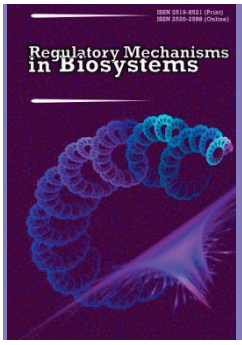

Regulatory Mechanisms in Biosystems

ISSN 2519-8521 (Print)
ISSN 2520-2588 (Online)
Regul. Mech. Biosyst.,
2024, 15(4), 674–678
doi: 10.15421/022497

The role of *PTPN22 rs2476601* and *STAT4 rs7574865* gene polymorphism in the incidence of rheumatoid arthritis

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Article info

Received 01.07.2024
Received in revised form 04.08.2024
Accepted 19.08.2024

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Taher, A. R., & Nassir, N. F. (2024). The role of PTPN22 rs2476601 and STAT4 rs7574865 gene polymorphism in the incidence of rheumatoid arthritis. Regulatory Mechanisms in Biosystems, 15(4), 674–678. doi:10.15421/022497

Rheumatoid arthritis (RA) is a chronic inflammatory condition that often affects many peripheral joints. It is characterized by a faulty immune system. This autoimmune disorder affects 1% of the population, with women having double the risk as men. Numerous signs point to the idea that genetics play an important role in the beginning of RA. Previous studies reported that some of the non HLA genes such as *PTPN22* and *STAT4* could be risk factors for the development of autoimmune diseases, including RA. The purpose of this study was to demonstrate the relationship between the single nucleotide polymorphisms, *PTPN22 rs2476601* and *STAT4 rs7574865*, and a higher risk of RA illness in the population of AL-Dewaniya, Iraq as well as the possibility of galectin 3 associating with the minor allele. One hundred and fifty participants were involved in this study; seventy-five of them were RA patients and the others were clinically healthy control. Blood samples were collected from both study groups and separated into 2 mL in EDTA tubes for genotypic study and 3 mL in gel tube for serological study (Gal-3). According to the results obtained, the frequencies of *PTPN22 rs2476601* G allele were 73 out of 150 (48.7%), 94 out of 150 (62.7%), while the frequencies of *PTPN22 rs2476601* A allele were 77 out of 150 (51.3%) and 56 out of 150 (37.3%) for RA and control respectively. The most prevalent genotype of *PTPN22* gene frequency was heterozygous (GA) followed by homozygous mutant (AA), then homozygous wild-type (GG). The *STAT4 rs7574865* G allele frequencies were 121 out of 150 (80.7%), 139 out of 150 (92.3%), whereas the *STAT4 rs7574865* T allele frequencies were 29 out of 150 (19.3%) and 11 out of 150 (7.3%) for RA and control respectively. The most prevalent genotype of *STAT4* gene frequency was the homozygous wild-type (GG) followed by the heterozygous (GT), then the homozygous mutant (TT). The observed results indicate that there is an association between *PTPN22* minor allele (A) and *STAT4* minor allele (T) with RA. Additionally, for the first time, the study investigated the relationship between Gal-3 (positive results) with minor alleles of the both genes, which shows an association between both minor alleles of both genes' polymorphism and high serum levels (positive results) of galectin-3 (Gal-3).

Keywords: *STAT4 rs7574865*; *PTPN22 rs2476601*; rheumatoid arthritis; galectin-3.

Introduction

The etiology of rheumatoid arthritis (RA), a long-lasting inflammatory disease, remains unclear. Symptoms include swelling, bone erosion, discomfort, and synovial damage. It affects approximately 1% of the population. Studies have shown that several genetic and environmental changes are associated with an aggravated possibility of emergent rheumatoid arthritis (RA) (Deane et al., 2017). Several genes and environments influence rheumatoid arthritis (RA) susceptibility. Among them are smoking, *STAT4*, *PTPN22*, antibodies to cyclic citrullinated peptides (CCP), and *HLA-DRB1* "shared epitope" alleles (Padyukov & Alfredsson, 2014).

The *rs2476601* single nucleotide polymorphism is located at 1p13. 2 in exon 14 of the *PTPN22* gene. A second genetic link associated with rheumatoid arthritis is lymphocyte-specific non-receptor tyrosine phosphatase, which regulates the level of lymphocyte function. Position 1858 of the human *PTPN22* cDNA contains a cytosine to thymine SNP that changes arginine (R) to tryptophan (W), disrupting the interaction between LYP and C-Src tyrosine kinase (Csk), preventing its formation. It promotes T cell stimulation and causes autoimmune disorders. Among the various HLA genes known to be associated with this disease, this gene has the highest risk of developing rheumatoid arthritis (Hou et al., 2020; Mikhaylenko et al., 2020).

