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STAT4 genetic polymorphisms and their association with rheumatoid arthritis susceptibility and disease severity; a molecular case-control study

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Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic autoimmune disease in which genetic factors play a critical role, and emerging evidence suggests that variants in the signal transducer and activator of transcription 4 (STAT4) gene may influence both susceptibility to the disease and the severity of its clinical expression.
Objectives: This study aimed to investigate the association between STAT4 genetic polymorphisms and the risk of developing RA, as well as their potential influence on disease activity.
Materials and Methods: This case–control study was conducted on 186 RA patients and 192 age- and sex-matched healthy controls from June 12, 2025, to January 16, 2026, at Baghdad Medical City Hospital in Baghdad, Iraq. Demographic and clinical data were collected, and disease activity was assessed using the disease activity score in 28 joints (DAS28). Peripheral blood samples were obtained for genomic DNA extraction using silica-membrane spin column kits, and STAT4 polymorphisms (rs7574865 and rs10181656) were genotyped by polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP). The association between STAT4 genetic polymorphisms and the risk of developing RA, as well as disease severity, was evaluated using statistical analysis.
Results: The results indicated that STAT4 gene variants showed strong associations with RA susceptibility: for rs7574865, the GT and TT genotypes compared to GG were linked to higher risk (OR = 1.69 and OR = 3.06, respectively), and for rs10181656, the CG and GG genotypes compared to CC similarly increased risk (OR = 1.66 and OR = 2.62). Among RA patients, DAS28 scores differed significantly across STAT4 genotypes, with higher scores observed in carriers of the risk-associated alleles for both polymorphisms.
Conclusion: STAT4 polymorphisms, particularly rs7574865 and rs10181656, were significantly associated with increased RA susceptibility and higher disease severity, highlighting their potential value as genetic markers in RA.

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction, and substantial functional disability, with a global prevalence of approximately 0.5–1% (1-4). Both environmental and genetic factors contribute to RA pathogenesis, with heritability estimates of up to 60%, underscoring the importance of genetic determinants of disease susceptibility and phenotype (5-7). Genome-wide association studies have identified multiple loci outside the human leukocyte antigen (HLA) region that modulate RA risk, many of which encode molecules involved in lymphocyte activation and cytokine signaling (8, 9). Among these, the signal transducer and activator of transcription 4 (STAT4) gene has emerged as a key candidate because of its central role in mediating interleukin-12 (IL-12), interleukin-23 (IL-23), and type I interferon signaling, thereby promoting Th1 and Th17 differentiation and the production of pro-inflammatory cytokines (10,11).

STAT4 polymorphisms, particularly the intronic single-nucleotide polymorphism rs7574865, have been repeatedly associated with RA susceptibility in diverse populations (12-14). A large meta-analysis of 15 studies including more than 16,000 RA cases and 16,000 controls demonstrated that the rs7574865 T allele confers a modest but consistent increase in RA risk across ethnic groups (12). Additional meta-analyses integrating STAT4 with other non-HLA loci, such as PTPN22, have confirmed the contribution of rs7574865 to RA

Key point

The results from this study indicated that signal transducer and activator of transcription 4 (STAT4) gene variants showed strong and clinically relevant associations with rheumatoid arthritis (RA) susceptibility. Both rs7574865 and rs10181656 polymorphisms demonstrated significantly elevated odds ratios for the GT/TT and CG/GG genotypes, respectively, highlighting their contribution to increased disease risk. Additionally, disease activity score in 28 joints (DAS28) varied markedly across STAT4 genotypes, with higher activity observed among carriers of the risk-associated alleles, and post-hoc comparisons confirmed significant differences for most genotype pairs. Collectively, these results underscore the role of STAT4 polymorphisms not only in predisposing individuals to RA but also in influencing the severity of disease expression.

susceptibility in major ethnic populations, indicating that STAT4 variation represents a shared genetic risk factor for autoimmunity (13). More recent case–control studies have extended these findings by examining STAT4 polymorphisms in different geographic cohorts and by exploring their association with clinical parameters and treatment response, reinforcing the role of STAT4 as a biologically plausible RA risk gene (14).

