Protein Tyrosine Phosphatase Non-receptor 22 Gene C1858T Polymorphism in Patients with Coexistent Type 2 Diabetes and Hashimoto’s Thyroiditis

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Background: A protein tyrosine phosphatase non-receptor type 22 (PTPN22) C1858T gene polymorphism has been reported to be associated with both Type 2 diabetes mellitus (T2DM) and Hashimoto’s thyroiditis (HT) separately. However, no study has been conducted to explore the C1858T polymorphism in T2DM and HT coexistent cases up to now.

Aims: The study aimed to determine whether a relationship exists or not between the PTPN22 C1858T polymorphism and this coexistent patient group.

Study Design: Case-control study.

Methods: Peripheral blood samples from 135 T2DM patients, 102 patients with coexistent T2DM+HT, 71 HT patients and 135 healthy controls were collected into ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes and genomic DNA was extracted. The PTPN22 C1858T polymorphism was analyzed using polymerase chain reaction (PCR) restriction fragment length polymorphism (RFLP) methods.

Results: Statistically significant differences were not observed between the patient and control groups. This study demonstrated a statistically significant association between both the CT genotype and the T allele in the female patient group with coexistent T2DM+HT (CT genotype: p=0.04; T allele: p=0.045) with a statistically significant association between the CT genotype and the mean values of body mass index (BMI) and free T3 levels (FT3) (BMI: p=0.044 and FT3: p=0.021) that was detected in the patient group with coexistent T2DM+HT. The minor genotype TT was observed in none of the groups in this study. The CT genotype frequency was [number (frequency)]: 5 (3.8%), 7 (6.86%), 5 (7.04%), 3 (2.22%), while the T allele frequency was 5 (1.86%), 7 (3.44%), 5 (3.53%) and 3 (1.12%) in the T2DM, T2DM+HT, HT and control groups, respectively.

Conclusion: Our data suggest that the PTPN22 1858T allele and the CT genotype are associated with increased risk in female patients for coexistent T2DM+HT. The CT genotype was associated with high mean BMI and free T3 values in the patient group with coexistent T2DM+HT. These results demonstrate that T allele carriers were more often in the T2DM+HT group than in the T2DM group. Therefore, the combination of T2DM and HT with female gender may have higher T allele carriage in comparison to the T2DM only and male groups. (Balkan Med J 2014;31:37-42).

Key Words: Hashimoto’s thyroiditis, polymorphism, protein tyrosine phosphatase non-receptor type 22, type 2 diabetes
one-third of the patients with T1DM eventually develop thyroid dysfunction (6, 7). The frequency of thyroid dysfunction in T2DM exceeds that in the general population. The frequency in T1DM has been reported as equal to that in T2DM because of the existence of elderly patients with T2DM (7). Type 2 diabetes is a complex disease diagnosed by elevated blood glucose, insulin resistance and impairment of beta cell function (8). Diabetes affects about 285 million people globally, is extremely common worldwide (9) and will affect 439 million adults by the year 2030 (10). Since 90% of diabetes mellitus patients have been diagnosed type 2 diabetes, T2DM is the most type of common diabetes mellitus in the world (9).

Hashimoto’s thyroiditis and T2DM are multifactorial diseases in which a genetic tendency combines with environmental risk factors to drive disease. Both of these diseases have a strong genetic component (11, 12). The concordance of Hashimoto’s thyroiditis is reported as 55% and 0% in monozygotic (MZ) and dizygotic (DZ) twins (13), whereas the concordance rate of T2DM is approximately 70% and 20-30% in MZ and DZ twins, respectively (14). If one parent has T2DM, the lifetime risk of occurrence the disease is about 40% in offspring and even higher if the mother is affected; the risk is close to 70% if both parents suffer from diabetes (14). In view of this strong genetic pattern of T2DM and HT, many candidate genes have been found in association with T2DM and HT. Protein tyrosine phosphatase non-receptor type 22 (PTPN22), CDK5 regulatory subunit associated protein 1-like 1 (CDKAL1), hematopoietically expressed homeobox (HHEX), cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B), insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2), fat mass and obesity associated (FTO), peroxisome proliferator-activated receptor gamma (PPARG), potassium inwardly-rectifying channel subfamily J member 11 (KCNJ11), transcription factor 7-like 2 (TCF7L2), notch 2 (NOTCH2), calcium/calmodulin-dependent protein kinase 1D (CAMK1D), a disintegrin and metalloproteinase with thrombospondin type 1 motif, 9 (ADAMTS9), JAZF zinc finger 1 (JAZF1), tetrascin 8/leucine rich repeat containing G protein coupled receptor 5 (TSPAN8/LGR5), and thyroid adenoma associated (THADA) have been defined as related to T2DM and the effects of single nucleotide polymorphisms (SNPs) in PPARG, KCNJ11, solute carrier family 30, member 8 (SLC30A8) have been confirmed as risks for T2DM (11, 15-19). The major histocompatibility complex (HLA), CD40 molecule (CD40), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), PTPN22, thyroglobulin, and TSH receptor primary genes have been reported to be associated with HT (12, 20).

