http://ijmpes.com
doi:10.34172/ijmpes.6285
Open Access Original Article
Original Article
APMI Press
Aras Part Medical International Press
A scientific publishing imprint of PMC Pharmaceutique France
Int J Med Parasitol Epidemiol Sci 2026;7(Suppl 1):S21-S27
eISSN 2766-6492
International Journal of Medical Parasitology & Epidemiology Sciences

Association of Mir-146a Rs2910164 and Mir-499 Rs3746444 Variants with Vitiligo Susceptibility: An Iraqi Case–Control Study

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Abstract

Introduction: Vitiligo is an immune-mediated depigmenting disorder with a complex genetic basis. Variants within precursor microRNAs may influence post-transcriptional regulation and thereby modify disease susceptibility.

Aim of this study was to determine whether miR-146a rs2910164 G/C and miR-499 rs3746444 T/C are associated with vitiligo in an Iraqi population.

Methods: This hospital-based case-control study included 84 patients with vitiligo and 90 healthy controls recruited at Baghdad Teaching Hospital between August and December 2025. Tetra-primer amplification refractory mutation system PCR was used to genotype both variations after genomic DNA was extracted from peripheral blood.

Results: The miR-499 rs3746444 TC genotype was more frequent among patients than controls (36.9% vs 30.0%) and was associated with vitiligo (OR = 2.97, 95% CI = 1.16–7.65; $P = 0.024$). The C allele was likewise associated with higher odds (OR = 1.91, 95% CI = 1.20–3.04; $P = 0.006$). After adjustment, the TC genotype remained independently associated with case status (adjusted OR = 3.43, 95% CI = 1.09–10.77; $P = 0.034$). No significant association was observed for rs2910164. Positive family history and diabetes were also retained in the multivariable model.

Conclusion: The findings identify rs3746444 as a candidate susceptibility locus in this Iraqi cohort and support its further evaluation in larger, independent populations with functional validation.

Keywords: Vitiligo, Mir-146a, Mir-499, Rs2910164, Rs3746444, Genetic susceptibility

Received: April 15, 2026, **Revised:** June 14, 2026, **Accepted:** June 28, 2026, **ePublished:** July 31, 2026

Introduction

Vitiligo is an immune-mediated disorder characterized by progressive loss of functional epidermal melanocytes, producing well-demarcated depigmented patches of skin and hair. Its frequent coexistence with other autoimmune diseases suggests partially shared genetic and immunological mechanisms. Environmental and genetic factors interact in the pathophysiology of vitiligo(1). Although the disorder can develop at any age, melanocytes in affected individuals may show increased vulnerability to external stressors before overt cell loss, with the degree of dysfunction varying by disease stage(2).

Oxidative stress, impaired melanocyte adhesion, and dysregulated innate and adaptive immunity contribute to melanocyte injury. Because melanogenesis generates reactive oxygen species (ROS), melanocytes are particularly vulnerable to oxidative damage and may increase expression of pro-inflammatory mediators(3). These events can activate type I interferon signaling and promote cytotoxic CD8+ T-cell responses against melanocytes, modulated by regulatory T cells (2).

Genome-wide association studies have identified approximately 50 distinct genetic loci associated with susceptibility to vitiligo. Many of the genes located within these regions encode proteins involved in immune regulation, whereas others influence melanocyte function or pathways associated with cell death. Because vitiligo is a polygenic disorder, numerous candidate genes have been evaluated for potential associations with disease susceptibility, including those encoding the major histocompatibility complex (MHC), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)(4). In recent years, the pathophysiology of vitiligo has also become a subject of study in noncoding RNAs and various types of genetic alterations including SNPs, nucleotide insertions and deletions, inversions, and chromosomal translocations. Aberrant expression of several microRNAs (miRNAs) involved in vitiligo-associated molecular pathways has been

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reported in various cell affected by the disease(5).

MicroRNAs (miRNAs) are brief, naturally occurring noncoding RNAs that regulate the expression of protein-coding genes after transcription, influencing both mRNA stability and translation. miRNA genes, similar to protein-coding genes, are transcribed from genomic sequences found throughout the human genome(5). The human miR-146 family includes two members, MIR146A and MIR146B, which are encoded on distinct chromosomes, allowing for potentially different regulatory patterns(6). MIR146A is located at 5q33.3, and the rs2910164 G>C polymorphism is found in the stem region of its precursor sequence. This nucleotide change transforms a G: U pair into a C: U mispairing, potentially impacting the folding and processing of pre-miR-146a(7).

