted	83.9974	NA	NA
diana_microt	MIMAT0004772	hsa-miR-499a-3p	ERBB4	2066	ENSG000000178568	NA	NA	NA	predicted	0.868	NA	NA
diana_microt	MIMAT0004772	hsa-miR-499a-3p	ESR1	2099	ENSG000000091831	NA	NA	NA	predicted	0.808	NA	NA
diana_microt	MIMAT0004772	hsa-miR-499a-3p	ESR1	2099	ENSG000000091831	NA	NA	NA	predicted	0.808	NA	NA
tarbase	MIMAT0004772	hsa-miR-499a-3p	GRB2	2885	ENSG000000177885	HITS-CLIP	negative	24389009	validated	NA	NA	NA
diana_microt	MIMAT0004772	hsa-miR-499a-3p	JAK2	3717	ENSG000000096968	NA	NA	NA	predicted	0.874	NA	NA
diana_microt	MIMAT0004772	hsa-miR-499a-3p	JAK2	3717	ENSG000000096968	NA	NA	NA	predicted	0.874	NA	NA
miranda	MIMAT0004772	hsa-miR-499a-3p	JAK2	3717	ENSG000000096968	NA	NA	NA	predicted	-1.0905	NA	NA
tarbase	MIMAT0004772	hsa-miR-499a-3p	MAP2K1	5604	ENSG000000169032	HITS-CLIP	negative	24389009	validated	NA	NA	NA
mirtarbase	MIMAT0004772	hsa-miR-499a-3p	MAPK1	5594	ENSG000000100030	HITS-CLIP		23824327	validated	NA	NA	NA
mirtarbase	MIMAT0004772	hsa-miR-499a-3p	MAPK1	5594	ENSG000000100030	HITS-CLIP	Functional MTI (Weak)	23824327	validated	NA	NA	NA
miranda	MIMAT0004772	hsa-miR-499a-3p	NCOA1	8648	ENSG000000084676	NA	NA	NA	predicted	-0.9538	NA	NA
miranda	MIMAT0004772	hsa-miR-499a-3p	NCOA1	8648	ENSG000000084676	NA	NA	NA	predicted	-0.9545	NA	NA
miranda	MIMAT0004772	hsa-miR-499a-3p	NCOA1	8648	ENSG000000084676	NA	NA	NA	predicted	-0.9915	NA	NA
diana_microt	MIMAT0004772	hsa-miR-499a-3p	PTEN	5728	ENSG000000171862	NA	NA	NA	predicted	0.763	NA	NA
diana_microt	MIMAT0004772	hsa-miR-499a-3p	RB1	5925	ENSG000000139687	NA	NA	NA	predicted	0.87	NA	NA
diana_microt	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG000000148737	NA	NA	NA	predicted	1	NA	NA
miranda	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG000000148737	NA	NA	NA	predicted	-1.0318	NA	NA

Database	Mature_mirna_acc	Mature_mirna_id	Target_symbol	Target_entrez	Target_ensembl	Experiment	Support_type	Pubmed_id	Type	Score	Disease_drug	Paper_pubmed ID
miranda	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	-1.034	NA	NA
miranda	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	-1.0518	NA	NA
miranda	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	-1.0679	NA	NA
miranda	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	-1.0697	NA	NA
miranda	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	-1.0844	NA	NA
miranda	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	-1.108	NA	NA
miranda	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	-1.131	NA	NA
miranda	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	-1.1373	NA	NA
miranda	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	-1.1388	NA	NA
miranda	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	-1.1508	NA	NA
miranda	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	-1.1883	NA	NA
mirdb	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	99.1834115	NA	NA
mirdb	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	98.19679896	NA	NA
mirdb	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	96.56561637	NA	NA
mirdb	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	96.49448491	NA	NA
pictar	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	24.0124	NA	NA
pictar	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	20.9435	NA	NA
pictar	MIMAT0004772	hsa-miR-499a-3p	TCF7L2	6934	ENSG00000148737	NA	NA	NA	predicted	20.8075	NA	NA