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PTPN22 Single-Nucleotide Polymorphisms in Iranian Patients with Type 1 Diabetes Mellitus

Farzaneh Abbasi[a], Samaneh Soltani[b], Amene Saghazadeh[b], Ehsan Soltaninejad[c], Arezou Rezaei[d], Alireza Zare Bidoki[b], Tayyeb Bahrami[c], Ali Akbar Amirzargar[b,e], and Nima Rezaei[d,e,f]

[a]Growth and Development Research Center, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran; [b]Molecular Immunology Research Center, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran; [c]Department of Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran; [d]Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran; [e]Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran; [f]Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran

ABSTRACT

Background: PTPN22 plays a crucial role in regulating the function of various cells of the immune system, particularly T cells. Polymorphisms of the PTPN22 gene have been associated with many autoimmune diseases, including type 1 diabetes (T1D) which is a T-cell-mediated disease.
Objective: The present study was aimed at genotyping of an Iranian population for five polymorphisms of the PTPN22 gene.
Methods: The study population consisted of 99 T1D patients and 100 healthy controls. We genotyped five single-nucleotide polymorphisms (SNPs) (rs12760457, rs1310182, rs1217414, rs33996649, and rs2476601) of the PTPN22 gene.
Results: Regarding the variant rs2476601, genotypes AG and GG were increased and decreased in T1D patients compared with controls, respectively. Further, alleles G and A of this SNP were found to be decreased and increased in T1D patients, respectively (p value = 0.001). However, T1D and control groups did not differ on genotype distribution or allele frequency for other investigated SNPs.
Conclusions: The PTPN22 rs2476601 minor allele (A) was associated with T1D in Iran, accounting for its pathophysiology in autoimmune diseases.

KEYWORDS
PTPN22; single-nucleotide polymorphisms; type 1 diabetes

Introduction

Type 1 diabetes mellitus (T1D) is a common complex trait characterized by immunological destruction of or damage to the insulin-producing islet β cells (Atkinson et al., 2001; Van Belle et al., 2011). It is considered a T cell-mediated autoimmune disease that may affect other organs and result in other complications. For example, diabetic nephropathy develops in approximately 40% of T1D cases and declines the survival rate of patients dramatically. In comparison with patients without nephropathy, there is a approximately sevenfold decreased survival rate for patients with T1D and nephropathy within 40 years since diabetes diagnosed (Andersen et al., 1983). Further, a 17-year follow-up study has calculated a rate of 0.80 per 100 patient years for

CONTACT Nima Rezaei rezaei_nima@tums.ac.ir Research Center for Immunodeficiencies, Children's Medical Center Hospital, Dr Qarib St, Keshavarz Blvd, Tehran 14194, Iran.

cardiovascular events in T1D patients who received conventional treatment (Colhoun et al.; Trial, 2005). As such epidemiological studies indicate that the incidence rate of T1D has increased within the last decades and influenced the whole world (Maahs et al., 2010). These facts about the burden of T1D provide the strong impetus toward imparting the etiological mechanisms of this multifactorial autoimmune disease arisen form the complex interaction between genetic and environmental risk factors.

As reviewed in Maahs et al. (2010), several risk factors have already been highlighted owing to their important impact on the incidence rate of T1D, and genotype is one of them, along with age, gender, race/ethnicity, etc. The most important genetic loci linked with T1D are related to the major histocompatibility complex (MHC) on chromosome 6p21, the insulin gene region on chromosome llpl5, and the CTLA-4 gene (cytotoxic T lymphocyte associated-4) on chromosome 2q33, which are recognized as IDDM (insulin-dependent diabetes mellitus) 1, 2, and 12 genes, respectively (Davies et al., 1994; Nisticò et al., 1996). It is, however, considered a polygenic disorder because genome-wide association studies have provided evidence linking T1D to more than 40 genetic loci (Davies et al., 1994; Barrett et al., 2009; Todd et al., 2007). Of note, a substantial number of candidates genes for T1D encode proteins (such as IL-2, IL-21, IL-10, IL-19, IL-20 and IL-27) important in immune system function (Barrett et al., 2009; Cooper et al., 2008).

