P-ISSN 1991-8941
E-ISSN 2706-6703
Vol. 20, No. 1 (2026)

Journal of University of Anbar for Pure Science
(JUAPS)

journal homepage: juaps.uoanbar.edu.iq

Open Access

Original Paper

Association of IL-17 and IL-21 gene polymorphisms and haplotypes with rheumatoid arthritis susceptibility in Iraqi patients

Hajar Khaled Masser [1], Mustafa Nuhad Al-Darraji [1], Rana Talib Mohsen [2*]

[1]Department of Biology, College of Science, University of Anbar, Al-Anbar, Iraq
[2]Department of Biotechnology, College of Science, University of Anbar, Al-Anbar, Iraq

ARTICLE INFO

Received: 01/06/2025
Accepted: 12/08/2025
Available online: 28/02/2026
April Issue
10.37652/juaps.2025.161064.1408

Cite @ JUAPS

Corresponding author
Rana Talib Mohsen
rana2011@uoanbar.edu.iq

ABSTRACT

Rheumatoid arthritis (RA) is a persistent inflammatory autoimmune disease that impacts joints and leads to gradual deterioration. Cytokines like IL-17 and IL-21 are associated with the etiology of rheumatoid arthritis due to their involvement in fostering inflammation and autoimmunity. This study investigated the association between single-nucleotide polymorphisms (SNPs) in IL-17F (rs2397084 and rs11465553) and IL-21 (rs2221903) genes and susceptibility to rheumatoid arthritis in an Iraqi cohort. The case-control study included 90 participants (50 RA patients and 40 healthy controls) from Ramadi, Al-Anbar, between November 2023 and January 2024. Genomic DNA was extracted from blood samples, and SNP genotyping was conducted using AS-PCR and ARMS-PCR techniques. Results showed a significant association between the C allele of IL-17F rs2397084 and RA susceptibility (frequency: 0.31 in patients vs. 0.16 in controls, $\chi^2 = 5.235, p = 0.022$), with genotype distributions of T/T (0.48), T/C (0.42), and C/C (0.10) in patients compared with 0.72, 0.22, and 0.05 in controls (p=0.063). The dominant model (T/C + C/C) indicated increased risk (OR=7.71, 95% CI: 1.43-41.53, p=0.008). For rs11465553, the A allele was more frequent in patients (0.38 vs. 0.06, $\chi^2 = 24.641, p < 0.001$), with genotype distributions of A/A (0.30), G/A (0.16), and G/G (0.54) in patients compared with 0.02, 0.08, and 0.90 in controls ($\chi^2 = 14.881, p = 0.001$). The dominant (OR=6.28, 95% CI: 1.43-27.60, p=0.0097) and recessive models (OR=11.64, 95% CI: 1.21-111.53, p=0.0095) confirmed this association. For IL-21 rs2221903, the T allele was more prevalent (71 in patients vs. 44 in controls,$\chi^2 = 6.378, p = 0.012$), with genotype distributions of T/T (n=23), T/C (n=25), and C/C (n=2) in patients compared with T/C (n=28), C/C (n=4), and T/T (n=8) in controls ($\chi^2 = 46.586, p < 0.001$). However, genetic model analysis showed no significant associations (e.g., dominant model OR=0.30, p=0.095). Deviations from Hardy-Weinberg equilibrium were observed for rs11465553 in patients (p<0.0001) and rs2221903 in controls (p=0.023), possibly reflecting disease effects or sample size limitations. These findings suggest that IL-17 and IL-21 genetic variations may contribute to RA susceptibility in the Iraqi population. Further studies in larger, multiethnic cohorts are warranted to confirm these associations and elucidate underlying mechanisms.

Keywords: *Iraqi population, Rheumatoid arthritis, rs2397084, rs11465553, rs2221903*

1 INTRODUCTION

Rheumatoid arthritis (RA) is a chronic immune-mediated condition that primarily affects synovial joints, leading to inflammation, pain, stiffness, and progressive joint destruction [1]. Its systemic nature also contributes to complications in multiple organ systems

and increased morbidity and mortality [2]. Rheumatoid arthritis results from a complex interaction among genetic susceptibility, environmental factors, and immune dysregulation, although its precise etiology remains unclear [3, 4]. Despite the need for prompt diagnosis and appropriate therapy to mitigate joint deterioration and improve outcomes, many patients with RA show poor responses to current treatments, highlighting the need for novel biomarkers and targeted therapies [1, 5]. Cytokines are crucial to the etiology of rheumatoid arthritis by mediating inflammatory pathways that drive synovial inflammation and joint degeneration [6]. Interleukin-17 (IL-17) and interleukin-21 (IL-21) are pivotal pro-inflammatory cytokines that facilitate inflammation and autoimmunity [7]. IL-17 is mainly synthesized by Th17 cells, promotes neutrophil recruitment to the synovium, induces the expression of other cytokines, and supports osteoclastogenesis [8, 9]. IL-21, secreted primarily by T follicular helper (Tfh) cells, enhances B cell activation, autoantibody production, and Th17 differentiation, further intensifying autoimmune responses [10, 11]. Genetic variations, particularly single-nucleotide polymorphisms (SNPs) in cytokine genes, may affect cytokine expression or protein function, potentially influencing RA susceptibility and disease progression [12, 13]. Polymorphisms such as rs11465553 and rs2397084 in IL-17A, and rs2221903 in IL-21, have been investigated across various populations for associations with RA risk [14–16]. However, findings remain inconsistent, likely due to ethnic differences, environmental factors, sample sizes, and methodologies [13, 17]. Several studies have examined the association between IL-17F and IL-21 gene polymorphisms and rheumatoid arthritis, focusing particularly on SNPs rs2397084, rs11465553, and rs2221903. For instance, a Pakistani study [18] reported a significant association between rs11465553 and RA, whereas rs2397084 showed no such association. In contrast, the IL-21 rs2221903 SNP yielded mixed findings: an Iraqi study [19] found no correlation with RA, whereas studies from Mexico and China demonstrated significant associations [13, 17]. These discrepancies suggest that genetic susceptibility to RA may vary by ethnicity and geographic region. However, data on Iraqi populations remain limited. Therefore, this study was designed to evaluate the association of IL-17F rs2397084 and rs11465553, and IL-21 rs2221903 polymorphisms with RA susceptibility among Iraqi patients, in an effort to address this knowledge gap and contribute to understanding the genetic factors influencing RA in Middle Eastern populations. This study focused exclusively on the genetic aspects of the disease. Despite the abundance of global research addressing the genetic basis of RA, data from Middle Eastern populations, including Iraq, remain significantly limited.

2 MATERIALS AND METHODS

2.1 Study population

This case-control study included 90 participants: 50 patients diagnosed with rheumatoid arthritis (RA) and 40 healthy controls. All participants were recruited from private medical laboratories in Ramadi, Al-Anbar province, between November 2023 and January 2024. The patient group consisted of 10 males and 40 females, aged 18 to 65 years. Rheumatoid arthritis was confirmed by specialist rheumatologists based on clinical evaluation and laboratory markers, including rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP). Only patients who met the ACR/EULAR classification criteria were included.