MiR-146a serves as an important negative-feedback regulator within the nuclear factor kappa B (NF-κB) signaling pathway. It plays a role in the resolution of T cell activation and the production of proinflammatory cytokines in myeloid cells by focusing on interleukin-1 receptor-associated kinase 1 (IRAK1) and tumor necrosis factor receptor-associated factor 6 (TRAF6)(8). MiR-146a has also been associated with the negative modulation of Toll-like receptor signaling and with negative regulatory proteins involved in airway remodeling, such as type II collagen and MMP-13 (matrix metalloproteinase 13). The increasing attention towards hsa-miR-146a has been driven by findings of its elevated expression across various tissues in individuals with rheumatoid arthritis, including serum or plasma, peripheral blood mononuclear cells, synovial fibroblasts, synovial tissue, and synovial-fluid monocytes(9).

MiR-499a (pre-miR-499 rs3746444; NM_002494.3) is located within intron 19 of the MYH7B gene on chromosome 20q11.22. The rs3746444 substitution changes an A: U base pair to a G: U mismatch within the precursor stem structure(10). Hsa-miR-499 contributes to inflammatory and autoimmune regulation, and reported targets include IL-17Rβ, IL-23α, IL-2R, IL-6, IL-2, and IL-18R. Among these mediators, IL-6 stimulates hepatic production of fibrinogen and C-reactive protein. More generally, miRNAs are approximately 22-nucleotide noncoding RNAs that regulate gene expression post-transcriptionally by altering mRNA stability and translation(11). miR-146a (rs2910164 G>C) and miR-499 (rs3746444 T>C) polymorphisms have also been proven to be involved in various autoimmune diseases, such as inflammatory arthritis(12), systemic lupus erythematosus(13), ankylosing spondylitis(14), and Graves' disease(15). These variants have also been studied for their association with various tumours including hepatocellular carcinoma(16,17), breast cancer and bladder cancer(18,19).

Thus, this research sought to investigate the potential association between the miR-146a rs2910164 C/G and miR-499 rs3746444 T/C polymorphisms and the heightened risk of vitiligo in Iraqi patients.

Materials and methods

Study design

This case-control study involved 174 participants, 84 of whom had vitiligo and 90 of whom were healthy controls. Between August 2025 and December 2025, all subjects were sourced from Medical City's Baghdad Teaching Hospital in Baghdad, Iraq. Clinical confirmation of the vitiligo diagnosis was obtained by the physician's decision. The University of Diyala – College of Medicine granted the project ethical permission (ethical code No.2025HH4955 in 9 September 2025).

Data and sample collection

All participants who had previously been enrolled in the study had given written consent. Direct interviews were used to gather data from each participant on their residence, family history, BMI, age, gender, and comorbidities using a pre-made formula. An EDTA tube containing five milliliters of venous blood was kept at -80 °C until it was time to extract the DNA.

DNA isolation

To extract genomic DNA, a commercial kit (Gsync TM DNA extraction kit fast organizer, Geneaid, Taiwan) was used in accordance with the directions provided by the manufacturer. To separate the genomic DNA, the entire blood was processed. A260/A280, the extracted DNA concentration, was determined by the Biospec Nano spectrophotometer.

Primers and Tetra-Amplification Refractory Mutation System

The miR-146a rs2910164 G/C and miR-499 rs3746444 T/C polymorphisms were genotyped by T-ARMS-PCR. This assay is based on 2 allele-specific inner primers (FI and RI) and 2 flanking outer primers (FO and RO) for each locus; primer sequences are shown in Table 1(20). The preparation of the amplification reaction was performed with AccuPower PCR PreMix (Bioneer, Korea) as per the guidelines provided by the manufacturer. Thermal cycling

Table 1. Primers' sequences and the length of the resulting fragments utilized for T-ARMS-PCR amplification

Primers	Sequence (5-3)	Fragment length
hsa-mir-146a; rs2910164 G>C	Forward: Fo GGCCTGGTCTCCTCCAGATGTTTAT	364bp
	Reverse: Ro ATACCTTCAGAGCCTGAGACTCTGCC	364bp
	FI (C allele): ATGGGTTGTGTCAGTGTCAGACGTC	169bp
	RI (G allele): GATATCCCAGCTGAAGAACTGAATTTGAC	249bp
hsa-miR-499; rs3746444 T>C	Forward: Fo GAGTGACCAGGCCCCTTGTCTCTATTAG Reverse: Ro	422bp
	TTGCTCTTTCACTCTCATTCTGGTGATG	422bp
	FI (C allele): ATGTTTAACTCCTCTCCACGTGACCG	206bp
	RI (T allele): GGGAAGCAGCACAGACTTGCTGTTAT	268bp

