Inflammation Research (2019) 68:195–201
https://doi.org/10.1007/s00011-018-1204-1

Inflammation Research

ORIGINAL RESEARCH PAPER

An association study in *PTPN22* suggests that is a risk factor to Takayasu's arteritis

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Received: 11 September 2018 / Revised: 15 November 2018 / Accepted: 19 November 2018 / Published online: 23 November 2018

Abstract

Objectives Takayasu's arteritis (TA) represents a rare autoimmune disease (AD) characterized by systemic vasculitis that primarily affects large arteries, especially the aorta and the aortic arch and its main branches. Genetic components in TA are largely unknown. *PTPN22* is a susceptibility *loci* for different ADs; however, the role of different *PTPN22* single-nucleotide polymorphisms (SNPs) in the susceptibility to TA is not clear. *Methods*: We evaluated the *PTPN22* R620W (C1858T), R263Q (G788A), and − 123G/C SNPs in a group of patients with TA and in healthy individuals from Mexico. Our study included 111 patients with TA and 314 healthy individuals. Genotyping was performed with the 5′ exonuclease (TaqMan®) assay.

Results Our data showed that the *PTPN22* R620W polymorphism is a risk factor for TA (CC vs. CT: OR 4.3, $p = 0.002$, and C vs. T: OR 4.1, $p = 0.003$); however, the *PTPN22* R263Q and − 1123G/C polymorphisms are not associated with this AD. In addition, the *PTPN22* CGT haplotype, which carries the minor allele of the *PTPN22* C1858T variant, was also associated with TA susceptibility.

Conclusion This is the first report documenting an association between *PTPN22* R620W and TA.

Keywords *PTPN22* · Single nucleotide polymorphism · R620W · Susceptibility · Takayasu's arteritis

Introduction

Takayasu's arteritis (TA) represents a rare systemic vasculitis that primarily affects large arteries, especially the aorta and the aortic arch and its main branches [1, 2]. Genetic components in TA are largely unknown; however, some researchers have carried out different genome-wide association (GWA) or candidate gene studies to identify TA susceptibility *loci* [3–5]. *PTPN22* is one of the most important susceptibility *loci* in different autoimmune diseases (ADs). This gene encodes the Lyp protein, a phosphatase protein expressed in different cells related to the immune system. The functional *PTPN22* R620W (C1858T) single-nucleotide polymorphism (SNP) affects different normal processes in B or T cells and other cells types related to the immune response [6–8]. In addition, *PTPN22* R620W has been associated with susceptibility to type 1 diabetes (T1D), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Graves' disease (GD) among others [9–13]. The *PTPN22* C1858T variant leads to a change in amino acids (C1858 = R620; arginine, 1858T = 620W; tryptophan) in exon 14 (located within the first proline-rich motif of Lyp), which affects the interaction with Csk (Lyp and Csk both are proteins that negatively regulate TCR signaling) in T cells [14–16], or the interaction between Lyp and PAD-4 in neutrophils altering various functions in the immune cells [13]. In addition, the *PTPN22* 1858T variant has been proposed as a gain-of function mutation, which, in turn, inhibits TCR signaling, decreased number and function of regulatory T cells, and

Responsible Editor: John Di Battista.

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T-helper activity; events recognized as risk factors to autoimmunity [7, 13–15].

On the other hand, the functional *PTPN22* R263Q (G788A) variant has been associated with protection against SLE or RA [13], while the *PTPN22* −1123G/C SNP confers RA susceptibility [17]. These variants, located within *PTPN22* (except R620W), have not been previously evaluated in patients with TA [18]. Thus, the aim of our study was to determinate the role of the *PTPN22* R620W, R263Q, and −1123G/C SNPs in a group of patients with TA (as well as with arterial damage) and in healthy individuals.

Methods

Patient selection

One hundred and eleven patients [101 women (91.0%) and 10 men (9.0%)] with TA and 336 healthy controls [314 women (93.4%) and 22 men (6.6%)] were included in our study. All patients and controls were over 18 years of age. The patients with TA were classified according to the 1990 College American Rheumatology criteria [19]. Angiographic classification was done according to the guidelines of the International Cooperative Study on TA [20]. Controls were healthy individuals with no family history of ADs or chronic inflammatory disease including asthma, obesity, arterial hypertension, cancer, type 2 diabetes, food and drug allergy, inflammatory bowel disease, or chronic and acute urticaria. The protocol was carried out according to the Declaration of Helsinki. All patients and healthy individual signed an informed consent letter. The Ethics, Biosecurity and Research committee of Hospital Juárez de México (HJM) approved this protocol (HJM 0421/18-I).