The control group included 16 males and 24 females with no known history of autoimmune disorders, chronic inflammatory diseases, or recent infections. All control subjects underwent clinical screening and provided a health declaration confirming the absence of immunological conditions and current medication use. None of the controls were smokers or were receiving immunosuppressive drugs.

2.2 Isolation of human genomic dna

Venous blood samples (5 mL) were collected in EDTA tubes under sterile conditions. Genomic DNA was extracted using the gSYNC DNA Extraction Kit (Geneaid, Taiwan, Cat. No. GS100).

2.3 Assessment of dna concentration and purity

The purity and concentration of the isolated DNA were evaluated using a NanoDrop spectrophotometer (Thermo Fisher Scientific, USA). DNA concentrations ranged between 10 and 50 ng/µL, with slight variations among samples. The A260/A280 purity ratios were between 1.7 and 2.0, indicating sufficient purity for downstream PCR amplification and molecular analysis.

2.4 Primer design and preparation

The primer sequences used to amplify the IL-17F gene polymorphisms (rs2397084 and rs11465553) were adopted from a previously published study (Ali et al.,

Table 1 Primers sequences of IL-17F (rs2397084 and rs11465553) and IL-21 (rs2221903)

SNP ID	Gene	Primer type	5' - Oligo Seq - 3'	Allele specify	Product size (bp)	Reference
rs2397084	IL-17F	F 1	TCCGGACGACCAGGGTCC	C	250	[18]
		F 2	CTCCGGACGACCAGGGTCT	T		
		R	CCAGGCTGTGTGGCTCCAGAA			
		F 1	TGACTGTTGGCTGCACCTGCA	A	170	
		F 2	ACTGTTGGCTGCACCTGCG	G		
		R	AAGGTGGAGGAGGAACTGGT			
rs2221903	IL-21	F 1	CAATGGGGTTTTGTTTTCTTA	A	228	custom-designed part of this study
		F 2	CAATGGGGTTTTGTTTTCTTC	C		
		F3	CAATGGGGTTTTGTTTTCTTG	G		
		F4	CAATGGGGTTTTGTTTTCTTT	T		
		R	TGAGTGATAGGGCACCTG			

2023), whereas the primers for the IL-21 gene (rs2221903) were custom-designed in this study using the NCBI Primer-BLAST tool based on the reference sequence NM_021803.3. All primers were synthesized by Macrogen Inc. (South Korea) according to standard specifications. The oligonucleotide primers for the amplification of IL-17F (rs2397084 and rs11465553) and IL-21 (rs2221903) polymorphisms, along with their expected product sizes, are summarized in Table 1.

2.5 Preparation of primers

Deionized distilled water (NFW) was used to dissolve the lyophilized primers to a concentration of 100 pmol/µL. A working solution of 10 pmol/µL was then prepared by transferring 10 µL from the master tube to a separate tube and diluting to 100 µL with NFW.

2.6 Components of the polymerase chain reaction (pcr)

Two different PCR techniques were employed in this study, depending on the nature of each SNP. Allele-specific PCR (AS-PCR) was used to detect the rs2221903 polymorphism in the IL-21 gene. For the rs2397084 and rs11465553 polymorphisms in the IL-17F gene, the amplification refractory mutation system PCR (ARMS-PCR) technique was used, which employs allele-specific primers to accurately determine genotypes. Each PCR reaction was performed in a total volume of 10 µL and consisted of 5 µL of 2× EasyTaq PCR Super Mix (TransGen Biotech, China), 1 µL of each primer (forward and reverse) at 10 pmol/µL, 2 µL of genomic DNA (10–50 ng/µL), and 1 µL of nuclease-free water. Table 2 details the components and their concentrations used in the PCR reactions.

Table 2 Components and Concentrations of the Polymerase Chain Reaction (PCR) Mixture for Genotyping

Component	Volume per reaction (μL)	Final concentration
Master Mix (2X)	5	1X
Forward Primer	1	10 pmol
Reverse Primer	1	10 pmol
DNA Template	2	
Nuclease-free Water	1	
Final reaction volume	10μ L	

2.7 Protocol for polymerase chain reaction

The thermal cycling conditions were optimized individually for each SNP based on annealing temperature and primer design. Details of the thermal profiles for each polymorphism are presented in Table 3.

Table 3 Thermal cycling conditions were optimized for each SNP

Stage	Cycles	IL-17 rs11465553	IL-17 rs2397084	IL-21 rs2221903
Initial Denaturation	1X	95°C for 5 min	95°C for 5 min	95°C for 5 min
Denaturation	35X	95°C for 30 sec	95°C for 30 sec	95°C for 30 sec
Annealing	35X	65°C for 30 sec	69.2°C for 30 sec	59°C for 30 sec
Extension	35X	72°C for 40 sec	72°C for 40 sec	72°C for 40 sec
Final Extension	1X	72°C for 5 min	72°C for 5 min	72°C for 5 min
Hold		4°C Hold	4°C Hold	4°C Hold

Agarose gel electrophoresis was used to confirm the amplification of allele-specific PCR products. Gels were prepared with 1.2% agarose in TAE buffer and stained using SYBR Safe DNA stain. A volume of 5 µL from each PCR product was loaded into individual wells, alongside a 100 bp DNA ladder (TransGen Biotech, China) for molecular weight estimation. The gel was run at a constant voltage of 5 V/cm for 45 minutes, and

bands were visualized under UV illumination using a transilluminator. The expected amplicon sizes were:

- IL-17F rs2397084: 250 bp for both T and C alleles (ARMS-PCR)
- IL-17F rs11465553: 170 bp for both G and A alleles (ARMS-PCR)
- IL-21 rs2221903: 228 bp for both C and T alleles (AS-PCR)

The presence of one or both allele-specific bands indicated homozygosity or heterozygosity, respectively, depending on the SNP. Band interpretation was based on the allele-specific primers used and the presence of diagnostic bands for each genotype.

2.8 Statistical analyses

Genotype and allele frequency analyses were carried out using SNPStats online software (SNPStats website) and SPSS version 25.0 (IBM Corporation, USA). Genotype and allele distributions of each single-nucleotide polymorphism (SNP) were calculated for both RA patients and control groups and expressed as percentages. Hardy-Weinberg equilibrium (HWE) was assessed for each SNP within the control group using the chi-square (χ^2) test to verify the population's genetic stability. A p-value greater than 0.05 was considered indicative of equilibrium. To evaluate the association between each SNP and susceptibility to rheumatoid arthritis, five genetic inheritance models were applied: codominant, dominant, recessive, overdominant, and log-additive. These models were analyzed using logistic regression to compute the odds ratio (OR), 95% confidence interval (CI), and p-value for each comparison. All statistical tests were two-tailed, and results were considered statistically significant when $p < 0.05$.