commenced with an initial denaturation at 95 °C for 5 minutes, followed by 30 cycles consisting of denaturation at 95 °C for 30 seconds, locus-specific annealing at 61 °C for 25 seconds for rs2910164, or at 60 °C for 27 seconds for rs3746444, and a locus-specific extension at 72 °C for 25 seconds. A final extension was run at 72 °C for 10 minutes. For rs2910164 the outer-primer control fragment was 364 bp, and the C- and G-specific products were 169 and 249 bp respectively. For rs3746444 fragment length for the outer-primer control is 422 bp, C allele is 206 bp, and T allele is 268 bp. To assess reproducibility, the genotyping process was repeated for 20% of the samples chosen at random; all duplicate results were concordant with the original genotypes.

Statistical analysis

Data were analyzed by using SPSS 25.0 (SPSS, Chicago). Continuous variables were presented as means ± SD and compared with Student's t-test. Categorical data are presented as number (percentage) and were analyzed by the Chi-square test. This test was also employed to determine the departure of different genotypes from HWE. The association between vitiligo and miRNA gene polymorphism was analyzed by binary logistic regression. From the test, the OR and corresponding 95% CI were obtained. A $P < 0.05$ was a statistically significant change for significant findings.

Results

The mean age of the patients was 25.94 ± 14.08 years (range = 9-59 years) compared with 23.41 ± 6.78 years (range = 8-47 years) for control group with no significant difference. Similarly, there was no notable difference between the two groups regarding sex distribution, residency, and BMI. However, 42.86% of patients had a positive a family history of vitiligo, compared to 3.33% of controls, indicating a highly significant difference. Furthermore, diabetes and psoriasis were more frequent among patients (10.71% and 8.33%, respectively) than controls (5.56% and 1.11%, respectively), although the difference exceeded the acceptable limit of significant (Table 2).

Molecular assay

This study examined the impact of two SNPs: one in miRNA-146a (rs2910164) and the other in miRNA-499 (rs3746444) on the susceptibility of vitiligo. In both SNPs, the frequency of different genotypes in patients and controls was in a good accordance with HWE.

miRNA-146a rs2910164

Tetra-ARMS-PCR employed to amplify and genotype the miRNA-146a gene fragments corresponding rs2910164. Figure 1 gel electrophoresis of the miRNA-146a rs2910164 gene polymorphism amplified with the PCR and the

Table 2. Demographic features of the study population

Variables	Patients(n = 84)	Controls(n = 90)	*P*-value
Age, years Mean ± SD Range	25.94 ± 14.08 9.0-59.0	23.41 ± 6.78 8.0-47.0	0.129
Sex Male Female	35(41.67%) 49(58.33%)	40(44.44%) 50(55.56%)	0.710
BMI, kg/m2 Mean ± SD Range	24.96 ± 4.53 15.11-32.51	25.95 ± 3.63 18.22-29.54	0.994
Residence Rural Urban	52(61.9%) 32(38.1%)	67(74.44%) 23(25.56%)	0.075
Family history No Yes	48(57.14%) 36(42.86%)	87(96.67%) 3(3.33%)	<0.001
Comorbidity No DM Hypertension Psoriasis	64(76.19%) 9(10.71%) 4(4.76%) 7(8.33%)	80(88.89%) 5(5.56%) 4(4.44%) 1(1.11%)	0.065

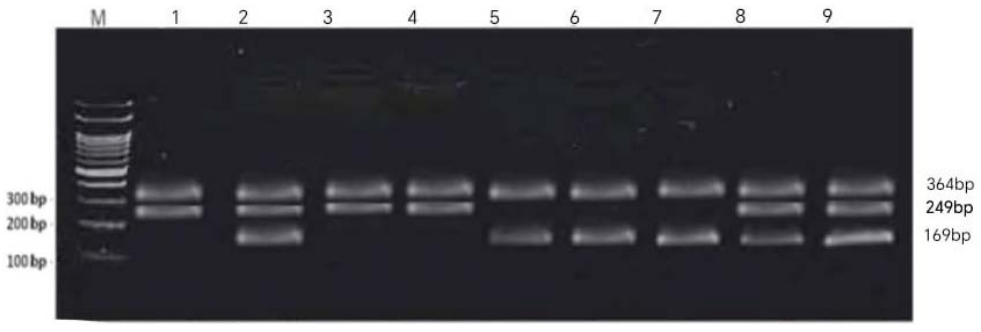

Figure 1. The matching PCR results from the T-ARMS-PCR were determined by agarose gel electrophoresis in order to detect the pre-miRNA-146a rs2910164 G/C polymorphism. M, DNA marker; lanes 2, 8 and 9, rs2910164 GC; lanes 1,3 and 4, GG; lane 5,6 and 7, CC

product was stained with ethidium bromide (Figure 1).