The gene PTPN22 (protein tyrosine phosphatase, non-receptor type 22 (lymphoid)) which is also known as PEP and LYP encodes a member of the non-receptor class 4 subfamily of the protein tyrosine phosphatase family. It is widely acknowledged as the third major genetic loci confronting with the risk of T1D. Protein tyrosine phosphates as a negative regulator of effector/memory T-cell pool are necessary to maintain the immune system in balance (Hasegawa et al., 2004). Particularly, the protein tyrosine phosphatase PTPN22 is expressed by both the innate and adaptive immune systems, explaining its influence over various cells of the immune system, such as B and T cells, monocytes, dendritic, and natural killer cells (Fousteri et al., 2013). rs2476601, also known as R620W, or 1858C>T, is the best investigated single-nucleotide polymorphism (SNP) in the PTPN22 gene. It has been associated with many autoimmune disorders, particularly T1D, Graves' disease, systemic lupus erythematosus (SLE), juvenile idiopathic arthritis (JIA), rheumatoid Arthritis (RA), and Hashimoto thyroiditis (Begovich et al., 2004; Cinek et al., 2007; Criswell et al., 2005; Hinks et al., 2005; Kyogoku et al., 2004; Smyth et al., 2004). The contribution of this SNP to T1D can be attributed to its downregulatory role in proliferation of $CD4^+$ T cells and in production of IL-2 (Aarnisalo et al., 2008).

Population-based genetic association studies (PBASs) examining the possible associations between the various SNPs of PTPN22 and susceptibility to T1D have been frequently accomplished in the American and European countries and to a lesser extent in Asia. On that account, we conducted the present study to investigate the possible associations of five SNPs (rs12760457, rs1310182, rs1217414, rs33996649, and rs2476601) of the PTPN22 gene with susceptibility to T1D in an Iranian population.

Materials and methods

Subjects

Blood samples were obtained from 99 Iranian T1D patients who were referred to the Children's Medical Center (CMC), the Pediatrics Center of Excellence in Tehran, Iran. All

participants have been previously diagnosed with T1D (insulin-dependent) by pediatric endocrinologists at the CMC, using following criteria (defined by the American Diabetes Association 2005): 1. signs and symptoms of diabetes (polydipsia, polyphagia, unexplained weight loss, hyperglycemia, glycosuria, ketonemia, and ketonuria) a random blood sugar level of 200 mg/dL (11.1 mmol/L) or higher, or 2 fasting blood sugar level of 126 mg/dL (7 mmol/L) or higher, or 3. 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher from the oral glucose tolerance test (Silverstein et al., 2004). Patients with other systemic diseases were excluded. The group of control subjects was set up from healthy members without a history of diabetes type 1 or type 2 or any other systemic disease. All the participants (patients and control subjects) enrolled in the present study were <18 years of age. They all were Iranian living in Tehran situated in the north-central part of Iran. Genomic DNA was extracted from leukocytes according to the phenol–chloroform protocol (Di Pietro et al., 2011).

All individuals enrolled in the study gave their written consent. This study was approved by the ethics committee of Tehran University of Medical Sciences (TUMS).

Genotyping

In the present study, SNPs of the PTPN22 were identified by means of polymerase chain reaction with the sequence specific primers (PCR-SSP) assay (PCR-SSP kit, Heidelberg University, Heidelberg, Germany). A PCR Techne Flexigene apparatus (Rosche, Cambridge, UK) was applied for the amplification of extracted DNA. PCR products were observed by 2% agarose gelelectrophoresis, and a picture was taken after visualization with a UV transilluminator. Five SNPs of the PTPN22 gene were investigated: rs12760457, rs1310182, rs1217414, rs33996649, and rs2476601. Laboratory personnel were blinded to the study.

Statistical analysis

For each one of the five investigated SNPs, genotype distributions and allele frequencies were calculated by direct gene counting. Pearson's chi-squared test was used in examining the differences in the distribution between T1D cases and healthy controls. All the statistical analyses of the present study were performed using the Epi Info statistical software (version 6.2, World Health Organization, Geneva, Switzerland).

Results

Allele frequencies

As summarized in Table 1, there was no difference in allele frequencies of four investigated SNPs (rs12760457, rs1310182, rs1217414, and rs33996649) of the PTPN22 gene between controls and patients with T1D. Analysis of rs2476601 polymorphism revealed that allele A was significantly overrepresented in TID patients compared with controls (p value = 0.001). Further, we found a significant decrease in allele G of this SNP in T1D patients (p value = 0.001).

Table 1. Allele frequencies of PTPN22 polymorphisms in patients with diabetes type 1 and controls.