Protein tyrosine phosphatase non-receptor type 22 (PTPN22) on chromosome 1p13.3-p13.1 encodes for the lymphoid tyrosine phosphatase (LYP), which is a 105 kDa protein and a strong suppressor of T-cell activation and T-cell proliferation. Recently, a functional SNP at nucleotide 1858 in codon 620 of PTPN22 (1858C >T; rs2476601 R620W) has been reported to be associated with T2DM and several autoimmune disorders such as T1DM, rheumatoid arthritis, systemic lupus erythematosus, Graves’ disease, Addison’s disease and HT (16, 17, 21). PTPN22 is one of the genes thought to be associated with both HT and T2DM.

Therefore, this study aimed to determine the extent of the relationship of PTPN22 with T2DM and HT separately, as well as with the coexistence of T2DM+HT in a Turkish population.

MATERIAL AND METHODS

Participants and study protocol

The study was approved by the Institutional Ethics Committee of Fırat University (vide No. 05 dated: 24.06.2010), Elazığ, Turkey. Patient and control group clinical data were obtained from the records of Elazığ Private Hayat Hospital (Internal Medicine Department) and Elazığ Training and Research Hospital (Endocrinology Department). Each participant was interviewed and provided written and oral consent before participating in this study.

The study population consisted of four groups: 1- T2DM group of 135 patients (83 female/52 male) 2- HT group of 71 patients (68 female/3 male), 3- T2DM+HT group of 102 patients (100 female/2 male) with both T2DM and HT. 4- A control group of 135 healthy volunteer subjects (70 female/65 male). The data of all participants included a detailed medical history, family history, height, weight, gender, age at the time of study, age of disease onset, clinical findings [for diabetics: body mass index (BMI), glycated haemoglobin (HbA1c) level, postprandial blood sugar and fasting plasma sugar; for Hashimoto’s thyroiditis: levels of thyroid stimulating hormone (TSH), free T4 value (FT4) and free T3 value (FT3)] were collected. The clinical and demographic characteristics of the patient groups are shown in Table 1. Participants who had another serious systemic or metabolic disorder were eliminated from the study. Hashimoto’s thyroiditis was diagnosed by the presence of hypothyroidism, elevated microsomal or thyroid peroxidase autoantibodies, reduced echogenicity of thyroid ultrasound and serum concentrations of FT3 and FT4. Serum concentrations of FT3, FT4 and TSH were determined by chemiluminescent assay using commercial kits. The normal ranges for serum FT4 and T3 were 0.8-1.9 ng/dL and 1.8-4.2 pg/mL, respectively. The normal range for serum TSH was 0.4-4.0 IU/mL. For anti-thyroglobulin antibody, less than 35 IU/mL was considered negative and for anti-thyroid peroxidase (anti-TPO) antibody, less than 40 IU/mL was considered as negative; these were determined by a chemiluminescent assay. All of the T2D cases were diagnosed according to the medical records and fasting and postprandial plasma glucose levels using American Diabetic Association criteria. The medical records indicate either (1) a fasting plasma glucose level ≥126 mg/dL or ≥7.0 mmol/L after a minimum 12-h fast or (2) a 2-h post glucose level [2-h oral glucose tolerance test (OGTT)] ≥200 mg/
to the manufacturer’s instructions. Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) were utilized for genotyping PTPN22 gene polymorphisms. The PCR protocol for the detection of this polymorphism was performed according to Zhang et al. (22). PCR reactions were performed at 95°C for 5 min followed by 36 cycles at 95°C for 30 s, at 64°C for 30 s, at 72°C for 30 s, and a final incubation at 72°C for 7 min. Using forward and reverse primers (as presented in the Table 2), target DNA was amplified by PCR (Biometra; Göttingen, Germany). After PCR, DNA fragments were digested with a specific restriction enzyme Rsal (Rsal; Fermentas, Hanover, USA); Rsal at 37°C overnight. The presence of the CC homozygous (wild-type) genotype was described by two bands at 176 and 42 bp, whereas the RFLP of the CT heterozygous variant was characterized by three bands at 218, 176 and 42 bp (as shown in Figure 1). Intact PCR samples before digestion provided a band at 218 bp (as shown in Figure 1). Samples were visualized on a 3% agarose gel. Ethidium bromide staining was used to detect the amplified fragments.