3 RESULTS AND DISCUSSION

3.1 Interpretation of gel electrophoresis results for IL-17F rs2397084

Figure 1 shows the ARMS-PCR amplification results for the IL-17F rs2397084 single-nucleotide polymorphism (SNP). Allele-specific primers were used to amplify the T and C alleles in separate reactions for each sample. The PCR products were electrophoresed on a 1.2% agarose gel, stained with SYBR Safe, and visualized under UV illumination. A 100 bp DNA ladder was loaded on the left side of the gel to estimate product size. The expected band length for both alleles was 250 base pairs (bp). Eight DNA samples were analyzed and distributed as follows: four from rheumatoid arthritis patients on the left (case) and four from healthy individuals on the right (control). Each sample included two lanes, one for the T allele and one for the C allele. Genotypes were determined based on the observed band patterns: a band appearing only in the T-specific lane indicates the T/T homozygous genotype; a band appearing only in the C-specific lane indicates the C/C homozygous genotype; and bands present in both lanes (T and C) indicate the T/C heterozygous genotype. The gel image displays all three genotype patterns across the samples, indicating genetic variation at the rs2397084 locus among both patients and controls.

The allele and genotype frequencies of the IL-17F rs2397084 polymorphism were analyzed in rheumatoid arthritis (RA) patients and healthy controls using allele-specific polymerase chain reaction (ARMS-PCR). The results revealed a significant association between the C allele and increased RA susceptibility in the Iraqi population, with notable differences in genotype distribution between the two groups. Hardy-Weinberg equilibrium (HWE) analysis was performed to confirm the accuracy of the genotyping process. Table 4 summarizes the allele frequencies, genotype distribution, and HWE analysis for this polymorphism. Figure 1 illustrates electrophoresis of PCR-amplified IL-17F rs1234567 products (250 bp) on a 1.2% agarose gel, showing sample genotypes.

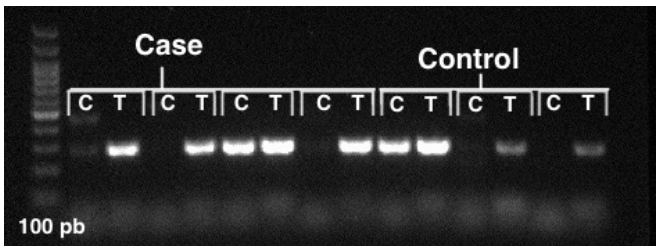

Fig. 1 Electrophoresis of DNA-PCR amplified products (250 bp) for the IL-17 2397084 SNPs on 1.2% agarose (5 V/cm2 for 45 min) showing genotypes for samples, DNA Ladder (100 bp)

Table 4 Allele frequency, genotype distribution, and Hardy-Weinberg Equilibrium (HWE) Analysis of IL-17F rs2397084

A. Allele frequency

Allele	All subjects count	All subjects prop.	Status = C count	Status = C prop.	Status = P count	Status = P prop.
T	136	0.76	67	0.84	69	0.69
C	44	0.24	13	0.16	31	0.31
Pearson Chi-Sq	5.235	DF = 1	P = 0.022			

B. Genotype distribution

Allele	All subjects count	All subjects prop.	Status = C count	Status = C prop.	Status = P count	Status = P prop.
T	30	0.33	9	0.22	21	0.42
C	53	0.59	29	0.72	24	0.48
Pearson Chi-Sq	5.514	DF = 2	P = 0.063			

C. Hardy-Weinberg Equilibrium (HWE) Analysis

Group	T / T	T / C	C / C	T	C	P-value
All subjects	53	30	7	136	44	0.39
Status = C	29	9	2	67	13	0.25
Status = P	24	21	5	69	31	1

In this study, the IL-17F rs2397084 polymorphism showed statistically significant differences in allelic distribution between rheumatoid arthritis (RA) patients and the control group. The frequency of the C allele was 0.31 among patients, compared with 0.16 in controls, and this difference was statistically significant (Chi-square = 5.235, df = 1, p = 0.022). Regarding genotype distribution, the T/T, T/C, and C/C genotypes were 0.48, 0.42, and 0.10 among patients, compared with 0.72, 0.22, and 0.05 in controls, respectively, with the differences approaching statistical significance (p = 0.063).

Hardy-Weinberg equilibrium (HWE) analysis for IL-17F rs2397084 indicated that both the rheumatoid arthritis (RA) patient group (p = 1.00) and the control group (p = 0.25) were in equilibrium, as the p-values were greater than 0.05. This suggests that the genotype frequencies for rs2397084 in both groups are consistent with the expected frequencies under HWE, indicating a stable genetic structure and reliable genotyping in the studied Iraqi population. The absence of deviation from HWE supports the validity of the allele and genotype frequency data, reinforcing the observed significant association of the C allele with RA susceptibility (χ^2 = 5.235, df = 1, p = 0.022). The equilibrium in both groups also suggests that factors such as population stratification, selection pressure, or genotyping errors are unlikely to have influenced the results for this SNP. Overall, these results suggest a potential association of the C allele with increased susceptibility to RA in the Iraqi sample.

In contrast, a Polish study [20] found no significant association between rs2397084 and RA susceptibility; however, it reported a relationship with longer disease duration, suggesting that this variant may be more relevant to disease progression than to the initial onset of RA. Similarly, a Turkish study conducted on 161 RA patients and 88 healthy controls using RFLP-PCR did not find any significant differences in the allelic or genotypic distribution of rs2397084, suggesting no association of this polymorphism with RA risk in the Turkish population [21].

In contrast, a recent Tunisian study by [22] documented a significant association between rs2397084 and RA susceptibility in the Tunisian population, as well as an association with improved response to biological therapy, highlighting its potential as a genetic biomarker to guide treatment decisions. Furthermore, a study conducted on a Pakistani sample by [23] supported the current findings, showing that the C allele was associated with increased RA risk. They also noted that this SNP causes an amino acid change in the IL-17 protein, which may confer functional effects that contribute to the inflammatory response. On the other hand, the study by Ali et al. [18], conducted in Pakistan, did not find a direct significant association between rs2397084 and RA but reported a possible association with disease duration, suggesting a potential role of this mutation in disease progression rather than its initiation. The variability in findings among these studies may be due to population differences (genetic and ethnic), environmental factors, or differences in analytical methodologies, such as the use of different techniques (RFLP, TaqMan, ARMS-PCR), sample size variation, or reliance on different clinical classification systems, emphasizing the importance of conducting large-scale local studies to understand the specific genetic influences in each population.

The analysis of genetic models for the IL-17F rs2397084 polymorphism revealed a significant association between this variant and susceptibility to rheumatoid arthritis (RA) in the Iraqi population. As shown in Table 5, the dominant model demonstrated significant differences, with carriers of the C allele (T/C + C/C) accounting for 51% of RA patients compared with 27.5%

of healthy controls (OR = 7.71, CI = 1.43-41.53, p = 0.008). Additionally, the overdominant model indicated a meaningful association (OR = 4.72, CI = 1.02-21.72, p = 0.034), while the log-additive model also showed a significant correlation (OR = 4.48, CI = 1.26–15.98, p = 0.012).