Genetic material

Nuclear DNA from patients with TA and controls was isolated from whole blood samples (4 mL) using the Invisorb Blood Universal Kit (Stratec molecular GmbH, Berlin, Germany), according to the manufacturer's specifications. Genetic material from each case and control was quantified, diluted, and stored at −20 °C until needed.

Genotyping of PTPN22 SNPs

Genotyping of the *PTPN22* R620W (rs2476601), R263Q (rs33996649), and −1123C/G (rs2488457) SNPs was obtained using the TaqMan 5′ allele discrimination assay. The fluorescence of probes was detected using Bio-Rad CFX Manager software on a CFX96 Real-Time PCR system (Bio-Rad, California, USA) following the manufacturer's instructions. To confirm the *PTPN22* genotypes identified in cases and controls, 40% of the all samples were repeated twice and the results were 100% reproducible.

Statistical analysis

The Hardy–Weinberg equilibrium (H-WE) for the three *PTPN22* SNPs of both cases and controls was estimated using the Finneti software (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). A Chi-square test was used to estimate the odds ratio (OR), 95% confidence intervals (CI), and *p* value. We used the Epidat 3.1 software (http://www.sergas.es/MostrarContidos_N3_T01.aspx?IdPaxina=62715) to obtain the OR, 95% CI, and *p* value. A *p* value of 0.05 or less was considered statistically significant. The *p* values for the three *PTPN22* SNPs were corrected by the Bonferroni test. Haplotypes and linkage disequilibrium (LD) were obtained using Haploview V 4.2 software [21]. Quanto software was used to determinate the statistical power of our study (http://hydra.usc.edu/gxe).

Results

Demographic and clinical characteristics in cases and controls

A total of 111 patients with TA were included in this study of whom 101 (91%) were women. In addition, 336 healthy controls were also included of whom 314 (93.4%) were women. Type 5 arterial damage was the most common observed in our study population (78.4%). Data related to age and the proportion of females to males in controls and patients with TA are shown in Table 1 along with the type of arterial damage in patients with TA.

H-WE and the statistical power of our study population

No deviation of the H-WE was observed in the genotype distribution of the *PTPN22* R620W, R263Q, and −1123C/G variants in either the patients with TA or controls (data not shown). The statistical power of our study was 84.9%.

Association analysis of PTPN22 R620W, R263Q, and −1123G/C in cases and controls

The genotype and allele frequencies of the *PTPN22* R620W polymorphism were different in cases and controls, and thus, this variant showed an association with TA susceptibility (Table 2). No association was identified between *PTPN22* R263Q and −1123G/C and TA (Table 2). Because TA was mainly expressed in women ($n = 101$; 91%), we removed the men from our analysis. Gender stratification also showed an

Table 1 Demographic characteristics in patients with TA and controls as well as type of arterial damage in TA patients

	Control *n* (%)	TA *n* (%)
Total	336 (100)	111 (100)
Age (SD)	49.2 ± 7.4	43 ± 15
Gender		
Female	314 (93.4)	101 (91.0)
Male	22 (6.6)	10 (9.0)
Type of arterial damage		
V		87 (78.4)
IIa	–	7 (6.3)
IIb	–	7 (6.3)
V + C	–	4 (3.6)
I	–	2 (1.8)
IV	–	2 (1.8)
V + P	–	1 (0.9)
III + C	–	1 (0.9)

TA Takayasu's arteritis, *SD* standard deviation, *V + C* type V + cardiac damage, *V + P* type V + pulmonary damage

association of *PTPN22* R620W (C1858T) in women with TA; the C/T heterozygous genotype and T allele frequency was higher in patients with TA than in controls (Table 3). Thus, our data show that this SNP is associated with TA susceptibility (CC vs. CT, OR 4.3, $p = 0.002$, and C vs. T; OR 4.1, $p = 0.003$, Table 3), even after applying the Bonferroni correction test (CC vs. CT, $p_c = 0.006$, and C vs. T; $p_c = 0.009$, respectively, Table 3). No patients with TA or controls were positive for the *PTPN22* C1858TT homozygous genotype. Our analysis showed that the genotype and allele frequencies of the *PTPN22* R263Q and −1123C/G variants were similar in patients with TA and healthy individuals. Thus, no association was identified between these *PTPN22* SNPs and TA susceptibility (Table 3). To note, no patient or control included in our study presented both *PTPN22* 1858T (620W) and 788A (263Q) alleles; that is, both variants are mutually exclusive.