**Statistical analysis**

All analyses were performed using the Statistical Package for the Social Sciences (SPSS 12.0, Chicago, IL, USA). Relationships between parameters were evaluated using Pearson’s correlation analysis. The Hardy-Weinberg equilibrium of the genetic distribution was analyzed with the chi-squared (X²) test. Differences in genotypic distributions between patients, females and male and controls were evaluated with the chi-squared or Fisher’s exact test. Allele frequencies between cases and controls were compared using Fisher’s exact test.

Odds ratios (OR) with 95% confidence intervals (CIs) were used for the assessment of risk factors. Taking into account the both PTPN22 CT and CC genotypes, one-way analysis of variance (ANOVA) was performed to compare the differences in the demographic properties (age, gender, height, weight) among the groups. P values less than 0.05 were considered statistically significant.

**RESULTS**

There were no statistically significant differences among the patients and control groups with regard to the genotypes and allele frequencies (p>0.05; as shown in Table 3 and 4). In this study, the genotype distributions of all groups were in Hardy-Weinberg equilibrium (T2DM, p=0.05; HT, p=0.09; T2DM+HT, p=0.13; controls p=0.02). The minor genotype TT was not detected in any of the groups. In the T2DM, the CC genotype was found in 130 patients (96.2%) and CT in 5 patients (3.8%); in the HT cohort, CC was found in 66 patients (92.95%) and CT in 5 patients (7.04%); in the T2DM+HT cohort, CC was found in 95 patients (93.13%) and CT in 7 patients (6.86%); and in the control cohort, CC was found in 132 patients (97.77%) and CT in 3 patients (2.22%), as shown in

**TABLE 1. Clinical characteristics of the patient groups**

<table>
<thead>
<tr>
<th></th>
<th>T2DM</th>
<th>HT</th>
<th>T2DM+HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samples (n)</td>
<td>135</td>
<td>71</td>
<td>102</td>
</tr>
<tr>
<td>Male/Female (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual age (years)</td>
<td>55.1±12</td>
<td>45±13.5</td>
<td>56±9.5</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>7.55±6.</td>
<td>1.83±3.1</td>
<td>Duration of disease (years)</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>47.9±12</td>
<td>38.4±13.9</td>
<td>T2DM: 49±9.8</td>
</tr>
<tr>
<td>Hight (m)</td>
<td>167.4±11</td>
<td>163.8±6.6</td>
<td>161.9±6.49</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.25±10.7</td>
<td>71.5±14.9</td>
<td>81±12.12</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.38±4.7</td>
<td>26.71±5.7</td>
<td>31.12±4.94</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.65±2.18</td>
<td>8.07±1.59</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>181.6±71.33</td>
<td>156±52.19</td>
<td></td>
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<tr>
<td>postprandial blood glucose (mmol/L)</td>
<td>252±14±92.50</td>
<td>252±70.14</td>
<td></td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>6.47±13.6</td>
<td>2.79±5.06</td>
<td></td>
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<tr>
<td>FT3 (pg M/L)</td>
<td>3.36±1.08</td>
<td></td>
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</tbody>
</table>

**TABLE 2. Primary sequences of PTPN22 gene**

| PTPN22 (rs2476601) Sense primer: 5’- ACT GAT AAT GCT TCA ACC G-3’ |
|-------------------------|-------------------------|
| PTPN22 (rs2476601) Antisense primer: 5’- TCA CCA GCT TCC TCA ACC AC-3’ |

**Genotyping**

Genomic DNA was extracted from 3 cc of peripheral blood using a commercial kit (Wizard; Promega Corp, Madison, USA) according

**FIG. 1.** Agarose gel electrophoresis indicating the presence of the Rs2476601 (C1858T) polymorphism in the protein tyrosine phosphatase non-receptor type 22 (PTPN22) gene.

