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Diagnostic and predictive relevance of protein tyrosine phosphatase receptor type C serum levels and rs10919563 variant in rheumatoid arthritis and tumor necrosis factor inhibitor outcomes

A. H. Kamel*, A. A. Abbas**, M. H. Alosami***

*Al-Iraqia University, Baghdad, Iraq
**Al-Nahrain University, Baghdad, Iraq
***University of Baghdad, Baghdad, Iraq

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Department of Microbiology, College of Medicine, Al-Iraqia University, Baghdad, Iraq. E-mail: Ahmed_Kamel@aliraqia.edu.iq

Department of Microbiology, College of Medicine, Al-Nahrain University, Baghdad, Iraq. E-mail: ahmed26770@nahrainuniv.edu.iq

Department of Medicine, Rheumatology Unit, College of Medicine, University of Baghdad, Baghdad, Iraq. E-mail: mohammadalosami@comed.uobaghdad.edu.iq

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Rheumatoid arthritis (RA) is an autoimmune disease characterized by the central role of immune dysregulation. There is growing evidence linking the pathophysiology of some autoimmune disorders to protein tyrosine phosphatase receptor type C (PTPRC), a crucial modulator of immune cell communication. The current study's objective was to assess the predictive and diagnostic ability of rs10919563 polymorphism and serum PTPRC levels in relation to RA patients' disease activity and tumor necrosis factor (TNF) inhibitor responsiveness. One hundred RA patients and one hundred healthy controls were subjected to case-control analysis. Enzyme-linked immunosorbent assay (ELISA) was used to measure serum PTPRC levels, and TaqMan real-time PCR was used to genotype PTPRC rs10919563. Following six months of TNF inhibitor treatment, scores from the clinical disease activity index (CDAI) were assessed to measure disease activity and medication response. Area under the curve (AUC) = 0.979 indicated very strong diagnostic performance, and serum PTPRC concentrations were considerably greater in RA patients than in controls. Higher disease activity and a decreased responsiveness to TNF inhibitors were linked to the AA genotype and the A allele of rs10919563. Higher serum levels of PTPRC as well as AA genotype also correlated with higher CDAI scores. In patients with RA, elevated serum levels of PTPRC and polymorphism rs10919563 are linked to high disease activity and poor therapy response. These results support PTPRC's potential clinical use as a RA biomarker for diagnosis, follow-up, and customized treatment.

Keywords: rheumatoid arthritis; PTPRC; rs10919563 polymorphism; tumor necrosis factor inhibitors.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune ailment that results in chronic inflammation and joint destruction, in the end resulting in substantial disability and compromised quality of life for affected people. The disease is characterized by its complexity, arising from the interplay of genetic, environmental, and immunological elements that cause and perpetuate immune dysregulation (Edilova et al., 2021; Daghestani et al., 2023; Bedeković et al., 2024). The prevalence of RA worldwide ranges from 0.5% to 1% among adults, with a higher incidence observed in women, especially between the ages of 30 and 60 years (Brown et al., 2024).

The pathogenesis of RA is strongly influenced by genetic susceptibility. Among the genes involved, PTPRC, additionally called CD45, has emerged as a critical modulator of immune cell activation and signaling (Rheinländer et al., 2018; Al Barashdi et al., 2021). PTPRC is a transmembrane phosphatase expressed on all hematopoietic cells except mature erythrocytes, and is important for controlling T and B cell receptor signaling, which are pivotal in keeping immune homeostasis and preventing autoimmunity (Schuette et al., 2016; Lopez-Pedrera et al., 2020).

Single nucleotide polymorphisms (SNPs) inside the PTPRC gene, together with rs10919563, have been implicated in susceptibility to RA and might moreover affect scientific manifestations and therapy effects (Cui et al., 2010; Plant et al., 2012; Castañeda et al., 2016; Ferreiro-Iglesias et al., 2015; Hakim & Shaaban, 2019; Daghestani et al., 2023). The unique mechanisms by which these genetic variations contribute to risk of disorder continue to be under research, however it is clear that PTPRC regulates crucial thresholds in T and B cell activation, and its dysregulation can make a contribution to chronic inflammation and tissue damage (Rheinländer et al., 2018; Al Barashdi et al., 2021).

