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ORIGINAL ARTICLE

PTPN22 +788 G>A (R263Q) Polymorphism is Associated with mRNA Expression but it is not a Susceptibility Marker for Rheumatoid Arthritis Patients from Western Mexico

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Abstract

PTPN22 represents an important non-*HLA* gene that has been strongly associated with rheumatoid arthritis (RA) pathogenesis. Several studies have reported a specific genetic variant for *PTPN22* (+788 G>A; rs33996649) that might be associated with decreased RA risk in Caucasian population; nevertheless, its specific role in western Mexican population has not been yet described. A case–control study with 443 RA patients and 317 control subjects (CS) was conducted. The genotyping was performed by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) technique and the *PTPN22* mRNA expression was determined by SYBR Green-based real-time quantitative-PCR assay. No association between the *PTPN22* +788 G>A polymorphism and RA susceptibility in western Mexican population was found when comparing genotype and allelic frequencies between RA patients and CS (G/G vs. G/A: OR 0.55, $p = 0.14$, 95% CI 0.22–1.32; G vs. A: OR 0.56, $p = 0.14$, 95% CI 0.23–1.36). The *PTPN22* mRNA expression increased 4.6-fold more in RA patients than in CS, and RA patients, carriers of *PTPN22* +788 G/A genotype, expressed 15.6-fold more than RA patients carrying the homozygous G/G genotype. Overall, these results showed that the *PTPN22* +788 G>A polymorphism is not associated with RA susceptibility in western Mexican population, whereas the presence of G/A genotype is associated with increased *PTPN22* mRNA expression in RA patients.

Keywords Rheumatoid arthritis · PTPN22 expression · +788 G>A polymorphism

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Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease, characterized by joint affection due to the presence of autoreactive T and B cells, which are overactivated and express several molecules as well as proinflammatory cytokines and autoantibodies, factors that promote the maintenance of the inflammatory process and ultimately, lead to disease progression (Smolen et al. 2018).

PTPN22 is the most important non-human leukocyte antigen (*HLA*) gene that has been implicated in the pathogenesis of several rheumatic and autoimmune diseases like RA. *PTPN22* is located at the 1p13.2 region and encodes the lymphoid tyrosine phosphatase (Lyp). Upon its binding to the C-terminal Src kinase (Csk), Lyp acts as a potent inhibitor of T-cell activation (Cohen et al. 1999; Stanford and Bottini 2014).

Due to the relevance of this molecule, several studies have been performed at genetic, transcriptional, and translational levels with the aim to identify how its regulation takes place (Brownlie et al. 2018). The genetic variants of *PTPN22* with a possible implication in its expression have been studied as potential risk factors in the development of autoimmune and/or inflammatory diseases in different populations (Chen et al. 2013; Machado-Contreras et al. 2016).

Two important *PTPN22* polymorphisms, 1858C>T (rs2476601) and -1123G>C (rs2488457), have already been described and associated with RA risk in Mexican population (Torres-Carrillo et al. 2012; Ruiz-Noa et al. 2017; Muñoz-Valle et al. 2017). The 1858C>T variant is a functional single-nucleotide polymorphism (SNP) which comprises a change from arginine (R) to tryptophan (W) at the position 620 and thus avoids the interaction between Lyp and Csk, leading to T-cell activation (Lee et al. 2007). The SNP -1123G>C is located at the promoter region and an association of this polymorphism with RA susceptibility in Chinese population was reported (Huang et al. 2012); however, its specific function has yet to be clarified. (Stanford et al. 2014).

Additionally, another SNP in *PTPN22* (+ 788 G>A; rs33996649) was described as a possible low-risk factor for RA in Caucasian population (Rodríguez-Rodríguez et al. 2011). This SNP is reported as a loss of function because it represents a change from arginine (R) to glutamine (Q) (R263Q) and therefore leads to a conformational change affecting the catalytic site of the protein (Stanford et al. 2014).

In Mexican population, only one study has been reported with a possible link between *PTPN22* +788 G>A polymorphism and protection against RA (López-Cano et al. 2017); nevertheless, in order to clarify these associations, more studies are needed to understand the involvement of this polymorphism, not only as a genetic association but also in the regard of its impact on the *PTPN22* regulation.

