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Short communication

Association between the *PTPN22* 1858C/T gene polymorphism and tuberculosis resistance

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ABSTRACT

Previous studies identified the functional polymorphism 1858C/T in the gene *PTPN22* in association with several autoimmune diseases and with resistance to tuberculosis (TB). This study is the first to investigate the association between pulmonary TB and the *PTPN22* 1858C/T polymorphism in the Brazilian Amazon. We conducted a case-control study involving a group of 413 individuals, comprised of 208 TB carriers and 205 controls. No significant association between the PTPN22 1858T allele frequency in controls (2.4%) and TB carriers (2.7%, $p = 0.982$, odds ratio (OR) = 0.89, 95% confidence interval = 0.37–2.13) was identified in the Brazilian Amazon population. An additional evaluation by meta-analysis, however, suggested a protective role of the T allele in relation to TB (pooled OR = 0.44, $p = 0.011$). These results suggest that the *PTPN22* 1858T allele serves as a protective genetic factor for TB in those individuals who carry this minor allele.

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1. Introduction

Tuberculosis (TB), a major public health issue, remains at epidemic levels worldwide. In 2011 the World Health Organization estimated that 8.7 million cases of TB occurred in the world, with 1.4 million deaths (including 430,000 deaths from TB among HIV-positive people), mostly in developing countries (WHO, 2012). The genetic influence on TB infection was established by several studies of monozygotic and dizygotic twins, linkage and candidate gene analysis, indicating that genetics may play a role in the susceptibility or resistance to TB infection (Hill, 2001; Moller and Hoal, 2010; Vannberg et al., 2011).

Several genes such as HLA and Toll-like Receptor genes (e.g., *TLR1* and *TLR2*) were implicated in the resistance to TB. In addition, polymorphisms in the cytokines genes such *TNF* and *IL1B*, *IL6* promoter polymorphisms were implicated as well (Azad et al., 2012; Lykouras et al., 2008; Vannberg et al., 2011; Yim and Selvaraj, 2010). Recently, data from Genome-Wide Association studies (GWAS) in African populations identifies 17 single nucleotide polymorphisms (SNPs) associated with tuberculosis (Thye et al., 2010). These SNPs were tested with a different case-control cohort and when combined with the GWAS data only two SNPs remained with association (Newport and Finan, 2011). On the other hand, these studies also identify a susceptibility locus for tuberculosis on chromosome 18q11.2 (Thye et al., 2010). Another susceptibility locus was identified at 11p13 in a Ghanaian population (Thye et al., 2012). However, these susceptibility loci and associated SNPs were not validated for different populations such as Chinese (Dai et al., 2011) and Indonesians (Png et al., 2012).

The polymorphism *PTPN22* 1858C/T was first associated with TB in 2005 (Gomez et al., 2005b). The *PTPN22* 1858T allele was primarily related to type 1 diabetes mellitus (T1D) (Bottini et al., 2004) and other autoimmune conditions, such as rheumatoid arthritis (Begovich et al., 2004) and systemic lupus erythematous (Kyogoku et al., 2004). The gene *PTPN22*, which encodes the protein tyrosine non-receptor phosphatase 22, is located in the chromosomal region 1p13.3-p13.1. This gene product is the intracellular protein phosphatase known as Lyp and is only expressed in cells of the immune system, including dendritic, T and B cells (Rhee and Veillette, 2012).

Lyp forms a protein complex with the intracellular tyrosine kinase (protein tyrosine kinase) Csk. The Csk protein tyrosine kinase is a potent suppressor of T-cell activation due to its ability to phosphorylate tyrosine residue at Src family kinases, thereby antagonizing the action of CD45, that mediates dephosphorylation of the inhibitory C-terminal SH2 domain of Lck. (Veillette et al., 2002). The polymorphism *PTPN22* 1858C/T promotes replacement of a tryptophan by an arginine at position 620 (R620W) in the P1 domain of Lyp, and this region has been shown to be critical for the interaction between Lyp and Csk (Bottini et al., 2004). As a

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result of the R620W substitution, this polymorphism results in a gain-of-function mutation by increasing the inhibitory activity of Lyp on T cells (Gianchecchi et al., 2012; Rhee and Veillette, 2012). Moreover, 1858T allele carriers also have more autoreactive B cells compared to carriers of the 1858C wild-type allele (Rieck et al., 2007). In addition, the 1858T allele is associated with a defect in central tolerance and peripheral B cells related to the calibration of the B cell receptor (Habib et al., 2012). These findings suggest that the 1858T allele is a gain-of-function polymorphism causing autoimmunity via compromising the induction of tolerance.

Considering the role of the *PTPN22* polymorphism 1858C/T in autoimmunity and TB, the goal of this study was to evaluate the association between the 1858T mutant allele and resistance to TB.