miRNA-499 rs3746444

T-ARMS-PCR products for miR-499 rs3746444 were resolved by agarose-gel electrophoresis and visualized with ethidium bromide (Figure 2).

Association of miRNA-146a rs2910164 with vitiligo

The heterozygous genotypes (GC) for SNP rs2267447 was a more prevalent genotype in patients (44.05%) than in controls (37.78%), however, this difference was not significant (OR = 2.03, 95%CI = 0.88-4.63, $P = 0.095$). The GC+CC genotype was significantly higher in patients than in controls under the recessive model (67.86% vs. 54.44%). However, the difference exceeded the threshold for significance. The C allele was more common in patients than in controls at the allelic level (45.83% vs. 35.56%), a difference which is borderline significant (OR = 1.53, 95%CI = 1.0-2.36, $P = 0.051$), as shown in Table 3.

Association of miRNA-499 rs3746444 with vitiligo

The rs3746444 TC genotype was more frequent among patients than controls (36.9% vs 30.0%) and was associated with higher odds of vitiligo relative to the TT genotype (OR = 2.97, 95% CI = 1.16–7.65; $P = 0.024$). Under the dominant model, TC+CC genotypes were more frequent among patients (55.95% vs 38.89%; OR = 2.00, 95% CI = 1.09–3.65; $P = 0.025$). At the allele level, the C allele was also more frequent among patients (37.5% vs 23.89%; OR = 1.91, 95% CI = 1.20–3.04; $P = 0.006$; Table 4).

Multivariate analysis

In order to find the independent risk factors for vitiligo, the result is depicted in Table 5. Each of positive family history (OR = 18.28, 95%CI = 10.12-76.63, $P < 0.001$), diabetes (OR = 11.9, 95%CI = 1.42-20.91, $P = 0.025$) and TC genotype of the SNP miRNA-499 rs3746444 (OR = 3.43, 95%CI = 1.09-10.77, $P = 0.034$) were independent factors Table 5.

Discussion

This case–control study assessed the impact of the pre-miRNA variants miR-146a rs2910164 G/C and miR-499 rs3746444 T/C on the susceptibility to vitiligo within an Iraqi population. The main discovery revealed a notable link between rs3746444 and vitiligo: the TC genotype and the C allele were more frequent among patients, and carriage of at least one C allele (TC+CC) was associated with approximately twofold higher odds of disease. Moreover, the TC genotype remained independently associated with vitiligo in the multivariable model. By contrast, rs2910164 showed no statistically significant association, although the higher frequency of the C allele among patients approached the significance threshold. Positive family history and diabetes were also retained as independent factors in the adjusted analysis. These results therefore provide population-specific evidence that miR-499 rs3746444 may contribute to vitiligo susceptibility, whereas the evidence for miR-146a rs2910164 remains inconclusive.

The absence of a significant association for miR-146a rs2910164 should be interpreted in the context of the biological and epidemiological complexity of this variant. The G-to-C substitution produces a mismatch

Table 3. The frequency of various miRNA-146a rs2910164 polymorphism genotypes and alleles in vitiligo patients and controls

miRNA-146a rs2910164	Patients (n = 84)	Controls (n = 90)	*P*-value	OR (95%CI)
Co-dominance GG GC CC HWE	 27(32.14%) 37(44.05%) 20(23.81%) 0.301	 41(45.56%) 34(37.78%) 15(16.67%) 0.096	 0.175 0.095 0.625	 1.0 2.03(0.88-4.63) 1.23(0.54-2.68)
Recessive modelGG+GCCC	64(76.19%) 20(23.81%)	75(83.33%) 15(16.67%)	0.242	1.0 1.56(0.74-3.3)
Dominant modelGGGC+CC	27(32.14%) 57(67.86%)	41(45.56%) 49(54.44%)	0.071	1.0 1.77(0.95-3.28)
Alleles G C	 91(54.17%) 77(45.83%)	 116(64.44%) 64(35.56%)	 0.051	 1.0 1.53(1.0-2.36)