Signal Transducer and Activator of Transcription 4 (*STAT4*), a transcription factor expressed in dendritic cells, macrophages, and lymphocytes, is encoded by exon 27 of the *STAT4* gene located on human chromosome 2q32. 2-q32. 3 (Goswami & Kaplan, 2017). *STAT4*, an important mediator of the immune system, is modulated by alterations in protein expression or activity, which affects how the immune system responds and functions. For example, the G>T mutation located in the third intron of the *STAT4* gene, known as the *rs7574865* polymorphism, is linked to the TT polymorphic genotype times and increases the risk of developing the disease (Durán-Avelar et al., 2016; Esparza Guerrero et al., 2023). The predominance of RA in Asian and European populations is associated with the variant T allele of the *STAT4 rs7574865* SNP (Blekeris et al., 2023; Budlewski et al., 2023).

Galectin-3 (Gal-3) principally represents a pro-inflammatory molecule in autoimmune and chronic inflammatory diseases (de Oliveira et al., 2015; Srejovic & Lukic, 2021). The serum levels of galectin-1 and galectin-3 present a good indicator to detect RA patients (Mendez-Huergo et al., 2019).

Additionally, Jeon and colleagues demonstrated that extracellular gal-3 may trigger inflammatory and immunological signaling events by phosphorylating *JAK2* and *STAT1*, *STAT3*, and *STAT5* (Jeon et al., 2010; Gupta, 2012).

Materials and methods

Blood samples. Blood samples (3 mL) were collected form 75 RA patients who referred to the Rheumatology and Medical Rehabilitation Clinic at Al-Dewaniya Teaching Hospital, Iraq and matched with 75

blood samples from clinically healthy individuals as control. The specimens were separated into 2 mL in a blood collection tube type EDTA-k2 (Ethylene diamine tetra acetic acid-di-potassium) for genotypic examination and 3 ml in a gel tube to measure Gal-3 levels in serum.

DNA extraction and genotyping. The genotyping used in this study at the Medical Biotechnology Department, Faculty of Medical Biotechnology, Al-Qasim Green University, Babylon, Iraq. Two milliliters of blood were drawn into EDTA tubes, which were then stored at -20 degrees Celsius until further analysis. *PTPN22 rs2476601* and *STAT4 rs7574865* were genotyped by using the allele-specific tetra primers amplification refractory mutation technique (T-ARMS-PCR).

The primer sequences for *PTPN22 rs2476601* and *STAT4 rs7574865*, that were used for the present study are designated for this study and displayed in Table 1.

The conditions of two PCR programs for *rs2476601* and *rs7574865* were fixed as shown in Table 2. The PCR results were visualized on a 2% agarose gel after being stained with ethidium bromide (EtBr). A 100 bp DNA ladder was used as a marker to assess the size of the PCR outcome and photographed on camera using a UV transilluminator. The collected samples were genotyped into potential genotypes for *PTPN22* (GG, AA, and GA) and *STAT4* (GG, TT, and GT). For *PTPN22* and *STAT4*, the major allele was G/G and the minor allele was A/T, respectively.

Table 1
Primer sequences of *PTPN22 rs2476601* and *STAT4 rs7574865* gene polymorphism

PTPN22 rs2476601			
Primer	Primer sequence	Product size, base pair (bp)	Reference
Forward outer	5′- CAATGAACTCCTCAAACTCAAGG -3′	330	By this study
Reverse outer	5′- ACTGATAATGTTGCTTCAACGGA -3′	Control band	
Forward inner (A allele)	5′- CCACAATAAATGATTCAGGTGTACA -3′	203	
Reverse inner (G allele)	5′- CCCCTCCACTTCCTGGAC -3′	170	
STAT4 rs7574865			
Forward outer	5′- ACACTTGACTGTTAATACGGATG -3′	401	By this study
Reverse outer	5′- CTTGCTTTAGGAGTTCTAATTTTC -3′	Control band	
Forward inner (G allele)	5′- AAAAGTTGGTGACCAAAATCTA -3′	243	
Reverse inner (T allele)	5′- CCACTGAAATAAGATAACCACTAATA -3′	206	