Position	Allele	Diabetes type 1 (n = 99) N %	Control (n = 100) N %	P value	OR (95% CI)
rs12760457	C	136 (71.6%)	144 (72.7%)	0.9	0.9 (0.6<OR<1.5)
	T	54 (28.4%)	54 (27.3%)	0.9	1.1 (0.7<OR<1.7)
rs1310182	A	92 (46.5%)	85 (42.5%)	0.5	1.2 (0.8<OR<1.8)
	G	106 (53.5%)	115 (57.5%)	0.5	0.8 (0.7<OR<1.3)
rs1217414	A	49 (25.25%)	61 (30.8%)	0.3	0.8 (0.5<OR<1.2)
	G	145 (74.7%)	137 (69.2%)	0.3	1.3 (0.8<OR<2.1)
rs33996649	C	192 (97.95%)	198 (99%)	0.4	0.5 (0.5<OR<3.1)
	T	4 (2%)	2 (1%)	0.4	2.1 (0.3<OR<16.4)
rs2476601	A	12 (6.1%)	0 (0%)	0.001	Undefined
	G	186 (93.9%)	200 (100%)	0.001	0 (0<OR<0.4)

Table 2. Genotype distribution of PTPN22 polymorphisms in patients with diabetes type 1 and controls.

Position	Genotype*	Diabetes type 1 (n = 95–99) N %	Control (n = 99–100) N %	P value	OR (95% CI)
rs12760457	CC	50 (52.6%)	54 (54.5%)	0.9	0.9 (0.5<OR<1.7)
	CT	36 (37.9%)	36 (36.4%)	0.9	1.1 (0.6 <OR<2)
	TT	9 (9.5%)	9 (9.1%)	0.9	1 (0.4<OR<3)
rs1310182	AA	26 (26.3%)	19 (19%)	0.3	1.5 (0.7<OR<3.1)
	AG	40 (40.4%)	47 (47%)	0.4	0.8 (0.4 <OR<1.4)
	GG	33 (33.3%)	34 (34%)	0.9	1 (0.5<OR<1.8)
rs1217414	AA	8 (8.24%)	9 (9.1%)	1	0.9 (0.3<OR<2.7)
	AG	33 (34.02%)	43 (43.4%)	0.2	0. 7 (0.4<OR<1.2)
	GG	56 (57.73%)	47 (47.5%)	0.2	1.5 (0.8<OR<2.8)
rs33996649	CC	94 (95.9%)	98 (98%)	0.4	0.5 (0.1<OR<3.1)
	CT	4 (4.1%)	2 (2%)	0.4	2.1 (0.3<OR<16.8)
	TT	0 (0%)	0 (%)	–	–
rs2476601	AA	0 (0%)	0 (0%)	–	–
	AG	12 (12.1%)	0 (0%)	0.001	Undefined
	GG	87 (87.9%)	100 (100%)	0.001	0 (0<OR<0.4)

*All of the genotypes investigated in the present study were in Hardy–Weinberg equilibrium among both control individuals and patients.

Genotype frequencies

As expected, control and T1D groups did not differ on the genotype distribution of four investigated SNPs in the PTPN22 gene, for example, rs12760457, rs1310182, rs1217414, and rs33996649. Regarding the variant rs2476601, genotype AG was significantly more prevalent in T1D patients compared with controls (p value = 0.001), while genotype GG was significantly less frequent in T1D patients compared with controls. Interestingly, none of the people, neither control subjects nor T1D patients, carry genotype AA of this SNP in the present case-control study. Genotype distribution of PTPN22 polymorphisms for T1D cases and control subjects is summarized in Table 2.

Discussion

PTPN22 and the pathogenesis of type 1 diabetes

A lack or low level of tolerance to self-antigens is that what causes T cells being reactive and contributing to the immune assault on self tissues. This assault, commonly known as

autoimmunity, is the major mechanism of tumor immune escape and transplant rejection (Sakaguchi et al., 2001). The thymus where CD25+ CD4+ regulatory T cells are developed plays a prominent role in sustaining tolerance to self-antigens. T1D, also known as insulin-dependent diabetes mellitus, is a chronic autoimmune disease where pancreatic B cells are destroyed. T cells and particularly type 1 T-helper cells (IFN-gamma) are thought to be chiefly responsible for the B-cell destruction (Wilson et al., 1998). Moreover studies indicate that reduced tolerance in patients with T1D is at least in part arisen from decreased ability of CD25+ CD4+ regulatory T cells to conquer T-cell proliferation (Lindley et al., 2004). It is thus well expected that main factors (including genetic and environmental) and mechanisms (including genetic and epigenetic) underlying the pathogenesis of T1D operate at the immune system balance and particularly at the TCR (T-cell receptor) signaling (Bottini et al.; Bluestone et al., 2010).