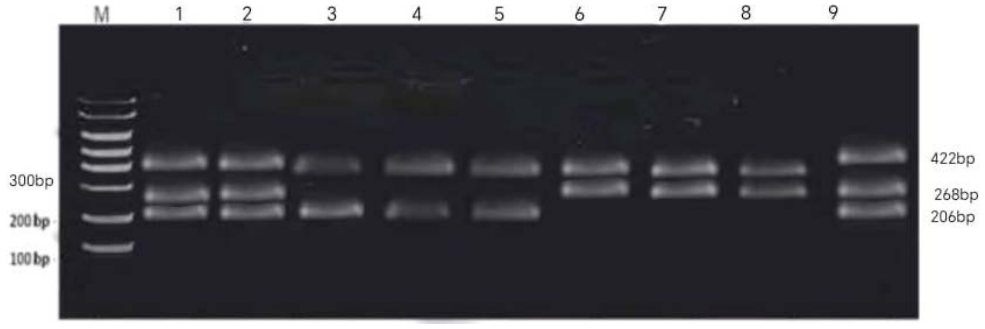

Figure 2. Pre-miRNA-499 rs3746444 T/C polymorphism detection using the T-ARMS-PCR electrophoresis pattern. M: DNA marker; lanes 6,7 to 8, rs3746444 TT; lanes 3,4 and 5, CC; lane 1,2 and 9, TC

Table 4. Genotype and allele distributions of miR-499 rs3746444 in patients with vitiligo and controls

miRNA-499 rs3746444	Patients (n = 84)	Controls (n = 90)	*P*-value	OR (95%CI)
Co-dominance TT TC CC HWE	37(44.05%) 31(36.9%) 16(19.05%) 0.115	55(61.11%) 27(30%) 8(8.89%) 0.097	0.048 0.024 0.273	1.02.97 (1.16–7.65)1.74 (0.64–4.70)
Recessive modelTT+TCCC	68(80.95%) 16(19.05%)	82(91.11) 8(8.89%)	0.057	1.0 2.41(0.97-5.98)
Dominant modelTTTC+CC	37(44.05%) 47(55.95%)	55(61.11%) 35(38.89%)	0.025	1.0 2.0(1.09-3.65)
Alleles T C	105(62.5%) 63(37.5%)	137(76.11%) 43(23.89%)	0.006	1.0 1.91(1.2-3.04)

Table 5. Multivariate logistic regression

Variables	Patients (n = 84)	Controls (n = 90)	*P*-value	OR (95%CI)
Residence Rural Urban	52(61.9%) 32(38.1%)	67(74.44%) 23(25.56%)	0.230	1.0 1.72(0.71-4.14)
Family history No Yes	48(57.14%) 36(42.86%)	87(96.67%) 3(3.33%)	<0.001	18.28(10.12-76.63)
Comorbidity No DM Hypertension Psoriasis	72(85.71%) 9(10.71%) 0(0%) 3(3.57%)	81(90%) 5(5.56%) 4(4.44%) 0(0%)	0.040 0.025 0.358 0.132	1.0 11.9(1.42-20.91) 3.68(0.23-59.52) 4.29(0.5-21.03)
miRNA-146a GG GC CC	27(32.14%) 37(44.05%) 20(23.81%)	41(45.56%) 34(37.78%) 15(16.67%)	0.228 0.103 0.539	1.0 2.3(0.85-6.27) 1.37(0.50-3.71)
miRNA-499 TT TC CC	37(44.05%) 31(36.9%) 16(19.05%)	55(61.11%) 27(30%) 8(8.89%)	0.043 0.034 0.486	1.0 3.43(1.09-10.77) 1.52(0.47-4.88)

in the precursor stem structure and may alter miR-146a maturation, abundance, or target recognition(7). Functionally, miR-146a participates in negative-feedback regulation of Toll-like receptor and NF-κB signaling through targets that include IRAK1 and TRAF6, thereby influencing innate and adaptive immune responses(8). Nevertheless, a plausible biological role does not necessarily imply a detectable disease association in every population. Meta-analytic evidence indicates that the direction and magnitude of the rs2910164 association vary across autoimmune phenotypes; the C allele has been associated with increased susceptibility to multiple sclerosis but with reduced susceptibility to several other inflammatory disorders(21). Consistent with this heterogeneity, Li et al. reported genotype-related differences in pro-inflammatory cytokine expression among patients with relapsing–remitting multiple sclerosis(22). The null finding in the present study may therefore reflect disease-specific effects, ethnic differences in linkage disequilibrium or background genetic architecture, environmental interactions, or limited statistical power rather than the complete absence of miR-146a involvement in vitiligo.