Analysis of PTPN22 haplotypes and LD in patients with TA and controls

Four haplotypes were identified of the combination of the *PTPN22* R620W (C1858T), R263Q (G788A), and −1123G/C SNPs in patients with TA and controls (Table 3). Only the *PTPN22* TGC haplotype, which carried the T allele of *PTPN22* C1858T, showed an association with TA; OR 4.14. $p = 0.0027$ (Table 4). The result of the association between the *PTPN22* TGC haplotype and TA was maintained even after running 100,000 permutations ($p = 0.01$) (Table 4). LD

Table 2 Genotype and allelic frequencies of the *PTPN22* R620W, R263Q, and −1123G/C polymorphisms and association analysis in patients with TA and controls

SNP	Population	Allele	Genotype *n* (%)						Allele *n* (%)				
		1 2	1 1	1 2	2 2	OR (11 vs. 12)	95% CI	*p*	1	2	OR	95% CI	*p*
PTPN22	Controls	C T	329 (97.9)	7 (2.1)	0 (0.0)	–	–	–	665 (99.0)	7 (1.0)	–	–	–
R620W	TA		102 (91.9)	9 (8.1)	0 (0.0)	4.1	1.51–11.41	**0.003***	213 (95.9)	9 (4.1)	4.01	1.48–10.91	**0.009****
PTPN22	Controls	G A	327 (97.3)	9 (2.7)	0 (0.0)	–	–	–	663 (98.6)	9 (1.4)	–	–	–
R263Q	TA		108 (97.3)	3 (2.7)	0 (0.0)	1.0	0.27–3.80	0.99	219 (98.6)	3 (1.4)	1.0	0.27–3.76	1.01
PTPN22	Controls	G C	127 (37.8)	158 (47.0)	51 (15.2)	–	–	–	412 (61.3)	260 (38.7)	–	–	–
-1123G/C	TA		35 (31.5)	62 (55.9)	14 (12.6)	1.4	0.89–2.29	0.14	132 (59.5)	90 (40.5)	1.08	0.79–1.47	0.62

Significant *p* values are reported in bold type

Cases and controls include women and men

TA Takayasu's arteritis, *OR* odds ratio, *CI* confidence interval, *SNP* single-nucleotide polymorphism

*$p_c = 0.009$; **$p_c = 0.027$ corrected *p* value for Bonferroni

Table 3 Genotype and allelic frequencies identified in women of the *PTPN22* R620W, R263Q and −1123G/C polymorphisms and association analysis in patients with TA and controls

SNP	Population	Allele	Genotype *n* (%)						Allele *n* (%)				
		1 2	1 1	1 2	2 2	OR (11 vs. 12)	95% CI	*p*	1	2	OR	95% CI	*p*
PTPN22	Controls	C T	307 (97.8)	7 (2.2)	0 (0.0)	–	–	–	621 (98.9)	7 (1.1)	–	–	–
R620W	TA		92 (91.0)	9 (8.9)	0 (0.0)	4.290	1.56–11.84	**0.002***	193 (95.5)	9 (4.5)	4.137	1.52–11.25	**0.003****
PTPN22	Controls	G A	305 (97.1)	9 (2.9)	0 (0.0)	–	–	–	619 (98.6)	9 (1.4)	–	–	–
R263Q	TA		98 (97.0)	3 (3.0)	0 (0.0)	1.037	0.27–3.91	0.96	199 (98.5)	3 (1.5)	1.037	0.28–3.89	1.01
PTPN22	Controls	G C	118 (37.6)	147 (46.8)	49 (15.6)	–	–	–	383 (61.0)	245 (39.0)	–	–	–
−1123G/C	TA		34 (33.66)	54 (53.47)	13 (12.87)	1.275	0.779–2.087	0.33	122 (60.4)	80 (39.6)	1.025	0.74–1.42	0.88

Significant *p* values are reported in bold type

TA Takayasu's arteritis, *OR* odds ratio, *CI* confidence interval, *SNP* single-nucleotide polymorphism

*$p_c = 0.006$; **$p_c = 0.009$ corrected *p* value for Bonferroni

Fig. 1 Linkage disequilibrium (LD) plot in PTPN22 in cases and controls. The analysis of PTPN22 R620W (C1858T), R263Q (A788G), and −1123G/C polymorphisms in patients with TA and controls showed that none of them were in LD ($r^2 < 0.8$). Thus, each allele of these SNPs showed an independent cosegregating

analysis between the *PTPN22* SNPs identified that none of the three *PTPN22* polymorphisms were in LD ($r^2 < 0.8$) (Fig. 1).