Based on this knowledge, the present study was performed with the aim to identify the association between *PTPN22* +788 G>A polymorphism and RA in a western Mexican population as well as the possible role for this polymorphism in the *PTPN22* mRNA expression.

Materials and Methods

Subjects

A total of 443 RA patients classified according to the 2010 American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) criteria were enrolled from the Rheumatology Department of Hospital Civil "Fray Antonio Alcalde", Guadalajara, Jalisco, Mexico. The group of control subjects (CS) has included 317 individuals recruited from the general population. The inclusion criteria for RA patients and CS were as follows: Mexican individuals from western Mexico (over 18 years of age), voluntary participation, and signature of informed consent letter. Patients with other rheumatic, inflammatory, or infectious diseases were excluded from this study. The ethical principles of the Declaration of Helsinki were followed, and this study was approved by the bioethics, biosafety, and research committee of the University of Guadalajara.

Clinical Variables

Erythrocyte sedimentation rate (ESR) determination was performed by the Wintrobe method. The ESR quantification was carried out visually after an hour and was reported as mm/h. The disease activity was evaluated by a rheumatologist, using the Disease activity score 28 (DAS28) index. The counting of tender and swollen joints of the 28 joints contemplated by the index was carried out. In addition, the patient global assessment was evaluated by the pain scale and ESR was used for the determination. Anti-cyclic citrullinated peptide (anti-CCP) antibodies concentration was determined by Enzyme-Linked ImmunoSorbent Assay (ELISA) test. This methodology implicates that coloration is directly proportional to the analyte concentration. The ELISA plate was read by a spectrophotometer at 450 nm according to the manufacturer's instructions. The concentrations were calculated in U/mL and a value < 5 U/mL was considered as negative. The rheumatoid factor (RF) and C-reactive protein (CRP) determination were carried out by turbidimetry test.

Genotype Analysis

Genomic DNA (gDNA) was obtained from peripheral blood leukocytes by previously described methods (Miller et al. 1988). The genotyping of *PTPN22* +788 G>A polymorphism was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP) technique. The target segment of the *PTPN22* gene containing the + 788 G>A polymorphism was amplified by using forward primer 5′-GAT GGA GCA AGA CTC AGA CAC-3′ and reverse primer 5′-CCC CAT GTT AGA AGA GCA GAT-3′ (Fragment length: 234 bp) (Huang et al. 2012). The PCR conditions were as follows: total volume of 14 µL containing 200 ng of gDNA, 1X of PCR Buffer, 1.0 mM of $MgCl_2$, 0.1 mM of dNTPs, 200 pmol of each primer, and 0.375 U of *Taq* DNA polymerase (Invitrogen,

Carlsbad, CA, USA). Cycling conditions were as follows: 5 min of initial denaturation at 95 °C; 35 cycles of denaturation at 95 °C; annealing at 58 °C; and extension at 72 °C for 40 s each one, followed by a final extension of 5 min at 72 °C. Finally, the digestion of the PCR product was carried out using the *MspI* enzyme at 2.5 U (New England Biolabs, Ipswich, MA, USA) for 1 h at 37 °C. The fragments produced were 143 and 91 bp (G/G genotype); 234, 143, and 91 bp (G/A genotype); and 234 bp (A/A genotype).

PTPN22 Expression

The blood samples were collected from RA patients and CS and total RNA was obtained by using Chomczynski and Sacchi method (Chomczynski and Sacchi 1987). Complementary DNA (cDNA) was obtained according to the reverse transcription PCR technique and *PTPN22* mRNA expression was determined by Real-Time PCR system using SYBR®Green qPCR method (forward primer 5′-ACA AGC CTG CAG AAT CTG TTC-3′ and reverse primer 5′-CTT GGT CCT TTG GGT TTT GA-3′). The specific pair of primers for *PTPN22* gene was obtained from Roche Applied Science (Universal ProbeLibrary; cat. no. 04,689,011,001). *GAPDH* was used as housekeeping gene (forward primer 5′-CCT TGC TCC TCC TGT TCG AC-3′ and reverse primer 5′-GCC CAA TAC GAC CAA ATC-3′) and relative expression quantification was determined by LightCycler® 96 System (Roche). The final concentration of primers for both *PTPN22* and *GAPDH* was 60 nM in a final volume of 10 µL. Cycling conditions were as follows: 10 min of preincubation step at 95 °C; 45 cycles of denaturation at 95 °C for 10 s; annealing at 60 °C for 15 s; and extension at 72 °C for 15 s, followed by melting curves at 95 °C for 5 s, 65 °C for 60 s, and 95 °C for 1 s.