Table 2
PCR conditions of *PTPN22 rs2476601* and *STAT4 rs7574865*

PTPN22 rs2476601			
Step	Temperature, °C	Time, second	Cycle
Pre- Denaturation	95	300	1 cycle
Denaturation	95	30	32 cycles
Annealing	56.5	30	
Extension	72	60	
Final extension	72	300	
STAT4 rs7574865			
Pre- Denaturation	95	300	1 cycle
Denaturation	95	30	32 cycles
Annealing	54	30	
Extension	72	60	
Final extension	72	300	

Enzyme-linked immunosorbent assay (ELISA) kits from Sunlong Inc. China were used to determine the levels of Gal-3 in the blood. The serum was labeled and stored at –20 °C in a deep freeze until all specimens were obtained.

Statistical analysis. The "Hardy-Weinberg equilibrium" status of each patient and control was evaluated using a chi-square test. To ascertain statistical significance ($P < 0.05$), a probability was employed. "Hardy–Weinberg equilibrium (HWE)" was examined in the control groups using "Fisher's exact test". If the study was found to be outside of HWE with a P value less than 0.05, it was considered to be in disequilibrium. By using direct counting, the differences in the allele/genotype distribution across the study groups were determined. When a discernible difference was found to exist, the odds ratio "OR" was calculated to determine the direction of the relevant components' association. P-values below 0.05 were considered statistically significant.

Results

Seventy-five individuals with rheumatoid arthritis were included in this case-control study: 53 females (71%) and 22 men (29%) their ages from 19 to 65 years old. Every patient met the 1987 updated criteria of the American College of Rheumatology (ACR) and had a diagnosis made by a qualified pathologist (Arnett et al., 1988). The patient group was matched with the same number and same gender of clinically healthy control. There was no history of RA or any other autoimmune disease among the controls or their first-degree relatives.

The findings demonstrated that there was a significant correlation between rheumatoid arthritis and several polymorphic markers of two genes, *PTPN22* and *STAT4*, for both study groups. The frequencies of *PTPN22 rs2476601* G allele were 73 out of 150 (48.7%), 94 out of 150 (62.7%), while the frequencies of PTPN22 rs2476601 A allele were 77 out of 150 (51.3%) and 56 out of 150 (37.3%) for RA and control respectively. The frequencies of *PTPN22 rs2476601* GG genotype (wild-type) were 20 of 75 (26.7%) and 30 of 75 (40%), the frequencies of *PTPN22 rs2476601* GA genotype (heterozygote mutant) were 33 of 75 (44%), 34 of 75 (45.3%), and the frequencies of *PTPN22 rs2476601* AA genotype (homozygote mutant) were 22 of 75 (29.3%), 11 of 75 (14.7%) for RA and control individuals respectively (Fig. 1).

The type of gene that carries the risk of RA is represented in two genotypes (AA and GA) with OR = 3.000; 95% CI = 1.197–7.518 (P = 0.017) and 1.456; 95% CI = 0.694–3.055 (P = 0.320) respectively. Also, variant allele (A) indicates the risk factor for RA with OR = 1.771; 95% CI = 1.117–2.806 (P = 0.015, Table 3).

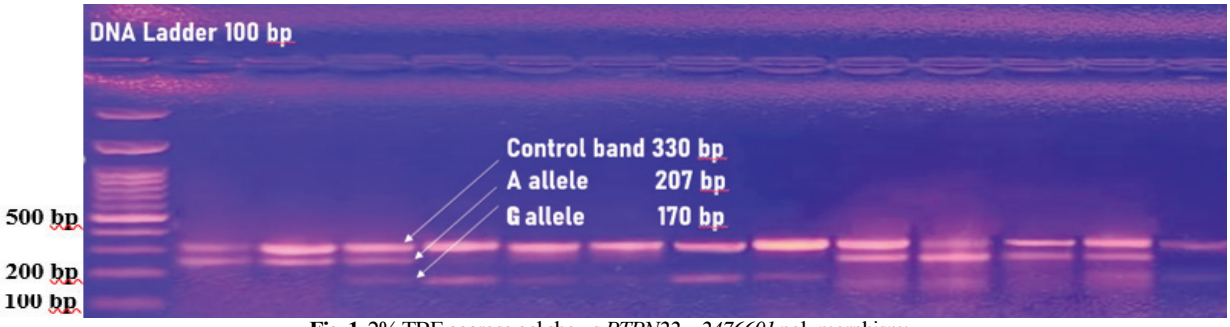

Fig. 1. 2% TBE agarose gel shows *PTPN22 rs2476601* polymorphism:
DNA ladder 100 bp, EtBr 0.5 µL, 100 V/cm^2, current 50 for 1 hour; electrophoresis pattern of T-ARMS-PCR