Analysis of PTPN22 genotypes and type of arterial damage in patients with TA

We carried out a comparison analysis between the *PTPN22* R620W, R263Q, and −1123G/C SNPs and the type of arterial damage in TA patients. The genotype frequencies of the *PTPN22* R620W, R263Q, and −1123G/C SNPs in patients with TA are shown in Table 5. Although 7 (of 87) patients with type 5 arterial damage were positive for the *PTPN22* C1858T C/T heterozygous genotype, this SNP was not associated with arterial damage when was compared with the other types of arterial damage or even combining all the types of arterial damage vs. type 5 (Table 5). On the other hand, the *PTPN22* R263Q and −1123G/C SNPs also showed no association with arterial damage (Table 5).

Table 4 Haplotypes formed by combinations of the *PTPN22* C1858T, 788G/A, and −1123G/C SNPs in patients with TA and controls

Haplotype	Frequency		OR	95% CI	*p* value	p_c
	TA	Controls				
CGG	58.9	59.6	0.97	0.71–1.34	NS	NS
CGC	35.1	37.9	0.89	0.69–1.24	NS	NS
TGC	4.5	1.1	4.14	1.52–11.25	**0.003***	**0.01***
CAG	1.5	1.4	1.04	0.28–3.87	NS	NS

Significant *p* values are reported in bold type

TA Takayasu's arteritis, *OR* odds ratio, *CI* confidence interval, *NS* not significant

*p_c = 0.01 corrected *p* value after 100,000 permutations

Table 5 Association analysis between genotypes of the *PTPN22* R620W, R263Q, and −1123G/C SNPs, and the type of arterial injury in patients with TA

Type of arterial damage	R620W		R263Q		−1123 G/C			Total	*p* value
	CC	CT	GG	GA	GG	GC	CC		
I	1	1	2	0	2	0	0	2	NS
II a	6	1	7	0	5	1	1	7	NS
II b	7	0	7	0	5	1	1	7	NS
III + C	1	0	0	1	0	1	0	1	NS
IV	2	0	2	0	0	2	0	2	NS
V[a]	80	7	85	2	48	27	12	87	NS
V + C	4	0	4	0	1	3	0	4	NS
V + P	1	0	1	0	0	1	0	1	NS
Total	102	9	108	3	62	35	14	111	NS

NS not significant, *V + C* type V + cardiac damage, *V + P* type V + pulmonary damage

[a]High frequency

Discussion

PTPN22 represents one of the most important ADs susceptibility *loci* [14]. *PTPN22* encodes Lyp, a phosphatase protein that interacts with Csk (a tyrosine-protein kinase). The Lyp/Csk complex is involved in the negative regulation of T-cell activation by restricting signaling downstream of the T-cell receptor (TCR) [14, 22]. The *PTPN22* C1858T polymorphism causes a change in an amino acid residue of arginine to tryptophan in exon 14 of Lyp (R620W). This alteration breaks the interaction between Lyp and Csk, affecting the activation of T cells [15, 16]. Some functional studies have documented that *PTPN22* R620W is a gain-of-function variant, which, in turn, reduces TCR signaling, decreases the number/function of regulatory T cells, and reduces T-helper cell activity [14, 22]. A reduction in TCR signaling has been recognized as a risk factor for autoimmunity [23]. Regarding this, two theories have been postulated. The first is based on thymic selection as a mechanism for establishing a predisposition to ADs. In the thymus, an increase in Lyp activity (*PTPN22* 620W allele as a gain-of-function leads to an increase in Lyp activity) would increase the threshold required for effective TCR signaling in the developing thymocytes. This event could lead to a lack of negative selection of autoreactive T cells. The second theory involves regulatory T cells, which, under physiological conditions, are thought to limit the emergence of autoimmunity. Impaired TCR signaling involving particularly the regulatory T cells may eventually boost autoimmunity, because an increase in Lyp activity could reduce its regulatory function [24].