Despite advances in therapeutic techniques, which include using TNF inhibitors, a great proportion of RA patients do now not attain the most efficient medical response or sustained remission. Estimates suggest that up to 30% of patients may also show insufficient response to TNF inhibitor therapy, highlighting a need for better predictors of treatment final results and a move toward personalized therapy (Canhão et al., 2015; Bek et al., 2017; Gilani et al., 2020). The identification of strong biomarkers and genetic predictors is therefore a chief research priority to promote patient stratification and guide individualized therapy.

Current evidence suggests that size of serum PTPRC levels, in combination with genotyping for PTPRC polymorphisms, ought to provide valuable information for predicting disease susceptibility, activity, and reaction to biological medication procedures (Cui et al., 2010; Castañeda et al., 2016; Ferreiro-Iglesias et al., 2016; Bek et al., 2017). However, further research is needed to make clear the medical purpose of these procedures.

Based on those considerations, the present research aims to analyze the diagnostic and predictive relevance of serum PTPRC levels and the rs10919563 variant in sufferers with RA from Iraq, with specific emphasis on their association with disease activity and response to TNF inhibitor therapy. By advancing our understanding of the genetic and molecular elements influencing RA, this study seeks to make contributions to more personalized and effective management of the disease (Plant et al., 2012; Ferreiro-Iglesias et al., 2016; Gilani et al., 2020).

Materials and methods

In compliance with the Declaration of Helsinki, the study was authorized by the Institutional Review Board (IRB) of Al-Nahrain University, College of Medicine (Approval No. 20221164), and each participant completed a written informed consent form. One hundred pa-

tients with RA and one hundred controls who were matched for age and sex made up this case-control study. The patients with RA were recruited from Baghdad Teaching Hospital Rheumatology Units and Al-Yarmouk Teaching Hospital, Baghdad, Iraq, over the period March to November 2023. All patients were adults aged 18 years or older and were selected with the help of a rheumatologist in line with the diagnostic standards of the American College of Rheumatology (ACR) 2021 and the European Alliance of Associations for Rheumatology (EULAR) 2022 update. Patients with pregnancy, malignancy, or different persistent or autoimmune diseases were excluded from the study.

Based on their clinical response to TNF inhibitor treatment (etanercept or infliximab) at six months, patients were divided into two groups as responders if their CDAI was ≤ 10 and as non-responders if their CDAI is > 10.

PTPRC levels were assessed using a sandwich ELISA kit (Elabscience, USA) according to the manufacturer's instructions. All procedures were performed as per the official manufacturer's instructions.

Rs10919563 SNP genotyping of the PTPRC gene was performed using TaqMan allelic discrimination real-time Polymerase chain reaction (PCR) on a Mic qPCR Cycler (Bio Molecular Systems, Australia). The specifically designed primers and probe sequences are presented in Table 1 and the PCR protocol applied is illustrated in Table 2.

Table 1
PTPRC primer sequence

Gene	Primer / probe name	Sequence 5`-3`
PTPRC	rs10919563-F	GATCCCAGACCAAACATCACCA
	rs10919563-R	AAGCTGAGTCATGGGTATAAGGGT
	rs10919563-P/G	FAM-TCACGTTTGACTATATGCA
	rs10919563-P/A	HEX-ACATTCACGTTTGATTATATGC

Table 2
Real-time PCR program

Steps	°C	m:s	Cycle
Initial denaturation	95	05:00	1
Denaturation	95	00:20	40
Annealing	60	00:20	
Extension	72	00:20	

SPSS version 25.0 (IBM Corp., USA) was used for all statistical tests. Any P-value with two tails less than 0.05 was deemed statistically significant. The Mann-Whitney U-test was used to evaluate non-parametric variables, and the independent t-test was used to compare parametric variables. The Chi-square test was used to assess categorical data. Through binary logistic regression, odds ratios (ORs) and 95% confidence intervals (CIs) were determined. PTPRC's diagnostic performance was assessed through the use of receiver operating characteristic (ROC) curve analysis.