The discovery of various substrates (including Lck, Zap70, Vav, CD3, TCRζ, and valosin containing protein) has led to recognition of direct and indirect roles for PTPN22 (Wu et al., 2006). For example, not only PTPN22 can exert enzymatic effects, but also its substrate, SKAP-HOM, serves as an adaptor (Bottini and Peterson, 2014). These properties are what enable PTPN22 (Lyp) to interfere with numerous immune signaling pathways (TCR signaling) and thereby influencing over various immune cells and their functions. Polymorphisms of the PTPN22 gene have so far been associated with many autoimmune diseases. Below, we will discuss these associations in addition to study findings SNP-by-SNP.

Study findings

rs12760457. To date, the possible associations of this SNP with susceptibility to various diseases, including autoimmune thyroid disease (AITD), idiopathic inflammatory myopathy (IIM), Graves' disease, type I psoriasis, systemic sclerosis (SS), RA, and T1D, have been investigated in both Asian and Caucasian ethnic compositions, such as White North Americans, United Kingdom (U.K.), French, Japanese and Han Chinese. There was no significant association between the individual SNP rs12760457 and all the aforementioned diseases (Ban et al., 2010; Carlton et al., 2005; Chinoy et al., 2008; Dieude et al., 2008; Martín et al., 2011; Steer et al., 2006; Smith et al., 2008; Taniyama et al., 2010; Xue et al., 2013). However, haplotypes containing this variant were correlated with AITD, RA, and T1D significantly (Ban et al., 2010; Steer et al., 2005; Taniyama et al., 2010). Only one study conducted in the Japanese population has examined the possible association between T1D and the SNP rs12760457 (Taniyama et al., 2010). We, like the Japanese study, found no significant difference in the genotype distribution/allele frequency of this SNP between T1D cases and controls.

rs1310182. In the U.K. population, the correlation between this SNP and T1D was significant ($p = 9.33 \times 10^{-13}$). It was, however, dependent on the SNP rs2476601 (corrected $p = 0.840$) (Smyth et al., 2008). As such, this SNP was not associated with T1D in the Sardinian population again (Zoledziewska et al., 2008). On the contrary, there was a significant association between this variant and T1D in the Japanese population (Taniyama et al., 2010). Interestingly, allele C was determined as the risk allele in this Japanese T1D population, standing in stark contrast to allele T in the White North American RA population (Carlton et al., 2005; Taniyama et al., 2010). The haplotypes containing this SNP were correlated with T1D in the various ethnic compositions, such as

United Kingdom and Japanese (Smyth et al.,2008; Taniyama et al., 2010). Regarding this variant, we confirmed the findings of European populations.

rs1217414. No correlation between this variant with T1D or RA was corroborated in both Caucasian and Asian ethnic compositions, including the White North American, United States, and Chinese populations (Carlton et al., 2005; Onengut-Gumuscu et al., 2006; Pei et al., 2014). However, there were significant associations between this SNP with Type 1 psoriasis, ankylosing spondylitis (AS) and SLE in the United Kingdom, Chinese Han, and European–American populations, respectively (Namjou et al., 2013; Smith et al., 2008; Tang et al., 2014). Our findings were consistent with both European and Asian studies.

rs33996649. This loss-of-function polymorphism of the PTPN22 gene, R263Q, was found to be non-polymorphic in the Chinese Han population at all, while its correlation with RA in a meta-analysis on six Caucasian cohort studies (Huang et al., 2012; Rodriguez-Rodriguez et al., 2011). A comprehensive meta-analysis on eight Caucasian cohort studies indicates no significant correlation between this variant and SS, and this correlation was found significant in a Spanish population merely, but not in other seven populations (Belgium, England, Germany, Italy, Netherlands, USA, and Sweden) (Diaz-Gallo et al., 2011). Moreover, it was indicated that this variant is closely corresponded with ulcerative colitis (UC), but not with Crohn's disease (CD), in Caucasian populations (Diaz-Gallo et al., 2011). To our knowledge, the present study investigated the association between the SNP rs33996649 in the PTPN22 gene and T1D for the first time and demonstrated no significant difference between T1D patients and controls in the Iranian population.