Table 3
Genotypes distribution and alleles frequency of *PTPN22 rs2476601* G>A polymorphism in RA patients and controls

Allele/ Genotype	RA, n = 75 (%)	Control, n = 75 (%)	OR	CI 95 %	P value
GG	20 (26.7)	30 (40.0)	1.00	RS	RS
GA	33 (44.0)	34 (45.3)	1.46	0.69–3.06	0.320
AA	22 (29.3)	11 (14.7)	3.00	1.20–7.52	0.017*
HWE	0.991				
G	73 (48.7)	94 (62.7)	1.00	RS	RS
A	77 (51.3)	56 (37.3)	1.77	1.12–2.81	0.015*

Notes: RA – rheumatoid arthritis, OR – odds ratio, CI 95% – confidence interval 95%, HWE – Hardy-Weinberg equilibrium, * – significant at P value <0.05; RS – GG/ G as reference.

The *STAT4 rs7574865* G allele frequencies were 121/150 (80.7%), 139/150 (92.3%), whereas the *STAT4 rs7574865* T allele frequencies were 29/150 (19.3%) and 11/150 (7.3%) for RA and control respectively. The *STAT4 rs7574865* homozygous wild type (GG) genotype frequencies were 48/75 (64%) and 64/75 (85.3%), the *STAT4 rs7574865* heterozygous genotype frequencies were 25/75 (33.3%), 10/75 (13.3%), and the *STAT4 rs7574865* homozygous mutant (TT) genotype frequencies were 2/75 (2.7%), 1/75 (1.3%) for RA and control individual respectively (Fig. 2).

The type of gene that carries the risk for RA is represented in two genotypes (TT and GT) with OR = 2.667; 95% CI = 0.235–30.274 (P = 0.412) and 3.333; 95% CI = 1.463–7.594 (P = 0.003) respectively. Also, mutant allele (T) indicated a risk factor for RA with OR = 3.029; 95% CI = 1.457–6.320 (P = 0.002, Table 4).

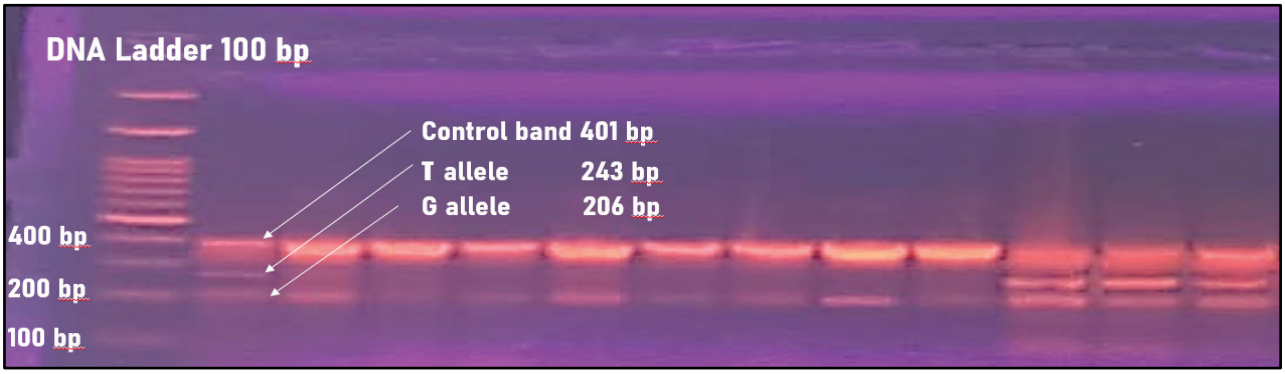

Fig. 2. ARMS PCR genotyping done for *STAT4 rs7574865* gene visualization in 2% agarose gel 100 V/cm^2, 1 hour, EtBr 0.5 µL, DNA ladder 100 bp

Table 4
Genotypes distribution and alleles frequency of *STAT4 rs7574865* G>T polymorphism in RA patients and controls