Beyond disease susceptibility, accumulating evidence suggests that STAT4 genetic variants may also influence RA severity and phenotype, including autoantibody positivity and measures of disease activity (10). In Syrian RA patients, the rs7574865 TT genotype has been linked to higher rates of anti-citrullinated peptide antibody (ACPA) positivity, although its effect on disease onset and severity appears modest compared with HLA-DRB1 shared epitope alleles (15). Other studies have indicated that STAT4 risk alleles are associated with increased STAT4 expression and may correlate with higher disease activity scores and radiographic damage, supporting a mechanistic link between genotype, STAT4 signaling, and clinical outcomes (16). However, findings across populations are not fully consistent, and data on the relationship between STAT4 polymorphisms and detailed severity indices remain limited. A study focusing on STAT4 genetic polymorphisms and their association with both RA susceptibility and disease severity could therefore help clarify these relationships and contribute to refining genetic markers for risk stratification and prognostication in RA.

Objectives

This study aimed to comprehensively investigate the role of STAT4 genetic polymorphisms in the pathogenesis of RA by examining their association with disease susceptibility and clinical severity. Specifically, the study sought to determine whether the rs7574865 and rs10181656 variants of the STAT4 gene are linked to an increased risk of developing RA and to evaluate the extent to which these polymorphisms influence disease activity, as measured by disease activity score in 28 joints (DAS28), among affected individuals. By integrating genetic profiling with clinical assessment, the study intended to clarify the contribution of STAT4 variants to both the onset and progression of RA within a molecular case–control framework.

Materials and Methods

Study design and participants

This molecular case–control study was conducted from June 12, 2025, to January 16, 2026, at Baghdad Medical City Hospital in Baghdad, Iraq. The study enrolled 186 patients with RA who fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA (17), along with 192 healthy individuals matched to the patient group by age and sex. Control participants had no history of autoimmune or chronic inflammatory diseases. All participants underwent clinical evaluation and provided blood samples for molecular analysis of STAT4 gene polymorphisms.

Inclusion and exclusion criteria

The study included adults who provided informed written consent and were able to undergo venous blood sampling for STAT4 genotyping, as well as complete demographic and clinical assessments, including DAS28 scoring for patients with RA. Participants were eligible if they had complete data on STAT4 polymorphisms (rs7574865 and rs10181656). Patients with RA were required to have a confirmed clinical diagnosis based on established criteria according to the 2010 ACR/EULAR classification criteria for RA, while healthy controls needed to be free of autoimmune or inflammatory diseases. Individuals were excluded if they had incomplete demographic, clinical, or laboratory data or an inability to provide adequate blood samples for molecular analysis.

Data collection

Data were collected from 378 participants, including 186 patients diagnosed with RA and 192 age- and gender-matched healthy controls. After obtaining informed written consent from all participants, demographic information (age, gender, smoking status, and body mass index [BMI]) was recorded from clinical documents or by participants' interviews. Venous blood samples were collected under sterile laboratory conditions for genomic DNA extraction and subsequent genotyping of STAT4 polymorphisms (rs7574865 and rs10181656). Clinical data for RA patients, including DAS28, were obtained through standardized clinical assessments performed by trained rheumatologists. All biological samples and clinical measurements were processed according to institutional protocols to ensure accuracy and consistency throughout the study.

Genomic DNA extraction and genotyping

Peripheral venous blood (3 mL) was collected aseptically into EDTA-anticoagulated tubes, and genomic DNA was

extracted using silica-membrane spin column purification kits following the manufacturer's protocol. DNA purity was assessed spectrophotometrically, and samples with A260/A280 ratios between 1.8 and 2.0 were considered suitable for downstream molecular analysis. DNA concentration and integrity were verified before aliquoting, and all extracts were stored at −20 °C until genotyping. STAT4 polymorphisms (rs7574865 G/T and rs10181656 C/G) were genotyped using polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP). PCR amplification was performed in a 25 µL reaction mixture containing approximately 50 ng of genomic DNA, 10 pmol of each primer, 1× PCR master mix, and nuclease-free water. Primer sequences were as follows: rs7574865 forward 5′-AGT TTG GGA GCA GCA GGT AA-3′ and reverse 5′-CTG AAC TGG AAG GCA GTG AC-3′ (338 bp product); rs10181656 forward 5′-CCT TCT CAG GGT CTC AGG AA-3′ and reverse 5′-GGT GGT GTT GAG GTTC-3′ (290 bp product). Thermal cycling conditions included an initial denaturation at 95 °C for 5 min, followed by 35 cycles of denaturation at 95 °C for 30 s, annealing at 60 °C for 30 s, and extension at 72 °C for 30 s, with a final extension at 72 °C for 7 min. Amplicons were first confirmed by electrophoresis on 2% agarose gels before restriction digestion. The rs7574865 PCR product was digested with PvuII, and the rs10181656 product with BstUI, and the resulting fragments were resolved on 3% agarose gels to determine genotype patterns.