rs2476601. Transmission disequilibrium test analyses and as well PBASs not only support a close correspondence between the functional SNP C1858T (R620W), rs2476601, of the gene PTPN22 and T1D, but also suggest this variant as the chief variant in the PTPN22 gene confronting with the risk of T1D in the White American and European populations, including Czech Republic, United States, France, Finland, Sweden, German, etc. (Cinek et al., 2007; Criswell et al., 2005; Cervin et al., 2008; Chelala et al., 2007; Kahles et al., 2005; Ladner et al., 2005; Onengut-Gumuscu et al., 2006; Onengut-Gumuscu et al., 2004; Qu et al., 2005; Steck et al., 2009). For instance, by resequencing the PTPN22 gene and its flanking chromosome region, two SNPs in linkage disequilibrium (LD) were suggested as the best candidates in correlation with T1D in the European population, which the first one was rs2476601 polymorphism and the second one was rs6679677, which is an intergenic SNP between the genes putative homeodomain transcription factor 1 and round spermatid basic protein 1 (Smyth et al., 2008), whereas, regarding Asia, no association between the SNP 1858C > T and T1D existed in the various Asian nations, such as Japan, Korea, and china (Kawasaki et al., 2006; Pei et al., 2014). Regarding this issue, a systemic analysis of the PTPN22 gene indicated five novel SNPs, which not included the SNP +1858C > T, and among them, −1123G > C (rs2488457) was the most significant SNPs in LD and associated with T1D in both Japanese and Korean populations (Kawasaki et al., 2006). Surprisingly, the authors ended their investigation with this conclusion that the association (−1123G > C and T1D) is more considerable compared with the association between +1858C > T and T1D not only in Asian populations, but also in a European population (Kawasaki et al., 2006). However, it seems that this finding has not been replicated in the other PBASs, for example, the study which delineates no significant association between T1D and the SNP −1123G > C or +2740 (rs1217412) in Czechs, while proving this correlation for the SNP +1858 (Cinek et al.,

2007), and also gene sequencing analyses, which supports the SNP +1858 as the best candidate, in this regard, as explained above (Cinek et al., 2007; Criswell et al., 2005; Cervin et al., 2008; Chelala et al., 2007; Kahles et al., 2005; Ladner et al., 2005; Onengut-Gumuscu et al., 2006; Onengut-Gumuscu et al., 2004; Qu et al., 2005; Steck et al., 2009). Our findings validated a significant association between the rs2476601 polymorphism and TID in the Iranian population for the first time.

Concluding remarks

Taken together, we demonstrated that relationships between genotype/allele distribution of SNPs of the PTPN22 gene and T1D in Iran, as a country in Western Asia, are more similar to that of the European than Asian populations. This finding is consistent with other study results which have indicated that the Iranian population displays the relationships between certain gene polymorphisms and susceptibility to common diseases (e.g., the associations proved between the C3435T polymorphism of the MDR1 (multidrug resistance) gene and ulcerative colitis (Farnood et al., 2007)) more similar to European and Western countries rather than Asian and Eastern countries. As well, the allele/genotype frequencies of certain SNPs, such as Arg194Trp and Arg399Gln variants within the XRCC1 (X-ray repair cross-complementing group 1) gene (Mohamadynejad and Saadat 2008), in Iranian populations, have been reported to be in the middle of frequencies related to European and Asian countries . More interestingly, there are different ethnic groups, particularly Bakhtiari, Persian, Arab and Azeri, in Iran who present the diverse profiles of certain genes, such as Killer cell immunoglobulin-like receptors (KIR) gene (Ashouri et al., 2009). The results of our study are remarkable; however, they should be interpreted with caution. All the control subjects carried the PTPN22 rs2476601 major allele. In addition, another study has shown that the minor allele of this variant is found in < 1.5% of healthy Iranian subjects (Almasi et al., 2014). Overall, it can be concluded that the PTPN22 rs2476601 is very rare in Iranian people and was monomorphic in the individuals enrolled in the present study. Further studies in different Iranian ethnicities with lager sample sizes are required to investigate whether an ethnicity-dependent distribution pattern for SNPs of PTPN22 exists in Iranian individuals and T1D patients.

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