Multiple inheritance models were analyzed to assess the association between the IL-17F rs2397084 polymorphism and susceptibility to rheumatoid arthritis (RA) in the Iraqi population. The codominant, dominant, overdominant, and log-additive models were assessed to determine the impact of the C allele on disease risk. The results demonstrated significant associations, particularly in the codominant and dominant models, suggesting that the presence of at least one C allele may significantly increase RA susceptibility, especially in heterozygous form. Table 5 presents the odds ratios, confidence intervals, and statistical significance for the different genetic models analyzed for IL-17F rs2397084.

Table 5 Analysis of Inheritance Models for IL-17F rs2397084 Polymorphism in Rheumatoid Arthritis Susceptibility.

Model	Genotype	Status = C	Status=p	OR (95% CI)	Pvalue	AIC	BIC
Codominant	T/T, C/T, C/C	29 (72.5%), 9 (22.5%), 2 (5%)	24 (49%), 21 (42.9%), 4 (8.2%)	1.00	—	—	—
Dominant	T/T, C/TC/C	29 (72.5%), 11 (27.5%)	24 (49%), 25 (51%)	7.71 (1.4341.53)	0.008	74.5	96.9
Recessive	T/T-C/T, C/C	38 (95%), 2 (5%)	45 (91.8%), 4 (8.2%)	3.36 (0.2545.29)	0.36	80.7	103.1
Over dominant	T/T-C/C, C/T	31 (77.5%), 9 (22.5%)	28 (57.1%), 21 (42.9%)	4.72 (1.0221.72)	0.034	77	99.4
Logadditive	—	—	—	4.48 (1.2615.98)	0.012	75.2	97.6

The analysis of genetic inheritance models for the IL-17F rs2397084 polymorphism revealed a significant association between this SNP and increased susceptibility to rheumatoid arthritis (RA) in the Iraqi population. As presented in Table 5, the dominant model (T/C + C/C vs. T/T) demonstrated strong statistical significance, with 51% of RA patients carrying at least one copy of the C allele compared with 27.5% of healthy controls (OR = 7.71, 95% CI: 1.43–41.53, p = 0.008). This suggests that a single C allele may substantially increase the risk of RA. Additionally, the overdominant model (T/C vs. T/T + C/C) showed a significant association (OR = 4.72, 95% CI: 1.02–21.72, p = 0.034), indicating that the heterozygous genotype may contribute independently to disease risk. The log-additive model also yielded significant results (OR = 4.48, 95% CI: 1.26–15.98, p = 0.012), supporting a dose-dependent relationship in which risk increases progressively with each additional C allele. On the other hand, the recessive model (C/C vs. T/C + T/T) did not show a statistically significant association (p = 0.36), suggesting that the homozygous mutant genotype (C/C) alone does not confer a significantly higher risk within this cohort, likely due to its low frequency in both groups. Collectively, these findings suggest that the C allele of rs2397084 may play a role in RA pathogenesis, particularly when present in a heterozygous state or under additive and dominant genetic effects, warranting further investigation into its potential functional implications.

3.2 Interpretation of gel electrophoresis results for IL-17F rs11465553

Figure 2 shows the electrophoretic pattern obtained from ARMS-PCR analysis of the IL-17F rs11465553 polymorphism. Allele-specific primers were used to amplify the A and G alleles in separate reactions for each DNA sample. The PCR products were resolved on a 1.2% agarose gel, stained with SYBR Safe, and visualized under UV illumination. 100 bp DNA ladders were loaded on both sides of the gel for accurate size estimation. The expected product size for both alleles was 170 base pairs (bp). A total of 12 DNA samples were analyzed: left side (control group), 4 healthy individuals; right side (case group), 8 patients with rheumatoid arthritis. Each sample had two separate lanes, one for the A allele and one for the G allele. The observed banding patterns were interpreted as follows: a band appearing only in the G-specific lane indicates the G/G genotype; a band appearing only in the A-specific lane indicates the A/A genotype; and bands present in both lanes (A and G) indicate the A/G heterozygous genotype. The image demonstrates clear band separation and confirms the presence of all three genotypes across the analyzed samples. The case group (right side) exhibits a higher proportion of A/G and A/A patterns, whereas the control group (left side) predominantly shows G/G and A/G genotypes, indicating variation in allele distribution.

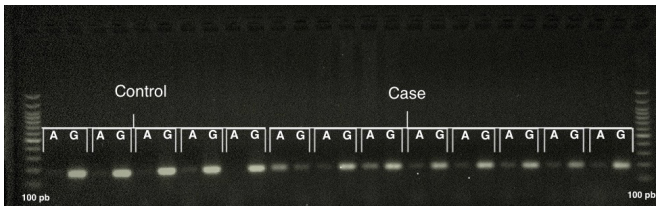

Fig. 2 Electrophoresis of DNA-PCR amplified products (170 bp) for the IL-17 rs11465553 SNPs on 1.2% agarose (5 V/cm2 for 45 min) showing genotypes for samples, DNA Ladder (100 bp).

The IL-17F rs11465553 polymorphism was investi-

gated to assess its association with RA susceptibility in the Iraqi population. The analysis showed a significantly higher frequency of the A allele among RA patients compared with controls, accompanied by significant differences in genotype distribution. A notable deviation from the Hardy-Weinberg equilibrium was observed in the patient group, potentially indicating a disease-related genetic imbalance. Table 6 presents the allele frequencies, genotype distribution, and HWE analysis for this polymorphism.

Analysis of the IL-17F rs11465553 polymorphism revealed significant differences in allelic and genotypic distributions between rheumatoid arthritis (RA) patients and healthy controls. At the allelic level, the frequency of the G allele was 0.62 in patients versus 0.94 in controls, while the A allele was 0.38 in patients versus 0.06 in controls. These differences were statistically significant (Chi-square = 24.641, df = 1, p<0.001). Regarding genotype distribution, the A/A genotype was observed in 0.30 of patients compared with 0.02 in controls, while the G/A genotype occurred in 0.16 of patients and 0.08 of controls. Conversely, the G/G genotype was more common in controls (0.90) than in patients (0.54), with statistically significant differences between groups (Chi-square = 14.881, df = 2, p = 0.001).

In contrast, the HWE analysis for IL-17F rs11465553 revealed a significant deviation from equilibrium in the RA patient group (p<0.0001) and the total population, while the control group remained in equilibrium (p = 0.12). This deviation in the patient group suggests a disease-related genetic imbalance, likely driven by the strong association of the A allele (frequency: 0.38 in patients vs. 0.06 in controls, p = 0.000) and the A/A genotype (0.30 in patients vs. 0.02 in controls, p = 0.001) with RA susceptibility. Such deviations are often observed in disease cohorts due to selection pressures or genetic associations with the disease phenotype. The equilibrium in the control group supports the representativeness of the healthy population, while the deviation in the patient group aligns with the significant genetic associations observed (e.g., dominant model OR = 6.28, p = 0.0097; recessive model OR = 11.64, p = 0.0095). Possible explanations for the deviation include the disease's influence on allele frequencies or non-random mating within the RA cohort, although the small sample size (50 patients) may also contribute. When compared with previous studies, the current findings align closely with those of Ali et al. [18], who also reported a significant association between rs11465553 and RA risk in a Pakistani population.