Results

The age of RA patients was 51.97 ± 10.51 years, which was the same as that of the controls, who were 50.48 ± 10.97 years (P = 0.328). The female ratio was likewise comparable (80% vs. 75%; P = 0.397). Nonetheless, notable variations were noted in other variables. RA patients presented higher frequencies of positive family history (34% vs. 0%, P < 0.001), smoking habit (30% vs. 13%, P = 0.003), and higher body mass index (BMI) values (28.9 ± 5.7 vs. 25.3 ± 4.3 kg/m², P < 0.001). Overweight and obesity were also more common in the patient group compared to controls (P = 0.001).When comparing RA patients to healthy controls, the median serum PTPRC was significantly higher (2.585 vs. 0.175 ng/mL, P < 0.001).

The results showed a higher frequency of the GA (heterozygous) and AA (mutant homozygous) genotypes of PTPRC rs10919563 amongst RA sufferers in comparison to the control; but, these variations did not reach statistical importance. No significant association was determined between the distribution of genotypes or alleles and disease risk below either the dominant or recessive genetic models. Additionally, the genotypic distributions in both sufferers and controls were consistent with Hardy-Weinberg Equilibrium (HWE). These findings suggest that the rs10919563 polymorphism of the PTPRC gene is not substantially associated with susceptibility to RA in this study population, as illustrated in Table 3, and the amplification plot (Fig. 1) shows good allelic discrimination with the TaqMan assay for genotyping of rs10919563.

Table 3
Genotype and allele distribution of the PTPRC polymorphism (rs10919563) in the patients and control group

Rs10919563 (G > A)	Patients (n = 100)	Control (n = 100)	OR (95%CI)	P-value
Genotypes				
GG	49 (49%)	61 (61%)	0.61 (0.35–1.07)	0.088
GA	41 (41%)	30 (30%)	1.62 (0.90–2.90)	0.105
AA	10 (10%)	9 (9%)	1.12 (0.43–2.89)	0.809
HWE*	0.062	0.075	–	–
Dominant model				
(GG+GA)	90 (90%)	91 (91%)	0.89 (0.34–2.29)	
(AA)	10 (10%)	9 (9%)	1.12 (0.43–2.89)	0.809
Recessive model				
(GG)	49 (49%)	61 (61%)	0.61 (0.35–1.07)	
(GA+AA)	51 (51%)	39 (39%)	1.62 (0.92–2.85)	0.088
Alleles				
G	139(69.5%)	152 (76%)	0.71(0.46–1.12)	
A	61 (30.5%)	48 (24%)	1.38 (0.89–2.16)	0.145

Note: * HWE – Hardy-Weinberg equilibrium.

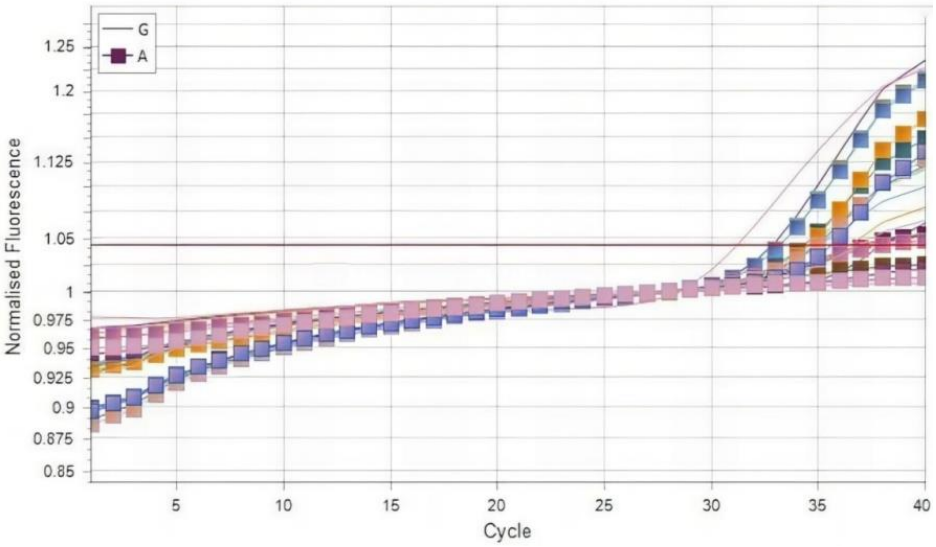

Fig. 1. Amplification plot for PTPRC (rs10919563)