Statistical Analysis

STATA 9.0 and GraphPad Prism 5.0 software were used. Categorical variables were expressed as percentage and n, discontinuous variables were presented in medians and percentiles (5–95). For categorical variables, chi-square test was performed. Inferential statistics were performed by Mann–Whitney *U* test and a significant *p* value less than 0.05 was taken. The minimum sample size for this study (142 individuals) was calculated using the Fleiss formula, which considered an average of previous studies where the frequencies of the polymorphism were resumed (cases and controls). In addition, a confidence level of 95% and a statistical power of 80% were taken; however, the final sample was increased to 443 RA patients and 317 CS. The statistical analysis to determine fold change of *PTPN22* mRNA expression between RA patients and CS was performed by using the $2^{-\Delta\Delta Cq}$ method and statistically significant differences were determined through the $2^{-\Delta Cq}$ method. The values were obtained from the following formulas: $\Delta Cq = (Cq_{PTPN22}\ \text{average} - Cq_{GAPDH}\ \text{average})$ and $\Delta\Delta Cq = (\Delta Cq_{RA} - \Delta Cq_{CS})$.

Results

Clinical and Demographic Variables

The RA patients enrolled in this study presented an average age of 49 years old and 90% of them were females. Regarding clinical variables, the majority of patients manifested a moderate disease activity (4.5 value according to DAS28 score) and the medium of disease evolution was 5 (0.5–28) years (Table 1). As for serological factors, RF and anti-CCP antibodies showed a medium of 74 IU/mL and 115.7 U/mL, respectively. Additionally, acute-phase reactants were determined; CRP value was 3.7 mg/L and ESR value was 37 mm/h. Most patients were under treatment, taking methotrexate (76%) and non-steroidal anti-inflammatory drugs (NSAIDs) (70%); the most common prescriptions were sulfasalazine (45%) and chloroquine (44%); and only 24% of patients were treated with steroids (Table 1).

Table 1 Clinical and demographic characteristics

Variables	RA patients $n=443$
Age (years)[a]	49 (28–72)
Gender % (n)[b]	
Male	10 (44)
Female	90 (399)
Disease status	
Disease evolution (in years)[a]	5 (0.5–28)
Clinical assessment	
DAS28[a]	4.5 (2.3–7.1)
RF (IU/mL)[a]	74 (1.8–529.8)
CRP (mg/L)[a]	3.7 (0.1–124.9)
ESR (mm/h)[a]	37 (11–60)
Anti-CCP (U/mL)[a]	115.7 (1.8–500)
Treatment % (n)[b]	
NSAIDs	70 (306)
Steroids	24 (103)
DMARDs	
Sulfasalazine	45 (194)
Chloroquine	44 (192)
Methotrexate	76 (330)

RA rheumatoid arthritis group, *NSAIDs* non-steroidal anti-inflammatory drugs, *DMARDs* Disease-modifying antirheumatic drugs, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS28* Disease Activity Score 28, *RF* rheumatoid factor, *Anti-CCP* anti-cyclic citrullinated peptide antibodies

[a]Data provided in medium (5th and 95th percentile)

[b]Data provided in percentages and *n*

Distribution of *PTPN22* +788 G>A Polymorphism

The genotypic and allelic frequencies of *PTPN22* +788 G>A polymorphism were in Hardy–Weinberg equilibrium ($p > 0.05$) in the western Mexican population. The distribution of genotypes behaved as follows: the most frequent genotype was G/G in both RA (97.5%) and CS (95.6%) group, whereas G/A was the least frequent genotype in this population; 2.5% for RA patients and 4.4% for CS, the presence of the homozygous A/A genotype was not observed (Table 2). When the genotypic and allelic frequencies were analyzed in both study groups, the G/G vs. G/A genotypes showed a OR = 0.55 ($p = 0.14$, 95% CI 0.22–1.32), while the OR value for the allelic frequencies was 0.56 ($p = 0.14$, 95% CI 0.23–1.36).