DAS28 scoring

Disease activity in RA patients was assessed using the DAS28, a validated composite index that incorporates clinical examination and laboratory markers. The DAS28 score was calculated using the number of tender joints (TJC28) and swollen joints (SJC28) out of 28 assessed joints, the patient's erythrocyte sedimentation rate (ESR), and the patient's global health assessment (GH, measured on a 0–100 mm visual analogue scale). The standard formula applied was:

$$DAS28 = 0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.70 \times \ln(ESR) + 0.014 \times GH.$$

Scores >5.1 indicate high disease activity, 3.2–5.1 moderate activity, 2.6–3.2 low activity, and <2.6 remission. This method is widely used in clinical and research settings to quantify RA disease severity (18).

Outcome measurement

The primary outcome of this study was assessing the association between STAT4 gene polymorphisms (rs7574865 and rs10181656) and RA susceptibility, assessed by comparing genotype distributions between RA patients and healthy controls and estimating odds ratios (ORs) using binary logistic regression. The secondary outcome was the evaluation of disease severity among RA patients according to STAT4 genotypes, measured using the DAS28, with comparisons of mean DAS28 values across genotypic groups and post-hoc analyses to determine pairwise differences.

Statistical analysis

Data analysis was conducted using SPSS software version 27 (IBM Corp., Armonk, NY, USA). Data normality was assessed by the Kolmogorov–Smirnov test. Categorical variables were compared between groups using the chi-square test, while continuous variables were analyzed using the independent t-test or one-way ANOVA, as appropriate. Binary logistic regression was applied to estimate the association between STAT4 gene polymorphisms and RA susceptibility, and results were expressed as OR with 95% confidence intervals. For comparisons of DAS28 scores across genotypes, post-hoc least significant difference (LSD) testing was conducted following significant ANOVA results. A two-tailed P value < 0.05 was considered statistically significant.

Results

The study included 378 participants, including 192 healthy controls and 186 patients with RA who were matched to the control group by age and gender. The demographic characteristics of the RA group and the healthy controls were broadly comparable. Both groups exhibited a similar distribution of males and females, with no statistically significant difference in gender proportions. Smoking status likewise did not differ meaningfully, as the proportions of smokers and non-smokers were closely aligned between groups and showed no significant association. Age and BMI were also comparable, with no notable or statistically significant differences observed. In contrast, marked differences were evident in the distribution of STAT4 gene polymorphisms. For the rs7574865 variant, the RA group demonstrated a substantially higher representation of the risk-associated genotypes (TT and GT) compared with controls, yielding a highly significant association. A similar pattern was observed for the rs10181656 variant, where the RA group showed a greater frequency of the susceptibility-linked genotypes (GG and CG), and also reached statistical significance (Table 1).

Binary logistic regression analysis demonstrated significant associations between STAT4 gene polymorphisms and RA susceptibility. For the rs7574865 variant, individuals carrying the GT genotype had higher odds of RA compared with the GG reference group, with an OR of 1.69, while the TT genotype showed an even stronger association, with an OR of 3.06, both reaching statistical significance. Similarly, for the rs10181656 variant, carriers of the CG genotype exhibited increased RA risk with OR = 1.66, and those with the GG genotype demonstrated an even greater susceptibility (OR = 2.62), each relative to the CC reference genotype. All associations for non-reference genotypes were statistically significant, indicating that both STAT4 polymorphisms contribute

Table 1. Distribution of demographic and clinical characteristics between patients with RA and healthy control individuals

Demographic and clinical data			Group		*P* value*
			Control (n= 192)	RA (n = 186)	
Gender		Female N (%)	101 (52.6)	96 (51.6)	0.847
		Male N (%)	91 (47.4)	90 (48.4)	
Smoking		No N (%)	89 (46.4)	92 (49.5)	0.545
		Yes N (%)	103 (53.6)	94 (50.5)	
STAT4 gene	rs7574865	GG	98 (51)	64 (34.4)	<0.001
		GT	74 (38.5)	82 (44.1)	
		TT	20 (10.4)	40 (21.5)	
	rs10181656	CC	102 (53.1)	70 (37.6)	0.004
		CG	70 (36.5)	80 (43)	
		GG	20 (10.4)	36 (19.4)	
Quantitative variables			**Mean ± SD**	**Mean ± SD**	***P* value****
Age (y)			47.54 ± 10.48	48.02 ± 11.30	0.670
BMI (kg/m²)			26.84 ± 3.87	27.31 ± 4.11	0.257

RA: Rheumatoid arthritis; BMI: Body mass index; SD: Standard deviation. *Chi-square, **Independent T-test.

meaningfully to RA susceptibility (Table 2).