Table 6 Allele Frequency, genotype distribution and Hardy-Weinberg Equilibrium (HWE) Analysis of IL-17F rs11465553

A. Allele frequency

Allele	All subjects Count	All subjects Prop.	Status = C Count	Status = C Prop.	Status = P Count	Status = P Prop.
G	137	0.76	75	0.94	62	0.62
A	43	0.24	5	0.06	38	0.38
Pearson Chi-Sq	24.641	DF = 1	P = 0.000			

B. Genotype distribution

Genotype	All subjects Count	All subjects Prop.	Status = C Count	Status = C Prop.	Status = P Count	Status = P Prop.
A/A	16	0.18	1	0.02	15	0.3
G/A	11	0.12	3	0.08	8	0.16
G/G	63	0.7	36	0.9	27	0.54
Pearson Chi-Sq	14.881	DF = 2	P = 0.001			

C. Hardy-Weinberg Equilibrium (HWE) Analysis

Group	AA	GA	GG	A	G	P-value
All subjects	63	11	16	137	43	< 0.0001
Status = Control	36	3	1	75	5	0.12
Status = Patients	27	8	15	62	38	< 0.0001

On the contrary, a study conducted in Poland [24] reported no significant differences in either allelic or genotypic distribution of rs11465553 between RA patients and controls. Moreover, the polymorphism was not associated with any clinical parameters, including age at diagnosis, rheumatoid factor status, or extra-articular manifestations (p = 1.00, OR = 0.98). Similarly, [25] found no consistent association between rs11465553 and RA across multiple ethnic groups in a comprehensive meta-analysis. However, another Pakistani study [26] confirmed a significant association, supporting the idea that ethnic and geographical factors may contribute to these discrepancies. Based on the totality of the evidence, rs11465553 in the IL-17F gene is a promising genetic marker warranting further investigation in the Iraqi population, particularly given the scarcity of regional studies on this SNP. The strong statistical association found in this study supports the potential of rs11465553 as a risk

factor for RA and calls for multicenter, multiethnic studies to further explore its biological and clinical implications.

The association between the IL-17F rs11465553 polymorphism and rheumatoid arthritis susceptibility was further assessed using different genetic inheritance models. As shown in Table 7, genetic model analysis revealed statistically significant associations: the dominant model (A/G + A/A vs. G/G) yielded OR = 6.28, 95% CI = 1.43–27.60, p = 0.0097; the recessive model (A/A vs. G/G + G/A) showed OR = 11.64, 95% CI = 1.21–111.53, p = 0.0095; and the log-additive model also demonstrated a meaningful association (OR = 3.65, 95% CI = 1.32–10.09, p = 0.0043). Collectively, these findings strongly suggest that rs11465553 is significantly associated with increased RA susceptibility in the studied Iraqi cohort, particularly in the presence of the A allele or A/A genotype.

A genetic model analysis of the IL-17F rs11465553 polymorphism was conducted to examine its contribution to RA susceptibility in the Iraqi cohort. The codominant, dominant, recessive, and log-additive models were evaluated, revealing significant associations with RA risk, particularly for the A/A genotype, which exhibited the highest odds ratios. These findings suggest a strong association between the A allele and disease susceptibility. Table 7 summarizes the odds ratios, confidence intervals, and p-values for the genetic models analyzed for IL-17F rs11465553.

Table 7 Analysis of Inheritance Models for IL-17F rs11465553 Polymorphism in Rheumatoid Arthritis Susceptibility

Model	Genotype	Status=C	Status=p	OR (95% CI)	P-value	AIC	BIC
Codominant	G/G	36 (90%)	26 (53.1%)	1.00	0.016	75.3	100.2
	A/G	3 (7.5%)	8 (16.3%)	3.00 (0.49-18.30)			
	A/A	1 (2.5%)	15 (30.6%)	15.03 (1.49-151.65)			
Dominant	G/G	36 (90%)	26 (53.1%)	1.00	0.0097	74.8	97.2
	A/G-A/A	4 (10%)	23 (46.9%)	6.28 (1.43-27.60)			
Recessive	G/G-A/G	39 (97.5%)	34 (69.4%)	1.00	0.0095	74.8	97.2
	A/A	1 (2.5%)	15 (30.6%)	11.64 (1.21-111.53)			
Overdominant	G/G-A/A	37 (92.5%)	41 (83.7%)	1.00	0.57	81.2	103.6
	A/G	3 (7.5%)	8 (16.3%)	1.65 (0.28-9.83)			
Log-additive	—	—	—	3.65 (1.32-10.09)	0.0043	73.4	95.8

The genetic model analysis of the rs11465553 polymorphism in the IL-17F gene revealed strong statistical evidence supporting a potential association between this variant and increased susceptibility to rheumatoid arthritis (RA). In the codominant model, the A/A genotype was observed in 30.6% of RA patients, compared with only 2.5% in healthy controls, yielding an odds ratio (OR) of 15.03 (95% confidence interval [CI], 1.49–151.65). This indicates a markedly elevated risk among individuals carrying two copies of the mutant allele. Additionally, the A/G genotype was found in 16.3% of patients and 7.5% of controls (OR = 3.00, 95% CI: 0.49–18.30). Overall, differences in genotype distribution under this model were statistically significant (p = 0.016), highlighting a potential genetic influence.

In the dominant model (A/A + A/G vs. G/G), 46.9% of RA patients carried at least one copy of the mutant A allele, compared with 10.0% of controls. The OR was 6.28 (95% CI: 1.43–27.60), with p = 0.0097, suggesting that a single A allele significantly increases disease risk. The recessive model (A/A vs. G/G + A/G) further emphasized this risk, with the A/A genotype again appearing in 30.6% of patients and 2.5% of controls. The OR in this model was 11.64 (95% CI: 1.21–111.53), with p = 0.0095, indicating that individuals homozygous for the A allele are at significantly greater risk than heterozygous or wild-type carriers.

In the log-additive model, the risk of RA increased progressively with each additional copy of the A allele, with an OR of 3.65 (95% CI: 1.32–10.09) and p = 0.0043. This dose-dependent pattern strengthens the evidence for a role of the A allele in RA susceptibility. In contrast, the overdominant model (A/G vs. A/A + G/G) did not demonstrate a significant difference (OR = 1.65, p = 0.57), suggesting that heterozygosity for this SNP does not confer a protective or intermediate effect. Taken together, these findings suggest that the rs11465553 polymorphism is significantly associated with RA risk in the studied Iraqi population. The presence of the A allele, whether heterozygous or homozygous, appears to substantially increase disease susceptibility, particularly under the dominant, recessive, and log-additive models, highlighting its potential utility as a genetic biomarker for RA.