Serum PTPRC levels were significantly greater in non-responders than in responders (median: 4.53 vs. 1.92 ng/mL, P < 0.001). Also, ROC curve analysis was used to evaluate the diagnostic performance of PTPRC in differentiating RA patients from healthy controls. The diagnosis accuracy of PTPRC was quite high, with an AUC of 0.979 (95% CI: 0.956–1.000). The sensitivity was 96% and the specificity was 100% at a cutoff value of 0.347 ng/mL. The P-value was < 0.001, indicating statistically significant findings (Fig. 2).

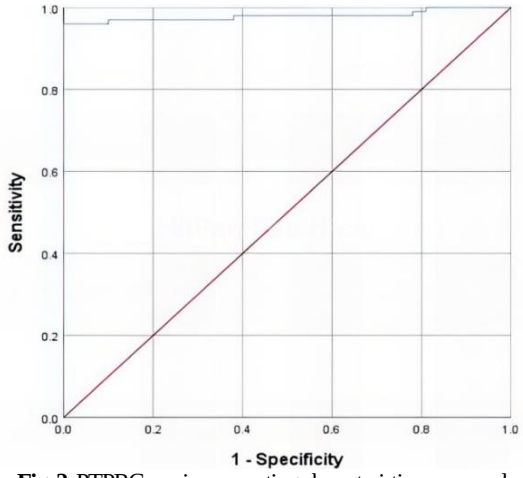

Fig. 2. PTPRC receiver operating characteristic curve used to distinguish between RA patients and the control group

According to the evaluation, the AA genotype of PTPRC rs10919563 became substantially linked to therapeutic non-response and was more prevalent among non-responders. While individual frequencies of the GG and GA genotypes did not vary significantly among groups, the combined presence of GG+GA genotypes became significantly higher amongst responders. Additionally, non-responders had a considerably higher frequency of the mutant A allele than did responders. As shown in Table 4, these results suggest that the AA genotype and the A allele of PTPRC rs10919563 may also serve as indicators for poor treatment response in RA patients.

Table 4
The genotype and allele distribution of the PTPRC polymorphism

Rs10919563 (G>A)	Non-responder (n = 50)	Responder (n = 50)	OR (95%CI)	P-value
Genotypes				
GG	22 (44%)	27 (54%)	0.66 (0.30–1.47)	0.318
GA	19 (38%)	22 (44%)	0.78 (0.35–1.73)	0.542
AA	9 (18%)	1 (2%)	10.75 (1.30–88.47)	0.027
Dominant model				
(GG+GA)	41 (82%)	49 (98%)	0.09 (0.01–0.76)	
(AA)	9 (18%)	1 (2%)	10.75 (1.30–88.47)	0.027
Recessive model				
(GG)	22 (44%)	27 (54%)	0.66 (0.30–1.47)	
(GA+AA)	28 (56%)	23 (46%)	1.49 (0.67–3.28)	0.318
Alleles				
G	63 (63%)	76 (76%)	0.53 (0.29–0.99)	
A	37 (37%)	24 (24%)	1.85 (1.00–3.43)	0.047

Serum PTPRC levels and disease activity, as determined by the CDAI score, have a substantial correlation. Median PTPRC concentrations increased progressively with higher disease activity, reaching their highest values in sufferers with excessive disease activity and the lowest in the ones in remission. Notably, patients inside the high disease activity group exhibited significantly elevated PTPRC levels in comparison to the ones in remission (P = 0.045). These findings suggest that PTPRC levels may also replicate disease severity in RA, as shown in Table 5.