Among patients with RA, DAS28 scores varied significantly according to STAT4 gene polymorphisms. For the rs7574865 variant, disease activity increased progressively across genotypes, with the GG group exhibiting the lowest scores and the TT group the highest, and the overall comparison demonstrated strong statistical significance. Post-hoc analyses confirmed that all pairwise differences between GG, GT, and TT genotypes were significant. For the rs10181656 variant, DAS28 scores were likewise higher among individuals carrying the CG and GG genotypes compared with the CC genotype, yielding a significant overall association. Pairwise comparisons showed modest but statistically significant differences between CC and CG and between CC and GG, whereas the comparison between CG and GG did not reach statistical significance (Table 3).

Table 2. The correlation between STAT4 gene polymorphisms and RA susceptibility using binary logistic regression

STAT4 gene polymorphisms		RA susceptibility		
		OR	95% CI	*P*-value
rs7574865	GG		Ref (1)	
	GT	1.69	1.08 – 2.64	0.020
	TT	3.06	1.64 – 5.70	< 0.001
rs10181656	CC		Ref (1)	
	CG	1.66	1.07 – 2.59	0.024
	GG	2.62	1.40 – 4.90	0.003

RA: Rheumatoid arthritis; OR: Odds ratio; CI: Confidence interval; RF: Reference.

Table 3. Comparison of DAS28 scores among patients with RA according to STAT4 gene polymorphisms

	STAT4 gene polymorphisms			
	rs7574865			*P* value*
	GG (n = 98)	GT (n = 74)	TT (n = 20)	
DAS28 score (Mean ± SD)	5.01 ± 0.75	5.46 ± 0.66	5.89 ± 0.71	<0.001
	Genotypes		Mean difference	*P* value**
	GG	GT	0.44	<0.001
		TT	0.87	<0.001
	GT	TT	0.43	0.002
	rs10181656			*P* value*
	CC (n = 102)	CG (n = 70)	GG (n = 20)	
	5.21 ± 0.75	5.48 ± 0.76	5.59 ± 0.76	0.026
	Genotypes		Mean difference	*P* value**
	CC	CG	0.27	0.033
		GG	0.38	0.016
	CG	GG	0.11	0.465

SD: Standard deviation *One-way ANOVA, **Post hoc LSD.

Discussion

In this molecular case–control study, STAT4 rs7574865 and rs10181656 polymorphisms were associated with RA susceptibility and with higher disease activity scores, suggesting that these variants may influence both risk and severity of RA in this Iraqi cohort. These findings are consistent with the growing body of evidence that implicates STAT4 as a non-HLA genetic contributor to RA and extend this association to a Middle Eastern population. Previous genome-wide association and candidate-gene studies in European, Asian and Latin American cohorts have shown that intronic STAT4 variants, especially rs7574865 and haplotypes including rs10181656, confer modest increases in RA risk (11,12,19,20). In Koreans, Lee et al identified a four-marker intronic haplotype (rs11889341–rs7574865–rs8179673–rs10181656) that independently increased RA susceptibility beyond HLA-DRB1, supporting a primary role for this locus in disease risk (11). Zervou et al showed that in a genetically homogeneous Cretan population, the STAT4 rs7574865 polymorphism was associated with RA susceptibility. The T allele and the T/T and G/T genotypes were linked to a higher risk of RA, supporting the involvement of STAT4 in disease predisposition (19). Palomino-Morales et al reported that the STAT4 rs7574865 polymorphism contributes meaningfully to autoimmune disease susceptibility in Colombians, showing that carriers of the rs7574865 T allele have an elevated risk of developing RA, with an odds ratio of 1.36 and a statistically significant association (20). A large-scale meta-analysis encompassing more than 15,000 RA cases and a comparable number of controls provided robust evidence that the STAT4 rs7574865 variant is consistently associated with increased RA susceptibility across diverse populations (21). Yüksel et al found no evidence that the STAT4 rs7574865 or rs10181656 polymorphisms contribute to RA susceptibility in the Turkish population, as neither variant showed meaningful associations with genotype distributions, clinical characteristics, or laboratory parameters among affected individuals. Their results contrast with findings from other populations, suggesting that the influence of STAT4 on RA risk may vary by ethnic background and highlighting the importance of population-specific genetic investigations (22). Similar direction and magnitude of effect for rs7574865 have been reported in Cretan Greeks, Colombians, and Koreans, as well as in large meta-analyses, indicating that the T allele and corresponding risk genotypes represent a shared susceptibility factor across multiple ethnicities (11,19-21). The comparatively higher odds ratios observed for the GT/TT and CG/GG genotypes in the present study fall within the upper range of previously reported estimates, which may reflect population-specific genetic structure, environmental exposures, or random variation related to sample size. Nonetheless, the direction of effect for both rs7574865 and rs10181656 aligns with the predominant pattern seen in most non-Turkish cohorts, strengthening the evidence that STAT4 variation contributes to RA susceptibility.

