Concise Report

**PTPN22 gene polymorphism in Takayasu’s arteritis**

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**Objective.** Takayasu’s arteritis (TA) is a chronic, rare granulomatous panarteritis of unknown aetiology involving mainly the aorta and its major branches. In this study, genetic susceptibility to TA has been investigated by screening the functional single nucleotide polymorphism (SNP) of PTPN22 gene encoding the lymphoid-specific protein tyrosine phosphatase.

**Methods.** Totally, 181 patients with TA and 177 healthy controls are genotyped by PCR-RFLP method for the SNP rs2476601 (A/G) of PTPN22 gene. Polymorphic region was amplified by PCR and digested with Xcm I enzyme.

**Results.** Detected frequencies of heterozygous genotype (AG) were 5.1% (9/177) in control group and 3.8% (7/181) in TA group (odds ratio: 0.75, 95% CI: 0.3, 2.0). No association with angiographic type, vascular involvement or prognosis of TA was observed either.

**Conclusion.** The distribution of PTPN22 polymorphism did not reveal any association with TA in Turkey.

**Key Words:** Takayasu’s arteritis, Single nucleotide polymorphism, PTPN22.

**Introduction**

Takayasu’s arteritis (TA), also known as pulseless disease, is a chronic granulomatous panarteritis characterized by the involvement of large vessels, especially the aorta and its major branches [1]. Cellular immunity may play the major role in disease pathogenesis as involved vessels are infiltrated mainly by γδ T cells, NK cells, cytotoxic T cells, Th1 cells and macrophages [2]. Previous studies showed an elevated ratio of CD4/CD8 T cells, increased number of HLA-DR+ circulating lymphocytes and markedly increased 65-kDa HSP expression in tissues along with the presence of γδ T cells [3]. Infections, autoimmunity and genetic factors are implicated in the pathogenesis of TA. Evidences of genetic susceptibility to TA have also been demonstrated in several studies. Especially, associations of TA with HLA-B52 and -B39 have been reported previously from Japan, whereas HLA-B5 was associated with TA in India [4, 5].

Lymphoid-specific protein tyrosine phosphatase (LYP) is encoded on chromosome 1p13 at PTPN22 gene and a single nucleotide polymorphism (SNP) of the gene has been demonstrated to be associated with several autoimmune disorders [6, 7]. LYP is involved in maintaining the resting phenotype of lymphocytes and in controlling signalling caused by an antigen, co-stimulation and cytokines [8]. The PTPN22 gene polymorphism causing an amino acid change (R620W) at the proline-rich motif of LYP has been shown to affect the protein–protein interaction with tyrosine kinase Csk in T-cell activation. Individuals carrying the variant allele of PTPN22 are suggested to have changes in the threshold for thymic selection with increased numbers of auto-reactive T cells escaping negative selection and be prone to autoimmunity. However, the mechanism of action remains to be clarified, as both gain and loss of function mechanisms have been reported [7, 9, 10]. An association of PTPN22 R620W polymorphism (rs2476601, A/G) was reported first with type 1 diabetes [11] and later also with myasthenia gravis [12], SLE [13] and RA [9]. However, there are also some inflammatory diseases such as IBD, psoriasis, multiple sclerosis, AS [6] and Behcet’s disease (BD) [14] with no association of this polymorphism.

**PTPN22 R620W polymorphism reveal a wide variation in allele frequencies among different populations, polymorphic allele being present highest in Scandinavia (15%), whereas is absent in Asian and African populations [15, 16]. Considering this spectrum of the diseases and variations among populations, we investigated the possible association of PTPN22 polymorphism with TA in this study.

**Materials and methods**

The study was designed as a case–control study enrolling 181 patients with TA (19 men, 162 women; mean age: 37 ± 11.7 yrs). Patients were classified according to the 1990 ACR criteria for the classification of TA [17]. Angiographic classification is done as proposed by the International Cooperative Study on TA in 1997 [18]. According to this classification, 39% (n = 70) of the patients had type 1 vessel involvement, 8.2% type 2a (n = 15), 1.1% type 2b (n = 2), 3.3% type 3 (n = 6), 4.4% type 4 (n = 8) and 44% type 5 (n = 80). As controls, 177 healthy blood donors (86 men, 91 women; mean age: 40 ± 9.7 yrs) were recruited. All patients and controls were enrolled with local ethics committee approval and provided their informed consent.

**Genotyping**

For genotyping, cellular DNA was isolated from 10 ml of peripheral blood using standard procedures. For the determination of PTPN22 alleles, PCR-based restriction fragment length polymorphism (RFLP) analysis was performed. DNA was amplified using the forward primer 5'GGC CTC AAT GAA CTC CTC AA 3' and reverse primer 5'AAT GTT GCT TCA

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with an assumed low effect size in this sample. The odds ratio: 0.75, 95% CI: 0.3, 2.0). AG genotype was not observed in the presence of autoantibodies (ANA) and co-existence with other autoimmune phenomena such as low-grade, continuous inflammation causing a long, usually biopsy-proven giant cell arteritis. In Turkey, it is somewhat lower compared with the Caucasian populations (5%). Considering previous findings in different ethnic communities, ethnic differences may account for this result.

Pathophysiology of TA is not exactly known but is thought to be multifactorial involving infectious agents (Mycobacterium tuberculosis, different types of viruses), autoimmunity and genetic influences [2]. Since cell-dependent autoimmunity may play a major role in pathogenesis, we investigated polymorphism of PTPN22 gene which is repeatedly shown to be associated with different autoimmune diseases and considered as one of the most common markers of susceptibility to autoimmunity [6]. However, in our study, no significant difference between TA and control group is observed, suggesting that LYP does not influence the pathogenesis of TA.

Our previous study in BD, another systemic disorder with autoimmune features, did also not reveal any association with PTPN22 gene polymorphism [14]. An important factor in genetic studies is the ethnic heterogeneity and there are ethnic differences regarding the frequencies of PTPN22 polymorphism in different populations. In Turkey, it is somewhat lower compared with the other Caucasian populations (5%). Considering previous findings on similarities of the Turkish population with the other European data, this was unexpected. However, low frequencies of this polymorphism have also been reported in populations such as Japanese and Mexican. Absence of a TA-PTPN22 association may also be related to this low prevalence and may not rule out an association in other, especially Caucasian, populations.

Another explanation for our results may be the lack of autoimmune features in TA. Although clinical spectrum of TA such as low-grade, continuous inflammation causing a long, generally unremitting disease course and tissue-infiltrating cell types such as T cells suggest the involvement of cell-mediated immunity, TA lacks some other autoimmune phenomena such as the presence of autoantibodies (ANA) and co-existence with other autoimmune disorders such as multiple sclerosis or type 1 diabetes. Granulomatous panarteritis is also uncommon in autoimmune diseases such as SLE. In this respect, it is interesting to note that PTPN22 is found to be associated with WG, but not with GCA [19, 20]. Although both disorders are accepted to be granulomatous vasculitides, WG patients also have ANCA and have medium-size vessel involvement with neutrophil infiltrations, whereas GCA have more resemblance to TA such as large-vessel-confined vasculitis without classical autoantibodies.

As a conclusion, a role of PTPN22 R620W polymorphism could not be demonstrated in TA pathogenesis. Low prevalence of this polymorphism in Turkey or pathogenetic differences with the classic autoimmune disorders may account for this result.

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