Analysis of PTPRC serum concentrations according to rs10919563 genotypes confirmed that the AA homozygous mutant genotype had the very highest median PTPRC level. However, the variations in PTPRC concentrations among the diverse genotypes were not statistically significant (P = 0.428) as evidenced in Table 6.

Table 5
PTPRC serum levels association with CDAI

CDAI score (n = 100)	PTPRC median (min–max), ng/mL
Remission	0.932 (0.092–2.541)
Low	1.670 (0.478–3.276)
Moderate	2.477 (0.083–9.870)
High	4.025 (0.208–9.984)
P-value	0.045

Table 6
PTPRC serum concentrations by PTPRC rs10919563 genotype

SNP gene	Genotypes	PTPRC median (min–max), ng/mL	P-value
PTPRC	GG	2.160 (0.083–9.563)	
rs10919563	GA	2.585 (0.092–9.984)	0.428
(G>A)	AA	2.913 (0.777–9.371)	

Analysis of disease activity in association with PTPRC rs10919563 genotypes revealed that the AA homozygous mutant genotype was most often related to high disease activity, suggesting a strong association with more severe clinical manifestations. In contrast, remission was most commonly observed among patients with the GG genotype. These variations in genotype distribution across disease activity groups were statistically significant (p< 0.001) as can be seen from Table 7.

Table 7
Genotype frequencies of PTPRC (rs10919563) in CDAI disease activity groups

SNP genes	Genotypes	CDAI score (n = 100)				P-value
		remission	low	moderate	high	
PTPRC rs10919563 (G>A)	GG	4 (8.2%)	19 (38.8%)	11 (22.4%)	15 (30.6%)	<0.001
	GA	0 (0.0%)	0 (0.0%)	17 (41.5%)	24 (58.5%)	
	AA	0 (0.0%)	2 (20.0%)	2 (20.0%)	6 (60.0%)	

Discussion

According to the study's findings, the average age of RA patients is 51.97 ± 10.51 years, with most occurrences between 40 and 60 years. The age span in this study conforms to findings such as in studies by Fadhil et al. (2023) and Lateef et al. (2025), where typical onset occurred in midlife. Current work revealed a higher female domination (80%) than male (20%), which is similar to a previous study (Awni et al., 2023). The current research supports the role of family history as an important risk factor for RA. Shared genetic features and environmental variables are responsible for the two to four times higher incidence of cases in first-degree relatives (FDRs) (Frisell et al., 2016; O'Neil et al., 2024). Also, the results of this study and other research (Qi et al., 2024) indicate that cigarette smoking plays a sizeable position in RA induction and pathogenesis. Cigarette smoke can cause cytotoxicity by increasing levels of pro-inflammatory cytokines in synoviocytes that resemble fibroblasts, in particular IL-1 and TNF-α, both critical to the inflammatory strategies of RA (Chang et al., 2014).

Findings of this study, with a mean BMI of 28.89 ± 5.67 in RA patients, emphasize the role of obesity as a risk factor for RA. Consistent with earlier evidence, excess adipose tissue has the potential to drive RA through induction of chronic low-grade inflammation resulting from adipokines – pro-inflammatory mediators such as CRP, IL-6, TNF-α, and IL-1β. These biomarkers were found at higher levels in obese individuals and in early RA (Shoelson et al., 2007; Lu et al., 2014; Feng et al., 2019).

We determined a considerable excess in serum levels of PTPRC in sufferers with RA as compared to normal controls, reflecting its role in RA pathogenesis. The protein's recognised feature in T- and B-cell signaling affords a foundation for its involvement in autoimmunity. The discovered upregulation may additionally replicate heightened immune activation, consistent with extended levels of different inflammatory biomarkers along with CRP and IL-6 (Rija et al., 2021), and makes a case for its inclusion as an immune-associated biomarker in RA.

These data indicate that PTPRC had sensitivity of 96% and specificity of 100% in distinguishing RA patients from controls. The variability in reported sensitivity and specificity between studies is likely a reflection of differences in methodological parameters such as sample size, diagnostic criteria, and cut-off thresholds.