The observed relationship between STAT4 risk genotypes and higher DAS28 scores in RA patients is also in line with several reports linking STAT4 variation to indices of disease activity and severity, although results across studies have been mixed. In an Egyptian cohort, STAT4 TT genotype was associated not only with RA susceptibility but also with more severe disease, supporting a role for this locus in modulating clinical phenotype in addition to risk (23). More recently, a study in Western Mexico found that rs7574865 GT and TT genotypes were associated with RA susceptibility and with moderate-to-high DAS28 scores and anti-CCP positivity, whereas no such association was observed in a Southern Mexican population (24). By contrast, the Turkish study reported no correlation between rs7574865 or rs10181656 genotypes and disease activity parameters (22). Against this background, the present demonstration that carriers of risk-associated alleles at both loci had higher DAS28 scores supports the hypothesis that STAT4 variants may contribute to more active disease in at least some populations, but also highlights that the relationship between genotype and severity is likely context-dependent.

Overall, our study demonstrates that STAT4 rs7574865 and rs10181656 polymorphisms are associated with increased susceptibility to RA and with higher disease activity in an Iraqi cohort, thereby reinforcing the importance of STAT4 as a non-HLA genetic determinant of RA and its clinical expression. These data complement prior work from European, Asian, African, and Latin American populations and suggest that STAT4 genotyping may, in the future, contribute to more refined genetic risk stratification and severity prediction, although validation in larger, multi-center cohorts and integration with other genetic and environmental factors will be required before clinical implementation.

Conclusion

This study demonstrates that STAT4 gene polymorphisms, particularly rs7574865 and rs10181656, are significantly associated with increased susceptibility to RA and with higher disease activity among affected patients. Individuals carrying the risk-associated genotypes exhibited markedly elevated odds of RA and higher DAS28 scores, underscoring the potential role of STAT4 variants in both disease onset and severity. These findings highlight STAT4 as a meaningful genetic contributor to RA pathogenesis and support its relevance as a potential biomarker for risk stratification and clinical assessment.

Limitations of the study

As a single-center molecular case–control study, the results may not be fully generalizable to broader or more diverse populations. Although genotyping was performed using validated PCR–RFLP methods, the analysis

was limited to two STAT4 polymorphisms, and other potentially relevant variants or gene–gene interactions were not assessed. Clinical data, including DAS28 scores, were collected at a single time point, preventing evaluation of longitudinal changes in disease activity. Additionally, unmeasured environmental or lifestyle factors may have influenced disease susceptibility or severity but were not fully controlled. Larger, multi-center studies incorporating additional genetic markers and longitudinal follow-up would help strengthen and extend these findings.

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Authors' contribution

Conceptualization: Hasanain. Alrashedi and Oras N. Hamad.
Data curation: Hasanain. Alrashedi and Muayad B. Kadhim.
Formal analysis: Muayad B. Kadhim.
Investigation: Oras N. Hamad and Muayad B. Kadhim.
Methodology: Hasanain. Alrashedi and Muayad B. Kadhim.
Project management: Oras N. Hamad.
Resources: All authors.
Supervision: All authors.
Validation: Muayad B. Kadhim.
Writing-original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

While preparing this work, the authors utilized AI (Grammarly, Perplexity, and Copilot) to refine grammar points and language style. Subsequently, they thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

The research was conducted in accordance with the principles outlined in the Declaration of Helsinki. Informed written consent was taken from all participants or their legally authorized representatives. This study was conducted at Baghdad Medical City Hospital in Baghdad, Iraq, and was derived from a research project, approved by the committee of ethics in scientific research, College of Medicine, University of Misan, Iraq (No: 42). Besides, the authors have ultimately observed ethical issues (including plagiarism, data fabrication, and double publication).

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