We recently identified an association between *PTPN22* R620W and GD and RA susceptibility [13, 25]. In our current study, we also identified an association of *PTPN22* R620W with TA susceptibility (in fact, this is the first report documenting an association between *PTPN22* and TA). Contrary to our results, in 2008, *PTPN22* was reported as not being risk factor in patients with TA in Turkey [18]. In addition, two microarray-based studies identified no association between *PTPN22* and TA [3, 4]. These three studies included patients from Turkey [3, 4, 18], and two of them included patients from the USA [3, 4]. The lack of concordance between our results and those published in the populations of Turkey (and USA) may be due to the sample size (the three studies included 181, 339, or 559 patients with TA from Turkey, while we included 111 patients) [3, 4, 18]. However, our data are also reliable, because the statistical power of our study was 84.9%, which was obtained taking into account the frequency of the *PTPN22* 1858T

allele in controls (2.2%), a ratio of three controls per case, a dominant model, the prevalence of TA, OR of 2, and a statistical significant of 0.05. In addition, the sample size of the European-derived North American patients with TA ($n = 112$ and $n = 134$) included in both studies was similar to ours ($n = 111$). Another difference is the ancestry, e.g., the Mexican population represents a mixed genetic background and includes people with Amerindian, Caucasian, and African ancestry [26]. Meanwhile, Asian and European-derived populations include closely related individuals [27]. Thus, the lack of ancestry informative markers in our study population makes our results susceptible to biases, and thus, it is necessary to carry out the other studies in Latin Americans (and in Mexicans) to validate our results. GWA or microarray-based studies have been successful in Asian and European-derived populations [27]; however, in mixed populations (like in Mexico), these finding have commonly not been replicated. For example, *PTPN22* is a risk factor for SLE in patients of European ancestry [28]; however, two GWAS carried out in Hispanic-American patients with SLE (with Mexican patients) did not replicate this finding [29, 30]. In addition, a third study also did not identify an association between this variant and SLE in Mexicans [13]. Other differences related to ancestry between Turkey and Mexico are the following: *PTPN22* R620W is not a risk factor for RA in patients from Turkey [31]; meanwhile, in Mexico, this variant is a risk factor for RA [13]. Thus, it is important to evaluate this polymorphism in patients with TA from the other ancestries to confirm our finding.

To note, we observed, in TA, a higher proportion of affected women compared to men, these data are similar to a previous study that reported in the Mexican population, where the ratio of other ADs such as RA, SLE, and GD in women compared to men is approximately 9:1, respectively [13]. In addition, the proportion of women affected with TA that we identified in our study is similar to that found in the other studies [32, 33]. Thus, because the ADs are more prevalent in woman that we removed the men. In fact, our study only included ten males and all were positive for the common genotype: *PTPN22* 1858CC, and thus, no statistical comparison was possible.

On the other hand, the *PTPN22* R263Q and −1123G/C SNPs were not risk or protection factors for TA. Previously, we and another groups identified *PTPN22* R263Q as being associated with protection against SLE, RA, and other ADs [13, 34, 35]; however, our data suggest that, in patients with TA, this polymorphism is not important. Finally, the *PTPN22* −1123C/G SNP also showed no association with TA susceptibility, contrary to what has been reported in other ADs including RA and ulcerative colitis [36, 37]. On the other hand, the *PTPN22* TGC haplotype, which carries the T allele of *PTPN22* C1858T, showed an association with TA susceptibility. This same *p* value (and OR) was observed when evaluating only the *PTPN22* 1858T allele in the patients with TA and controls (Table 3). This means that the susceptibility to TA observed is related to the *PTPN22* 1858T allele.

To determine if the *PTPN22* SNPs are associated with arterial damage in patients with TA, we evaluated their relationship with this clinical characteristic. Although we found seven patients with type 5 (this type was the most common in our study population) arterial damage who were heterozygous but positive for the *PTPN22* 1858C/T genotype, we did not identify any association when it was compared with the other types of arterial damage (Table 5). Similar results were observed with the *PTPN22* R263Q and −1123G/C SNPs. Thus, no association of the *PTPN22* SNPs with arterial damage was identified in patients with TA. This result is similar to what was previously reported in the population in Turkey [18]. However, one limitation of our analysis (by type of arterial damage) is the low sample size and statistical power.

On the other hand, we recently identified a high frequency of insertion of the IS6110 and HupB genes in aortic tissue from patients with TA and concluded that the arterial damage may be related to the previous infection with *M. tuberculosis* [38]. These findings are interesting, because TA has been associated with tuberculosis (TB). Some studies have found that the *PTPN22* T allele (620W, which causes susceptibility to different ADs) is associated with protection against TB [39, 40]. However, the other studies have not replicated this finding [41, 42]. Thus, different studies are required to determine the role of *PTPN22* R620W in patients with TA who are positive for TB.

Conclusion

Our data suggest that *PTPN22* R620W is a risk factor for developing TA (However, other studies must be carried out to confirm our findings in other Latin American populations including Mexico); meanwhile, the *PTPN22* R263Q and −1123C/G SNPs are neither risk or protection factors for TA. In addition, our data suggest that *PTPN22* R620W is not associated with arterial damage in patients with TA.

Funding There is no financial support for this work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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