The frequency for G allele was 99% for RA patients and 98% for CS, the A allele presented a very low frequency in both RA (1%) and CS (2%) groups. No statistically significant difference, neither genotypes nor alleles was found (Table 2).

PTPN22 +788 G>A Polymorphism and Clinical Variables

A comparison between genotypes and clinical variables was performed (Table 3). The RA patients carrying the G/G genotype presented higher levels of CRP (3.9 mg/L) than carriers of G/A genotype (0.7 mg/L; $p = 0.03$). However, the rest of the clinical variables were similar between both groups.

PTPN22 mRNA Expression in Study Groups

The *PTPN22* mRNA expression levels in RA patients and CS were determined. Interestingly, the RA group expressed 4.6-fold more than the CS group, this could probably reflect a regulation mechanism due to a hyperactivation of autoreactive lymphocytes in RA (Fig. 1a). This indicates that patients with RA have a higher

Table 2 Genotypic and allelic frequencies of *PTPN22* +788 G>A polymorphism

Genotype	RA		CS		*p* value	OR (CI 95%)	*p* value
	%	*n* = 443	%	*n* = 317			
G/G	97.5	432	95.6	303	0.141	1	–
G/A	2.5	11	4.4	14		0.55 (0.22–1.32)	0.14
A/A	0	0	0	0		–	–
Allele	RA		CS		*p* value	OR (CI 95%)	*p* value
	%	*n* = 892	%	*n* = 634			
G	99	875	98	620	0.144	1	–
A	1	11	2	14		0.56 (0.23–1.33)	0.14
HWE = 0.69							

HWE Hardy–Weinberg equilibrium, *RA* rheumatoid arthritis group, *CS* control subjects group

Table 3 Clinical variables stratified according to *PTPN22* +788 G>A genotypes

Variable	Genotype		
	G/G	G/A	*p* value
DAS28 (VSG)[a]	4.5 (2.3–7.1)	3.9 (2.4–6.7)	0.37
RF (IU/mL)[a]	73.6 (1.8–510.7)	83.1 (11.8–529.8)	0.57
CRP (mg/L)[a]	3.9 (0.1–124.9)	0.7 (0.03–17.7)	**0.02***
ESR (mm/h)[a]	37 (11–60)	33 (9–52)	0.26
Anti-CCP (U/mL)[a]	115.0 (1.8–500)	177.3 (7–500)	0.39

The *p* value corresponds to the statistical analysis performed by Mann–Whitney U test

ESR erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS28* Disease Activity Score 28, *RF* rheumatoid factor, *Anti-CCP* anti-cyclic citrullinated peptide antibodies, *G/G* wild homozygous genotype for the G allele, *G/A* heterozygous genotype for the G and A alleles

[a]Data provided in medium (5th and 95th percentile)