2. Results and discussion

A case-control association study was conducted with a total of 413 individuals including 208 unrelated individuals with pulmonary TB. These patients were enrolled at the Tuberculosis Reference Center where they were seen for diagnosis and treatment of TB (Policlínica Cardoso Fontes) and at the Hospital Geral Adriano Jorge in Manaus, Brazil. The diagnosis of pulmonary TB was established with a sputum smear and/or culture for *Mycobacterium tuberculosis*. Additionally, 205 healthy controls were selected. The following procedure was used to include individuals as controls: controls were randomly selected by inviting people who lived in the same area as the patients to take part in the study. This approach is much more appropriate and sensitive than convenience control samples collected from blood banks, healthy professionals, students etc., because the procedure has the advantage that controls are taken from the same admixed population and are more likely to be exposed to the same environmental factors. Individuals were considered healthy if their medical history did not reveal any chronic diseases; endemic infectious diseases, or autoimmune diseases and if their physical examination and blood tests (e.g., glucose) corroborated their history. Any individual with one or more of these conditions was excluded from the control sample. For individuals who satisfied the medical history requirement and the TB patients, blood samples were collected, and genomic DNA was extracted. The DNA samples were registered and stored in a DNA bank. At the beginning of the study, a random number was selected, and the corresponding control and appropriate number of sequentially numbered controls were taken from the DNA bank. For the present study, the selected controls samples from DNA bank are matched for age and sex. This study was approved by the respective local ethics and research committees, and participants provide written informed consent.

Genotype frequencies occurred in Hardy–Weinberg equilibrium in patients and controls. No association between the *PTPN22* 1858C/T genotype and allele frequencies in the cohort of cases and those in the controls was observed (Table 1). The homozygous TT genotype was absent from patients and controls. The frequency of the T allele in control individuals was substantially lower (2.7%) than that previously reported for the European population (Orozco et al., 2005; Seldin et al., 2005) (range 7.4–15.3%) and was also quite similar to that reported for other Latin American populations (Gomez et al., 2005b; Ramirez et al., 2012; Torres-Carrillo et al., 2012) (range 2.0–4.3%). Therefore, the frequency of the T allele was also higher than that reported for Colombian TB patients (Gomez et al., 2005b). Clearly, differences based on ethnicity and geographical distribution are evident with regard to the frequencies of *PTPN22* polymorphism. In Europe, a south-to-north gradient ranging from 2.1% to15.5% was observed for the T allele (Totaro et al., 2011). In addition, *PTPN22* is not polymorphic in East Asian populations (Sahin et al., 2009). Native Brazilian populations are not polymorphic for this genetic variation; however, these individuals are highly susceptible to TB infection (Basta et al., 2006, 2010; Coimbra and Basta, 2007; Zembrzuski et al., 2010). It's important to note that some authors have been proposed that additional variants in PTPN22 gene are also important for disease susceptibility as well as *PTPN22* 1858C/T (Kawasaki et al., 2006; Orru et al., 2009). Some of these variants may be in linkage disequilibrium across the gene with *PTPN22* 1858T (Kawasaki et al., 2006). However, it should be stressed that PTPN22 1858C/T is a functional polymorphism and the role of this SNP in inflammatory responses it is well demonstrated (Gianchecchi et al., 2012; Vang et al., 2013).

To improve statistical power and determine the common effect size of the *PTPN22* 1858C/T polymorphism with a bigger sample, a meta-analysis was performed (Fig. 1). The searches were performed by two different researchers to identify studies involving the *PTPN22* 1858C/T polymorphism (rs2476601) and TB by Medline, Scopus, Scirus, EMBASE, and Lilacs until October 2012. The terms "tuberculosis", "*PTPN22* 1858 polymorphism", and "rs2476601" were used as keywords. Only three studies were identified in the literature (Table 2) (Gomez et al., 2005b; Kouhpayeh et al., 2012; Lamsyah et al., 2009), and the data were analyzed in conjunction with the data from the present study (Fig. 1). All statistical calculations were made using *RevMan* 5.1 and *StatsDirect* software. We assume a dominant genetic model (TT + CT vs. CC) for association analysis.

A total of 616 pulmonary TB patients and 725 controls from the four studies were included in the meta-analysis. The final analysis of the association between the T allele and TB (using a dominant genetic model) demonstrated that the combined effect (pooled OR) of the four studies was 0.44 ($p = 0.006$). A post-hoc power analysis shows 81% of statistical power (using a *G*Power* software for calculations). These results suggest a protective effect of the T allele on pulmonary TB; however, due to the small number of studies included in the meta-analysis, these results should be considered with caution. Regarding the fact that the number of studies

Table 1
PTPN22 1858C/T variant genotype and allele frequencies in TB and control subjects from Brazilian Amazon population.

PTPN22 1858C/T	Tuberculosis n(%)	p-Value HWE[a]	Controls N (%)	p-Value HWE[a]	p-Value	OR (95% confidence interval)
Genotypes	208		205			
CC	198 (95.2)	0.722	194 (94.3)	0.693	0.977	1.01 (0.76 – 1.32)
CT	10 (4.8)		11 (5.4)		0.982	0.87 (0.37 – 2.16)
TT	0 (0)		0 (0)		–	–
Alleles	416		411			
C	406 (95.8)		399 (97.3)		0.776	1.03 (0.85 – 1.26)
T	10 (2.4)		11 (2.7)		0.982	0.89 (0.37 – 2.13)

Genotyping of the PTPN22 1858C/T polymorphism was performed as previously described[5]. The PCR primer sequences were 5′-TCACCAGCTTCCTCAACCACA-3′ and 5′-GATAATGTTGCTTCAACGGAATTTA-3′. PCR was performed as follows: denaturation at 95 °C for 3 min and 30 cycles of denaturation at 95 °C for 30 s, annealing at 60 °C for 30s and extension at 70 °C for 30 s. The amplification product was digested with *XcmI* enzyme and analyzed by agarose gel electrophoresis. Genotypes and allele frequencies were compared between cases and controls by χ^2 test that combined 2 × 2 contingency tables. All *p*-values were two-tailed.

[a] Hardy–Weinberg Equilibrium.

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