In contrast, the association observed for miR-499 rs3746444 was consistent across several comparisons. Relative to the TT genotype, the TC genotype was associated with higher odds of vitiligo (OR = 2.97), while the C allele was associated with an approximately 1.9-fold increase in disease odds. The association persisted for the TC genotype after adjustment for relevant covariates (adjusted OR = 3.43). Because the confidence intervals were relatively wide, the magnitude of these estimates should be interpreted cautiously; however, their consistency supports rs3746444 as a candidate susceptibility locus in this cohort.

The present findings are broadly compatible with evidence implicating rs3746444 in immune-mediated disease. Associations between this variant and rheumatoid arthritis have been reported(23), and Yang et al. observed higher erythrocyte sedimentation rate and C-reactive protein levels among heterozygous carriers, suggesting a possible relationship with inflammatory activity(11). A broader meta-analysis likewise identified an association between miR-499 rs3746444 and autoimmune-disease susceptibility, although the effect varied by ethnicity and disease category(24). Evidence from other conditions is less consistent: associations have been described for recurrent spontaneous abortion and several cancers(25,26), whereas meta-analytic or case–control data have not supported associations with coronary artery disease or pulmonary tuberculosis(27,28). Collectively, this variability suggests that rs3746444 is unlikely to exert a uniform effect across diseases; its phenotypic consequences may depend on ancestry, environmental exposure, disease mechanism, and interactions with other genetic variants.

A mechanistic explanation for the observed association

remains provisional. The rs3746444 substitution is located within the pre-miR-499 sequence and can affect precursor processing, mature miRNA production, and interactions with target transcripts (29-31). Altered miR-499 activity could consequently modify post-transcriptional regulation of inflammatory, immune, or apoptotic pathways relevant to melanocyte injury. Such a mechanism is biologically plausible in vitiligo, in which immune dysregulation and stress-related melanocyte loss interact (2,5); nevertheless, the present study did not measure miR-499 expression, target-gene regulation, cytokine profiles, or melanocyte function. The genetic association therefore cannot establish the molecular pathway or demonstrate causality.

The strong association with a positive family history is consistent with an inherited component of vitiligo susceptibility and supports investigation of regulatory variants in this population. Diabetes was also independently associated with case status; however, this finding should be interpreted cautiously because few participants had diabetes, diabetes type was not specified, and the confidence interval was wide. The result should therefore be regarded as hypothesis-generating rather than evidence of a direct etiological relationship.

Several study features support the internal validity of the findings, including comparable age and sex distributions between groups, genotype distributions consistent with Hardy–Weinberg equilibrium, and repeat genotyping of a randomly selected sample subset. Important limitations remain. The sample was relatively small and recruited from a single center, reducing statistical power and generalizability. Only two candidate variants were evaluated, and population stratification, gene–gene interactions, and gene–environment interactions were not assessed. No correction for multiple genetic comparisons was reported, and the absence of functional assays precluded biological validation. These limitations are especially relevant to the borderline rs2910164 C-allele result and the wide confidence intervals in the multivariable analysis.

Overall, miR-499 rs3746444 may represent a candidate genetic susceptibility marker for vitiligo in the studied Iraqi population, but it is not a clinically validated predictive biomarker. Replication is required in larger independent multicenter cohorts, preferably with ancestry-informed analyses and standardized vitiligo phenotyping. Integration of genotype data with miRNA expression and downstream target measurements would help determine whether rs3746444 has a functional role in vitiligo pathogenesis.

Conclusions

In this Iraqi case–control sample, miR-499 rs3746444, but not miR-146a rs2910164, was associated with vitiligo susceptibility, with the TC genotype remaining significant after multivariable adjustment. This finding identifies rs3746444 as a candidate locus for further investigation; however, replication in larger independent cohorts and functional validation are required before any clinical application. Further large-scale studies are warranted to validate these implications.

Authors' Contribution

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Competing Interests

There are no conflicts of interest.

Data Availability Statement

The datasets used and/or analyzed during the present work are accessible from the corresponding author upon reasonable request.

Ethical Approval

The University of Diyala - College of Medicine granted the project ethical permission (ethical code No.2025HH4955 in 9 September 2025). All participants gave informed consent and volunteered to donate blood during recruitment.

Funding

This study was self-funded by the authors and received no external financial support from any funding organization.

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