The rs10919563 SNP in the PTPRC gene, that is positioned in an intronic region on chromosome 1q31, is linked with autoimmune disease susceptibility, consisting of RA (Daghestani et al., 2023). This observation has been mentioned despite the fact that the recessive model GA+AA was more common in RA patients, though this was not statistically significant. Lack of association can be explained by diverse factors such as population-specific allelic frequencies, environmental interaction, and the minute regulatory role of intronic polymorphisms (Mikhaylenko et al., 2020). Since RA has a polygenic architecture, rs10919563 could modulate disease susceptibility indirectly through interaction with other loci of susceptibility or epigenetic regulators.

This study demonstrated significantly increased serum levels of PTPRC in TNF inhibitor therapy non-responding RA patients, suggesting that PTPRC might play a potential role as a biomarker of therapeutic resistance. Overexpression of PTPRC may promote overproduction of excess TNF-α and improve T and B cell signaling to initiate chronic inflammation and reduced drug efficacy. These findings activate exploration of PTPRC as a candidate for stratification of RA affected patients for precision therapy.

This study found that while the G allele of PTPRC rs10919563 can also result in a better response to TNF inhibitor medication, the AA genotype and A allele are linked to a worse response in RA. These results are consistent with earlier research that found a link between this polymorphism and treatment response, especially in RA patients who tested positive for it (Cui et al., 2010; Castañeda et al., 2016). However, contrary evidence is also present, e.g., a lack of association among Portuguese populations (Canhão et al., 2015) and inconclusive results in meta-analyses (Hakim & Shaaban, 2019). Such heterogeneity of results can be explained by ethnic genetic heterogeneity, environment, or study design or method of response assessment heterogeneity. Functionally, the rs10919563 variant, within intron 3 of PTPRC, may affect gene expression and modulate immune cell signaling thresholds, which in turn affects TNF inhibitor efficacy (Cooper, 2010; Stanford et al., 2012). The above findings enhance the incorporation of genetic profiling as part of personalized treatment protocols in RA.

Serum PTPRC levels and CDAI scores in RA patients were found to be statistically significantly positively correlated in this study; patients with the highest PTPRC levels had high disease activity and those with the lowest were in remission. Biologically, PTPRC (CD45) is a key controller of immune signaling, particularly T-cell activation. Higher PTPRC expression in active disease may reflect heightened immune activation and inflammatory response, which favors its use as a biomarker for disease activity in RA.

Although the connection was not statistically significant, the study discovered that RA patients with the AA genotype of the PTPRC rs10919563 polymorphism had higher median serum PTPRC levels than those with the GA or GG genotypes. Despite the fact that the A allele has been suggested to improve PTPRC transcription through changes in transcription factor binding or mRNA balance (Stranger et al., 2007), our findings suggest that the polymorphism will not impact serum PTPRC expression immediately in RA. Since PTPRC plays a role in T- and B-cellular signaling, the SNP can have an effect on immune responsiveness through mechanisms independent of protein ranges inside the circulation.

This study revealed a strong correlation among PTPRC rs10919563 genotypes and RA disease activity, in which the GG genotype had much less severe, and GA and AA genotypes had higher CDAI scores. These findings agree with Canhão et al. (2015), who illustrated the G allele with better response to therapy and lowered disease activity, although reversed outcomes were identified within Portuguese patients. Functionally, the G allele has the ability to strengthen immune regulation with the aid of favorable alternative splicing of CD45, lowering inflammation, while the A allele has the ability to intensify inflammatory responses, resulting in extra severe RA phenotypes (Hakim & Shaaban, 2019).

Conclusion

This study shows that in patients with RA, elevated serum levels of the PTPRC and rs10919563 polymorphism are associated with higher disease activity and a worse response to TNF inhibitor treatment, indicating a possible role in disease monitoring and patient stratification. The mutant allele A was correlated with an increased risk of non-responsiveness and aggravated manifestations of disease, thus documenting its potential as a genetic biomarker.

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