3.3 Interpretation of electrophoresis results for rs2221903 polymorphism (il-21)

Figure 3 illustrates the electrophoresis results for allele-specific PCR (AS-PCR) used to detect the rs2221903 single-nucleotide polymorphism (SNP) in the IL-21 gene. This analysis was conducted using four allele-specific primers targeting each possible nucleotide (A, C, G, and T). The PCR products were loaded into four separate lanes per sample, with each lane corresponding to a specific allele. A visible band appears only in the lane containing the primer that matches the allele present

in the sample.

PCR products were resolved on a 1.2% agarose gel stained with CyberSafe and visualized under UV illumination. A 100 bp DNA ladder was loaded on the left side of the gel to estimate band size. The expected size of the amplified product is approximately 228 base pairs (bp). A total of eight samples were analyzed: left side (case group), four samples from patients with rheumatoid arthritis (RA); right side (control group), four samples from healthy individuals. Each sample is represented by four consecutive lanes (A, C, G, T). Genotypes were interpreted based on the position of the visible band(s) within these four lanes: a band appearing only in the T lane indicates a T/T genotype; a band appearing only in the C lane indicates a C/C genotype; and bands appearing in both C and T lanes indicate a C/T heterozygous genotype.

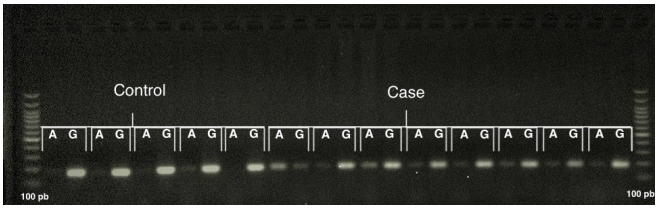

Fig. 3 electrophoresis of DNA-PCR amplified products (228bp) for the IL-21 rs2221903 SNPs on 1.2% agarose (5 V/cm2 for 45 min) showing genotypes for samples, DNA Ladder (100 bp).

The IL-21 rs2221903 polymorphism was examined to evaluate its role in RA susceptibility among Iraqi patients. The results indicated a significantly higher frequency of the T allele in RA patients compared with controls, with significant differences in genotype distribution, particularly for the T/T genotype. A deviation from the Hardy-Weinberg equilibrium was observed in the control group, suggesting potential population stratification or sample size limitations. Table 8 summarizes the allele frequencies, genotype distribution, and HWE analysis for this polymorphism. Figure 3 displays the electrophoresis of PCR-amplified IL-21 rs1234569 products (228 bp) on a 1.2% agarose gel, showing the sample genotypes. The current study found statistically significant differences in the allelic and genotypic distributions of the IL-21 gene polymorphism rs1234569 between patients with rheumatoid arthritis (RA) and healthy individuals, suggesting a possible association between this polymorphism and disease susceptibility.

Table 8 Allele Frequency, genotype distribution and Hardy-Weinberg Equilibrium (HWE) Analysis of IL-17F rs11465553

A. Allele frequency

Allele	All subjects Count	All subjects Prop.	Status = C Count	Status = C Prop.	Status = P Count	Status = P Prop.
T	115	0.64	44	0.55	71	0.71
C	65	0.36	36	0.45	29	0.29
Pearson Chi-Sq	6.378	1	0.012	1		

B. Genotype distribution

genotype	All subjects Count	All subjects Prop.	Status=C Count	Status=C Prop.	Status=p Count	Status=p Prop.
C/C	6	0.07	4	0.1	2	0.04
T/C	53	0.59	28	0.7	25	0.5
T/T	31	0.34	8	0.2	23	0.46
Pearson Chi-Sq	46.586	2	0.000			

C. Hardy-Weinberg Equilibrium (HWE) Analysis

Group	N11	N12	N22	N1	N2	P-value
All subjects	31	53	6	115	65	0.012
Status = Control	8	28	4	44	36	0.023
Status = Patients	23	25	2	71	29	0.18

The total number of T alleles among all participants was 115, compared with 65 for the C allele, with a Chi-square value of 6.378 and a p-value of 0.012. When stratified by group, the T allele appeared in 71 RA patients versus 44 healthy controls, while the C allele was present in 29 RA patients and 36 controls, supporting the hypothesis of the T allele's association with increased RA risk. Regarding genotypic distribution, the T/C genotype was the most frequent among all participants (n = 53), followed by T/T (n = 31) and C/C (n = 6). The Chi-square test for genotype distribution showed a highly significant value of 46.586 ($p<0.001$). In subgroup analysis, the T/T genotype was most common among RA patients (n = 23), followed by T/C (n = 25) and C/C (n = 2). Among controls, the T/C genotype was most frequent (n = 28), followed by C/C (n = 4) and T/T (n = 8). This variation supports a potential association between the T/T genotype and increased RA risk, whereas the C/C genotype may confer a protective effect.

The HWE analysis for IL-21 rs2221903 showed a deviation from equilibrium in the control group (p =

0.023) and the total population (p = 0.012), while the RA patient group remained in equilibrium (p = 0.18). The deviation in the control group is unexpected, as healthy populations are typically in HWE unless affected by factors such as population stratification, small sample size, or genotyping errors. The control group's deviation may reflect the relatively small sample size (40 individuals) or genetic diversity in the Iraqi population, potentially influenced by regional factors in Al-Anbar. The equilibrium in the RA patient group suggests a stable genetic structure, supporting the reliability of the observed associations, particularly the higher frequency of the T allele (71 in patients vs. 44 in controls, p = 0.012) and the T/T genotype (n = 23 in patients vs. n = 8 in controls, p<0.001). The deviation in the control group warrants caution in interpreting the genetic model results for rs2221903, which showed no significant associations (e.g., overdominant model p = 0.054), and highlights the need for larger control cohorts to confirm these findings.

These findings are consistent with those of Ibrahim et al. [27], who conducted a study in Egypt involving 60 participants (40 RA patients and 20 healthy controls). Their study reported statistically significant differences in both genotypic and allelic distributions for rs2221903 (p = 0.002 and p = 0.001, respectively), concluding that this SNP is a susceptibility locus for RA. Conversely, other studies have reported no significant association between this polymorphism and RA susceptibility. For instance, [28] conducted a study in Poland involving 422 RA patients and 338 healthy controls and found no association between rs2221903 and disease occurrence. Similarly, the Iraqi study [19], which included 60 RA patients and 20 healthy individuals, reported no significant differences in genotype or allele distribution, concluding that there were no significant differences in genotype distribution or allele frequency between the RA and control groups. It is noteworthy that while some studies did not associate this polymorphism with disease susceptibility, they did link it to disease activity. Study [28] found that the CT and CC genotypes were significantly more common among patients with high disease activity (DAS28 > 2.5), with a p-value of 0.035. Additionally, [13] demonstrated that haplotype analysis combining rs2221903 and rs2055979 within the IL-21 gene was significantly associated with both susceptibility and disease activity, with the AT haplotype being significantly associated with RA (p = 0.006; OR = 1.395). The discrepancies among these findings may be attributed to several factors, including differences in sample size. For example, the control group in the study [19] consisted of only 20 participants, potentially reducing the analysis's statistical power. Geographic variation within Iraq, between Baghdad and Al-Anbar, may also reflect genetic background diversity, along with differences in genotyping methods and clinical classification criteria. Therefore, the current study confirms that rs2221903 may serve as a potential genetic marker for RA susceptibility in the studied population, highlighting the need for larger, multicenter studies to evaluate this polymorphism in diverse ethnic and environmental contexts.