[b]Data provided in mean ± SEM

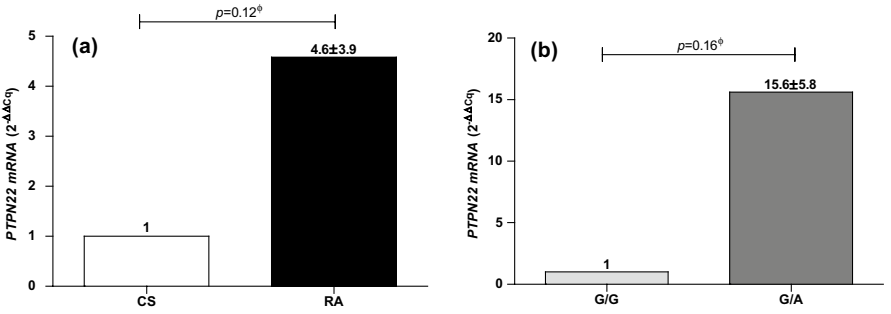

Fig. 1 *PTPN22* mRNA expression in study groups. **a** *PTPN22* mRNA expression was determined in 11 RA patients and 11 CS. **b** *PTPN22* mRNA expression in RA patients was stratified according to *PTPN22* +788 G>A genotypes. The mean values are shown on top of each group. The relative expression was evaluated by $2^{-\Delta\Delta Cq}$ method, which is a normalized method that represents the fold change of the gene expression in a group in regard to a reference gene and a control group. The $2^{-\Delta Cq}$ results (Φ) are also shown; this method represents an expression measure of the target gene compared with a reference gene in each group; however, it does not compare fold changes taking into account both study groups (Student's *t* tests)

relative *PTPN22* mRNA expression compared to CS evaluated by $2^{-\Delta\Delta Cq}$ analysis; however, the data obtained through the $2^{-\Delta Cq}$ method did not show statistically significant differences ($p = 0.12$).

In order to establish if the *PTPN22* mRNA expression was associated with the presence of the *PTPN22* +788 G>A polymorphism, RA patients were stratified according to the G/G and G/A genotypes. This analysis showed that RA patients, carriers of G/A genotype, presented an increased *PTPN22* mRNA expression (15.6-fold) in comparison with the presence of the homozygous G/G genotype (Fig. 1b).

Therefore, the relative expression of *PTPN22* evaluated through the $2^{-\Delta\Delta Cq}$ method showed that RA patients, carriers of the heterozygous G/A genotype, have a higher expression compared to the carriers of the wild-type G/G genotype. The expression evaluated through $2^{-\Delta Cq}$ did not show significant differences ($p = 0.16$).

Discussion

The genetic factors associated with the pathogenesis of RA have increased over time; nevertheless, its etiology remains unclear (Deane et al. 2017). The *HLA* and some non-*HLA* genes have been studied in several populations with the objective to find risk factors to clarify how the development of this pathology takes place (Diogo et al. 2014; Messemaker et al. 2015).

The *PTPN22* gene belongs to the group of non-*HLA* genes and has been associated with the RA pathogenesis (Zhang et al. 2011; Stanford et al. 2014; Chang et al. 2016). The Lyp protein is encoded by the *PTPN22* gene, and it acts as an active regulator of the immune system by its inhibitory role in T-cell activation. Several studies of *PTPN22* genetic variants have been conducted (Carlton et al. 2005; Goh et al. 2017). Particularly, two *PTPN22* SNPs, 1858C>T and -1123G>C, have been widely described both worldwide and in the Mexican population (Torres-Carrillo et al. 2012; Ruiz-Noa et al. 2017; Muñoz-Valle et al. 2017).

This study provides relevant information about another less-studied polymorphism, located at the + 788 position of *PTPN22*, which represents a change from guanine (G) to adenine (A), and its association with the pathogenesis of RA as well as with the expression of *PTPN22* at mRNA level.

There are a few previous studies in which this polymorphism has been studied, some of them reported an association between the heterozygous genotype G/A and lower RA risk in the European population (Rodriguez-Rodriguez et al. 2011). In this regard, a recent meta-analysis performed by Bae and Lee revealed that *PTPN22* +788 G>A polymorphism was significantly associated with decreased risk of some autoimmune diseases ($p < 0.001$) such as systemic lupus erythematosus (SLE) ($p = 0.001$), RA ($p = 0.008$), and ulcerative colitis (UC) ($p = 0.016$) (Bae and Lee 2018).

In Mexican population, there is only one study conducted by López-Cano et al. about this *PTPN22* +788 G>A polymorphism and its association with RA (López-Cano et al. 2017). In spite of the fact that in this study an association between the G/A genotype (OR 0.28, $p = 0.045$) and decreased RA risk was reported, we considered that these results lack robustness because the confidence interval does not meet sufficient criteria to make this statement (G/G vs. G/A: OR 0.28, $p = 0.045$, 95% CI 0.08–1.05; G vs. A: OR 0.29, $p = 0.046$, 95% CI 0.08–1.06).