Allele/ Genotype	RA, n = 75 (%)	Control, n = 75 (%)	OR	CI 95%	P value
GG	48 (64.0)	64 (85.3)	1.00	RS	RS
GT	25 (33.3)	10 (13.3)	3.33	1.46–7.59	0.003
TT	2 (2.7)	1 (1.3)	2.67	0.24–30.27	0.412
HWE	0.880				
G	121 (80.7)	139 (92.7)	1.00	RS	RS
T	29 (19.3)	11 (7.3)	3.03	1.46–6.32	0.002

Notes: RA – rheumatoid arthritis, OR – odds ratio, CI 95% – confidence interval 95%; RS – GG/G as reference.

To determine Gal-3 serum levels, ELISA was used, and the results indicate that there are substantial variations between the levels of Gal-3 in RA patients and healthy controls (4.23 ± 0.59 and 3.55 ± 0.46 for RA and control cases, respectively). P value was less than 0.001.

The study tested whether the *PTPN22 rs2476601* and *STAT4 rs7574865* polymorphism were linked to the occurrence of high serum galectin-3 levels. In the experimental group there was a significant correlation with the minor allele of the *PTPN22 rs2476601* in RA patient groups, positive results for Gal-3, in comparison with controls (P = 0.033, OR = 1.68, 95% CI = 1.04–2.70) for Gal-3 positive patients. However, no significant differences were found among Gal-3 negative compared with healthy controls (P = 0.052, OR = 2.51, 95% CI = 0.97–6.53). This conclusion suggests that the susceptibility to RA conferred by the *PTPN22 rs2476601* A allele differs according to the status of the Gal-3 serum level of the RA patients (Table 5, 6). Moreover, a significant correlation was established between *STAT4 rs7574865* minor allele and positive results of Gal-3 in RA groups (P = 0.003, OR = 3.01, 95% CI = 1.41–6.39). No association was observed with the T allele in comparison of Gal-3 negative RA patients and healthy controls (P = 0.061, OR = 3.16, 95% CI = 0.90–11.10).

Table 5
The association of *PTPN22 rs2476601* in the RA group and Gal-3

Variant of experiment	No.	*PTPN22 rs2476601*			G	A
		GG	GA	AA		
Control	75	30	34	11	94	56
Gal-3 positive	65	19	27	19	65	65
P	0	RS	0.562	0.034*	RS	0.033*
OR (95% CI)	0	1.00	1.25 (0.58–2.70)	2.72 (1.06–6.97)	1.00	1.68 (1.04–2.70)
Gal-3 negative	0	1	6	3	8	12
P	0	RS	0.099	0.047	RS	0.052
OR (95% CI)	0	1.00	5.30 (0.60–46.51)	8.18 (0.77–87.20)	1.00	2.51 (0.97–6.53)

Notes: * – significant at P-value <0.05; ** – highly significant at P-value <0.01; GG – wild-type as referent; OR – odds ratio; Gal-3 – galectin-3; 95% CI – confidence interval; RS – GG/G as reference.

Table 6
The association of *STAT4 rs7574865* in the RA group and Gal-3

Variant of experiment	No.	*STAT4 rs7574865*			G	T
		GG	GT	TT		
Control	75	64	10	1	139	11
Gal-3 positive	65	42	21	2	105	25
P value	RS	RS	0.006**	0.346	RS	0.003**
OR (95% CI)	0	1.00	3.20 (1.37–7.47)	3.04 (0.27–34.68)	1.00	3.01 (1.41–6.39)
Gal-3 negative	0	6	4	0	16	4
P value	0	RS	0.035	0.760	RS	0.061
OR (95% CI)	0	1.00	4.27 (1.02–17.83)	0	1.00	3.16 (0.90–11.10)

Notes: see Table 5.

Discussion

Autoimmune disease typically results from a combination of genetic predisposition and environmental factors. The complex genetic susceptibility to autoimmunity often involves multiple genes that regulate immune cell functions. Although less common, single-gene mutations that affect critical regulatory processes can also cause autoimmunity (Pisetsky, 2023). The susceptibility to RA has been linked to two main genes: *STAT4* (signal transducer and activator of transcription 4) and protein tyrosine phosphatase non-receptor type 22 (*PTPN22*). *PTPN22*, which is encoded by the *PTPN22* gene on chromosome 1p13, is crucial for the negative regulation of T cell activation and development (Bin Huraib et al., 2020; Jović et al., 2022).