Genetic model analysis of the IL-21 rs2221903 polymorphism showed no statistically significant associations in the Iraqi cohort, suggesting no clear relationship between this variant and susceptibility to rheumatoid arthritis (RA). As presented in Table 9, none of the tested genetic models demonstrated significant differences (p > 0.05).

In the dominant model, the odds ratio (OR) was 0.30 with a 95% confidence interval (CI) of 0.07–1.30 and a p-value of 0.095. The overdominant model showed an OR of 0.25 (CI: 0.06–1.11) with a p-value of 0.054, which approached statistical significance but remained inconclusive. The recessive model showed an OR of 1.82 (CI: 0.20–16.59) with a p-value of 0.6, indicating no association. Similarly, the log-additive model produced an OR of 0.56 (CI: 0.18–1.72) with a p-value of 0.3. To further elucidate the role of the IL-21 rs2221903 polymorphism in RA susceptibility, various inheritance models, including codominant, dominant, recessive, overdominant, and log-additive, were analyzed. The results indicated a near-significant association in the overdominant model and a trending association in the dominant model, suggesting that the C allele may act as a protective factor against RA.

Table 9 Analysis of Inheritance Models for IL-17F rs11465553 Polymorphism in Rheumatoid Arthritis Susceptibility

Model	Genotype	Status=C	Status=p	OR (95% CI)	Pvalue	AIC	BIC
Codominant	T/T, C/T, C/C	8 (20%), 28 (70%), 4 (10%)	23 (46.9%), 24 (49%), 2 (4.1%)	—	0.15	79.8	104.7
Dominant	T/T, C/T-C/C	8 (20%), 32 (80%)	23 (46.9%), 25 (53.1%)	0.30 (0.07–1.30)	0.095	78.7	101.1
Recessive	T/T-C/T, C/C	36 (90%), 4 (10%)	47 (95.9%), 2 (4.1%)	1.82 (0.20–16.59)	0.6	81.2	103.6
Overdominant	T/T-C/C, C/T	12 (30%), 28 (70%)	25 (51%), 24 (49%)	0.25 (0.06–1.11)	0.054	77.8	100.2
Log-additive	—	—	—	0.56 (0.18–1.72)	0.3	80.4	102.8

Collectively, these findings suggest that the rs2221903 polymorphism may not play a substantial role as a genetic

susceptibility marker for RA in the studied Iraqi population. Although certain models, such as the overdominant model, exhibited borderline trends, all results remained statistically nonsignificant. These observations highlight the importance of conducting further large-scale studies across diverse populations to elucidate any potential role of this variant in RA pathogenesis. Genetic analysis of IL-21 rs2221903 revealed no statistically significant association with rheumatoid arthritis susceptibility in the studied Iraqi cohort. Although certain models, such as the overdominant model, approached significance, all findings remained below the conventional threshold. These results underscore the need for further large-scale studies to clarify the potential role of this polymorphism in diverse populations.

4 CONCLUSION

This study provides compelling evidence for significant associations between the IL-17F polymorphisms (rs2397084 and rs11465553) and the IL-21 polymorphism (rs2221903) with rheumatoid arthritis (RA) susceptibility in the Iraqi population. The C allele of IL-17F rs2397084 and the A allele of rs11465553 were significantly more frequent in RA patients compared with controls, with the A/A genotype of rs11465553 showing a particularly strong association with disease risk. Similarly, the T allele and T/T genotype of IL-21 rs2221903 were more prevalent among RA patients, suggesting a potential role in increasing RA susceptibility. These findings underscore the importance of genetic variations in IL-17F and IL-21 as potential risk factors for RA pathogenesis in the Iraqi cohort, consistent with some regional studies but divergent from others, highlighting population-specific genetic influences. The observed deviations from the Hardy-Weinberg equilibrium in certain groups further suggest disease-related genetic imbalances warranting further exploration. However, the study's limitations, including the relatively small sample size and focus on a single geographic region, necessitate cautious interpretation of the results. Future research involving larger, multiethnic cohorts, coupled with functional studies to elucidate the molecular mechanisms of these polymorphisms, is essential to validate these associations and explore their clinical implications. Such investigations could enhance risk prediction, facilitate personalized therapeutic strategies, and improve the management of RA in Middle Eastern populations.

Acknowledgement

N/A

Funding source

No funds received.

Data availability

N/A

DECLARATIONS

Conflict of interest

The authors have no conflict of interest.

Consent to publish

N/A

Ethical approval

This protocol study was appropriately approved by the Ethical Approval Committee of the University of Anbar-College of Dentistry / Department of Oral and Maxillofacial Surgery as official number of documents 2024/9/11-–149. Participants were informed fully on the manner and content of the study as well as the fact that participation was voluntary prior to collection of the samples. They were informed about procedures to be carried out and given simplified explanation using verbal informed consent.

REFERENCES

[1] Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Research. 2018;6(1). 10.1038/s41413-018-0016-9

[2] Rawla P. Cardiac and vascular complications in rheumatoid arthritis. Rheumatology. 2019;57(1):27–36. 10.5114/reum.2019.83236

[3] Padyukov L. Genetics of rheumatoid arthritis. Seminars in Immunopathology. 2022;44(1):47–62. 10.1007/s00281-022-00912-0

[4] Romão VC, Fonseca JE. Etiology and Risk Factors for Rheumatoid Arthritis: A State-of-the-Art Review. Frontiers in Medicine. 2021;8. 10.3389/fmed.2021.689698

[5] Zhang X, Miao M, Zhang R, Liu X, Zhao X, Shao M, et al. Efficacy and safety of low-dose interleukin-2 in combination with methotrexate in patients

with active rheumatoid arthritis: a randomized, double-blind, placebo-controlled phase 2 trial. Signal Transduction and Targeted Therapy. 2022;7(1). 10.1038/s41392-022-00887-2

[6] Meher J, Patel S, Siddiqui MS, Nanda R. AB0008 ROLE OF IL-23/TH17 AXIS CYTOKINES IN RHEUMATOID ARTHRITIS. In: Scientific Abstracts. BMJ Publishing Group Ltd and European League Against Rheumatism; 2023. p. 1183.2-1183. 10.1136/annrheumdis-2023-eular.4023

[7] Koper-Lenkiewicz OM, Sutkowska K, Wawrusiewicz-Kurylonek N, Kowalewska E, Matowicka-Karna J. Proinflammatory Cytokines (IL-1, -6, -8, -15, -17, -18, -23, TNF-α) Single Nucleotide Polymorphisms in Rheumatoid Arthritis-A Literature Review. International Journal of Molecular Sciences. 2022;23(4):2106. 10.3390/ijms23042106