In the present study, 443 RA patients and 317 CS from western Mexico were included. The obtained results indicate that the *PTPN22* +788 G>A polymorphism is not associated with RA, neither protection nor susceptibility when genotype and allelic frequencies between both study groups were compared (G/G vs. G/A: OR 0.55, $p = 0.14$, 95% CI 0.22–1.32; G vs. A: OR 0.56, $p = 0.14$, 95% CI 0.23–1.36).

Moreover, in this study, the genotypic and allelic frequencies are similar to those reported by López-Cano et al. in Mexican population as well as some other reports performed worldwide. Our study shows that the G/G genotype is the most frequent (97.5% in RA patients and 95.6% in CS), followed by G/A genotype (2.5% in RA patients and 4.4% in CS). In agreement with previous reports, the homozygous A/A polymorphic genotype was not found (Díaz-Gallo et al. 2011; López-Cano et al. 2017; Bae and Lee 2018).

With regard to the *PTPN22* +788 G>A polymorphism, we consider that it is important to identify the frequency distributions in several Mexican populations, in order to provide detailed information of the specific role of this polymorphism in RA pathogenesis. The results presented above could be explained by the fact that genetic diversity of Mexican-mestizo populations varies according to the geographical region of the country (Rangel-Villalobos et al. 2009; Rubi-Castellanos et al. 2009; Martínez-Cortés et al. 2017). The ancestral differences reported indicate that there is greater Native American ancestry in the central and southern regions, while in the western and northern regions there is a greater predominant European ancestry (Rangel-Villalobos et al. 2009). The previously reported percentages of ancestry for the state of Jalisco (West) were 28% Amerindian, 67% European, and 5% African (Rangel-Villalobos et al. 2009). On the other hand, for Mexico City population, it was reported a 50% Amerindian, 46% European, and 4% African ancestry (Rangel-Villalobos et al. 2009). Therefore, future studies of frequency and association of *PTPN22* +788 G>A polymorphism in different regions of the country with a different genetic diversity of the Mexican-mestizo population will be required.

Furthermore, the aim of this study was to determine the *PTPN22* mRNA expression in RA patients and CS, likewise its association with the presence of *PTPN22* +788 G>A genotypes in the RA group. The results showed the increased *PTPN22* expression of 4.6-fold more in RA patients than in CS. These results differ with those reported by Remuzgo-Martínez et al. where a slight decrease in the *PTPN22* mRNA expression was observed (p = ns). However, so far there are not enough studies in which *PTPN22* mRNA expression was reported in RA patients and CS, and therefore more studies need to be carried out in order to determine how *PTPN22* mRNA expression is related with this pathology (Remuzgo-Martínez et al. 2017).

Regarding *PTPN22* mRNA expression stratified by genotypes, it was found that RA patients carrying the G/A genotype expressed 15.6-fold more than those carrying the G/G genotype. The study performed by Remuzgo-Martínez et al. was the only one to make this association; however, statistically significant differences were not found (Remuzgo-Martínez et al. 2017). These results suggest that the presence of the A allele is associated with high *PTPN22* mRNA expression.

One of the most important limitation of this study is the lack of inclusion of patients with the homozygous A/A genotype due to the low frequency of this allele reported worldwide. Another important limitation is the heterogeneity in the treatment of the RA patients studied, which could reflect differences in *PTPN22* mRNA expression.

In conclusion, the present study suggests that *PTPN22* +788 G>A polymorphism is not associated with RA susceptibility in western Mexican population. In addition,

RA patients showed higher *PTPN22* mRNA expression than CS and this expression was increased in RA patients carrying the G/A genotype. It should be, however, taken into account that only a few studies have described the *PTPN22* +788 G>A polymorphism and its implication in RA pathogenesis. Further studies are required to determine the specific role of *PTPN22* +788 G>A polymorphism in *PTPN22* mRNA expression as well as its role in RA pathogenesis.

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Compliance with Ethical Standards

Conflict of interest The authors report no conflict of interest.

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