The differentiation and proliferation of Th1 and Th17 cells are mostly dependent on a transcription factor encoded by the *STAT4* gene, which is found on chromosome 2q33 (Kang, 2015; Klak et al., 2020). *The STAT4* gene is responsible for transducing signals caused by important cytokines such as interleukin-12 (IL-12), interleukin-23 (IL-23), and interferon (IFN-Y), which are important in the development of autoimmune disorders (Stephanou et al., 2009).

Various studies have shown that *PTPN22 rs2476601* (Abbasi et al., 2017; Abbasifard et al., 2020; Schulz et al., 2020; Tizaoui et al., 2022) and *STAT4 rs7574865* (Orozco et al., 2008; Bravo-Villagra et al., 2024) are associated with RA susceptibility. Otherwise, many other studies reveal that those genes are not associated with RA (Alizadeh et al., 2016; Nezaratian et al., 2017; Jasiem, 2022).

This study shows a significant correlation between minor alleles of *PTPN22 rs2476601* and *STAT4 rs7574865* and RA susceptibility, which is linked with some regional studies (Abbasifard et al., 2020; Tizaoui et al., 2022). However, other local studies have demonstrated no association with RA (Jasiem, 2022).

Hameed Neamaa et al. (2018) and Jasiem (2022) found that there is no correlation between the *PTPN22 rs2476601* minor allele and RA among the Iraqi individuals, which is distinct from this study. However, they reported that the heterozygous genotype has a risk of RA.

STAT4 rs7574865 has been investigated in the Iraqi population in Hasan et al. (2022), which shows an association between *STAT4* and Hepatitis type 1 which is also an autoimmune disease which is linked with the observations of this study.

In this study, a significant correlation was found among *PTPN22 rs2476601* and *STAT4 rs7574865* with RA susceptibility, which is supported by a regional study (Ghorban et al., 2019) that found an association between *PTPN22* genotype and allele with RA in Iranian individuals. Worldwide, many studies indicate a significant association between *PTPN22 rs2476601* and *STAT4 rs7574865* with RA (Orozco et al., 2008; Budlewski et al., 2023). El-Lebedy et al. (2017) showed an association of *STAT4 rs7574865* with RA, but, it demonstrated that *PTPN22 rs2476601* was not associated with RA.

As far as known, the only member of the chimera-protein galectin family is a 35 kDa protein called galectin-3. An increasing number of studies have shown that galectin-3 has a pro-inflammatory role in the etiology of RA.

This study found that Gal-3 levels were greater in patients with RA than in control with a significant value less than 0.001 indicating that these types of chimera proteins are potentially represented as serological markers used to investigate RA patients. This indication is supported by other Iraqi studies (Shakir, 2020; Almurshedi et al., 2023) and other global studies (Gruszewska et al., 2020; Pedersen et al., 2023).

Interestingly, few studies have shown that RA patients significantly have low levels of Gal-3 in circulation compared to control subjects (Mendez-Huergo et al., 2019) in contrast to this study which indicates high levels of Gal-3 in RA patients.

Nielsen et al. (2023) demonstrated that patients with early and chronic RA had persistently increased plasma levels of Gal-3 compared with control individuals, which is similar to the findings of this study which involved individuals who were established as RA patients recently.

For the first time, this study examined the association between minor alleles of two gene polymorphisms which can be considered as risk factors related to RA with galectin 3, which is demonstrated as a pro-inflammatory molecule that can be used as a potential serological marker to investigate RA. The study reveals an association between minor alleles of both genes polymorphism (*PTPN22 rs2476601* and *STAT4 rs7574865*) and positive results of Gal-3 in RA patients in comparison with healthy control individuals.

Conclusion

Our study concluded a correlation between Iraqi RA susceptibility and the *PTPN22 rs2476601* and *STAT4 rs7574865* gene polymorphisms. Additionally, the study finds that among the *PTPN22* gene genotypes, heterozygous (GA) is the most preventive. In addition, the most common *STAT4* gene variant was homozygous wild-type (GG). For the first time, the study found a correlation between minor alleles in the *PTPN22 rs2476601* and *STAT4 rs7574865* genes and galectin 3 positive results. This may indicate that these chimeric proteins have significant roles as pro-inflammatory molecules in individuals with RA and are linked to variant gene polymorphism.

The authors declare that there are no conflicts of interest.

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