[8] Garg MK, S Kumar P, Nandagopal S, Shukla K, Gopalakrishnan M. AB0349 ENDOCRINE DYSFUNCTION IN PATIENTS WITH RHEUMATOID ARTHRITIS AND THEIR RELATIONSHIP TO DISEASE SEVERITY. Annals of the Rheumatic Diseases. 2023;82:1358–1359. 10.1136/annrheumdis-2023-eular.4515

[9] Ibrahim ME, Fattah SA, Abdelfattah M, Mehanna E. AB0003 INTERLEUKIN 17A RS2275913 GENE POLYMORPHISM IS RELATED TO SEVERITY AND DISEASE ACTIVITY OF RHEUMATOID ARTHRITIS AND INCREASED SERUM IL17A LEVELS IN EGYPTIAN PATIENTS. Annals of the Rheumatic Diseases. 2023;82:1180. 10.1136/annrheumdis-2023-eular.3237

[10] Higashioka K, Yoshimura M, Sakuragi T, Ayano M, Kimoto Y, Mitoma H, et al. Human PD-1hiCD8+ T Cells Are a Cellular Source of IL-21 in Rheumatoid Arthritis. Frontiers in Immunology. 2021;12. 10.3389/fimmu.2021.654623

[11] Saevarsdottir S, Stefansdottir L, Sulem P, Thorleifsson G, Ferkingstad E, Rutsdottir G, et al. Multiomics analysis of rheumatoid arthritis yields sequence variants that have large effects on risk of the seropositive subset. Annals of the Rheumatic Diseases. 2022;81(8):1085–1095. 10.1136/annrheumdis-2021-221754

[12] Wang M, Wu J, Lei S, Mo X. Genome-wide identification of RNA modification-related single nucleotide polymorphisms associated with rheumatoid arthritis. BMC Genomics. 2023;24(1). 10.1186/s12864-023-09227-2

[13] Carreño-Saavedra NM, Reyes-Pérez IV, Machado-Sulbaran AC, Martínez-Bonilla GE, Ramírez-Dueñas MG, Muñoz-Valle JF, et al. IL-21 (rs2055979 and rs2221903)/IL-21R (rs3093301) Polymorphism and High Levels of IL-21 Are Associated with Rheumatoid Arthritis in Mexican Patients. Genes. 2023;14(4):878. 10.3390/genes14040878

[14] Dhaouadi T, Chahbi M, Haouami Y, Sfar I, Abdelmoula L, Ben Abdallah T, et al. IL-17A, IL-17RC polymorphisms and IL17 plasma levels in Tunisian patients with rheumatoid arthritis. PLOS ONE. 2018;13(3):e0194883. 10.1371/journal.pone.0194883

[15] Yu M, Hou J, Zheng M, Cao Y, Alike Y, Mi Y, et al. IL-21 gene rs6822844 polymorphism and rheumatoid arthritis susceptibility. Bioscience Reports. 2020;40(1). 10.1042/bsr20191449

[16] Ren K, Tang J, Nong L, Shen N, Li X. Association between interleukin-21 gene rs6822844 polymorphism and rheumatoid arthritis susceptibility. Bioscience Reports. 2019;39(8). 10.1042/bsr20190110

[17] McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. The New England Journal of Medicine. 2011;365(23):2205-19. PMID: 22150039. 10.1056/NEJMra1004965

[18] Ali Y, Kausar M, Farooq M, Farooqi N, Ul Islam Z, Khan S, et al. Association of IL-17F rs2397084 (E126G), rs11465553 (V155I) and rs763780 (H161R) variants with rheumatoid arthritis and their effects on the stability of protein. PLOS ONE. 2023;18(9):e0285874. 10.1371/journal.pone.0285874

[19] Al MBMJM, et al. Impact of Interleukin-21 Gene Polymorphism on IL-21 Serum Level in Iraqi Rheumatoid Arthritis Patients. Iraqi journal of biotechnology. 2022;21(2)

[20] Paradowska-Gorycka A, Wojtecka-Lukasik E, Trefler J, Wojciechowska B, Lacki J, Maslinski S. Association between IL-17F gene polymorphisms and susceptibility to and severity of rheumatoid arthritis (RA). Scandinavian journal of immunology. 2010;72(2):134-41. 10.1111/j.1365-3083.2010.02411.x

[21] Yang Y, Yan J, Huang Y, Xu H, Zhang Y, Hu R, et al. The cancer pain related factors affected by celecoxib

together with cetuximab in head and neck squamous cell carcinoma. Biomedicine & Pharmacotherapy. 2015;70:181–189. 10.1016/j.biopha.2015.01.018

[22] Marwa OS, Kalthoum T, Wajih K, Kamel H. Association of IL17A and IL17F genes with rheumatoid arthritis disease and the impact of genetic polymorphisms on response to treatment. Immunology Letters. 2017;183:24-36. 10.1016/j.imlet.2017.01.013

[23] Amin A, Sheikh N, Mukhtar M, Saleem T, Akhtar T, Fatima N, et al. Association of interleukin-17 gene polymorphisms with the onset of rheumatoid arthritis. Immunobiology. 2021;226(1):152045. 10.1016/j.imbio.2020.152045

[24] Pawlik A, Kotrych D, Malinowski D, Dziedziejko V, Czerewaty M, Safranow K. IL17A and IL17F gene polymorphisms in patients with rheumatoid arthritis. BMC Musculoskeletal Disorders. 2016;17:208. 10.1186/s12891-016-1064-1

[25] Nong J, Wang J, Gao X, Zhang Q, Yang B, Yan Z, et al. Circulating CD137+CD8+ T cells accumulate along with increased functional regulatory T cells and thoracic tumour burden in lung cancer patients. Scandinavian Journal of Immunology. 2019;89(6). 10.1111/sji.12765

[26] Ibrahim ME, Shahba AA, Mohamed WS, Hazzaa SM. Interleukin-21 gene rs2221903 polymorphisms in rheumatoid arthritis patients. International Journal of Advanced Research in Medicine. 2023;5(2):9-17. 10.22271/27069567.2023.v5.i2a.472

[27] Terrier B, Geri G, Chaara W, Allenbach Y, Rosenzwajg M, Costedoat-Chalumeau N, et al. Interleukin-21 modulates Th1 and Th17 responses in giant cell arteritis. Arthritis & Rheumatism. 2012;64(6):2001-11. 10.1002/art.34327

[28] Malinowski D, Paradowska-Gorycka A, Safranow K, Pawlik A. Interleukin-21 gene polymorphism rs2221903 is associated with disease activity in patients with rheumatoid arthritis. Archives of Medical Science. 2017;13(5):1142-7. 10.5114/aoms.2017.68945

How to cite this article

Masser HK, Al-Darraji MN, Mohsen RT. Association of IL-17 and IL-21 gene polymorphisms and haplotypes with rheumatoid arthritis susceptibility in Iraqi patients. Journal of University of Anbar for Pure Science. 2026; 20(1):29-41. doi:10.37652/juaps.2025.161064.1408