**Columns 1:** The image of the first PCR intact product samples are undigested (218 bp). **Columns 2, 3, 4:** RFLP of the CC homozygous (wild-type) variant digested into two bands of 176 and 42 bp. **Columns 5, 6, 7:** RFLP of the CT heterozygous variant digested into three bands of 218, 176 and 42 bp. The TT variant was not detected. M: 100 bp DNA marker.

dL or ≥11.1 mmol/L on more than one occasion with symptoms of diabetes. Impaired glucose tolerance (IGT) was defined as a fasting plasma glucose level ≥100 mg/dL (5.6 mmol/L) but ≤126 mg/dL (7.0 mmol/L) or a 2-h OGTT ≥140 mg/dL (7.8 mmol/L) but ≤200 mg/dL (11.1 mmol/L).

**Results**

There were no statistically significant differences among the patients and control groups with regard to the genotypes and allele frequencies (p>0.05; as shown in Table 3 and 4). In this study, the genotype distributions of all groups were in Hardy-Weinberg equilibrium (T2DM, p=0.05; HT, p=0.09; T2DM+HT, p=0.13; controls p=0.02). The minor genotype TT was not detected in any of the groups. In the T2DM, the CC genotype was found in 130 patients (96.2%) and CT in 5 patients (3.8%); in the HT cohort, CC was found in 66 patients (92.95%) and CT in 5 patients (7.04%); in the T2DM+HT cohort, CC was found in 95 patients (93.13%) and CT in 7 patients (6.86%); and in the control cohort, CC was found in 132 patients (97.77%) and CT in 3 patients (2.22%), as shown in
Table 3. C allele frequencies were identified as 265 (98.14%), 197 (96.56%), 137 (96.47%), 267 (98.88%), while the T allele frequency was 5 (1.86%), 7 (3.44%), 5 (3.53%) and 3 (1.12%) in the T2DM, T2DM+HT, HT and control groups, respectively (shown in Table 4). T allele frequencies were higher in the HT and T2DM+HT groups compared to the T2DM group.

CC genotype frequencies in females were 78 (94%), 94 (94%), 64 (94.1%) and 70 (100%) in the T2DM, T2DM+HT, HT and control groups, respectively. C allele frequencies in females were 5 (6%), 6 (6%), 4 (5.9%) and 0 (0%) in the T2DM, T2DM+HT, HT and control groups, respectively. In males, the C allele frequencies were 104 (100%), 3 (75%), 5 (83.3%) and 127 (97.7%). T allele frequencies in males were 0 (0%), 1 (25%), 1 (16.7%) and 3 (2.3%) in the T2DM, T2DM+HT, HT and control groups, respectively (shown in Table 5).

Our data suggest that a statistically significant association between both the CT genotype and T allele was detected in females with coexistent T2DM + HT (CT genotype: p=0.04; T allele: p=0.045).

When the genotypes of all patients were compared with the demographic characteristics (age, height, sex, weight, BMI, HbA1C, fasting and postprandial blood sugar levels, TSH, FT3, age at onset, duration of disease), their genotypes were not observed in any association (p>0.05). On the other hand, a statistically significant relationship between the CT genotype and the mean values of BMI and free T3 (FT3) was observed only in the T2DM+HT patient group (BMI: p=0.044; FT3: p=0.021). In this group, the mean BMI values in the CC and CT genotypes were 31.4 and 27.5, respectively. The mean values of FT3 in the CC and CT genotypes were 3.285 and 4.176, respectively.

In the control group consisting of 70 female and 65 male healthy subjects, the average age was identified as 38.62, while the standard deviation was 13.97.

**DISCUSSION**

Some recently published papers have reported islet autoimmunity and inflammation as the two most important mechanisms in the pathogenesis of T2DM (23-26). In one study, young people diagnosed with T2DM were reported to express beta-cell auto-antibodies by 10 to 75%. In another study, 11% of young people with clinically diagnosed T2DM, all four auto-antibodies were found (23). Importantly, inflammation is prominent in older cases and inflammatory cytokines such as TNF-α, IL-1, IL-6, MCP-1 and IL-8 have been found to take part in insulin signaling pathways and the progression of insulin resistance (24). The insulin resistance observed in T2DM and obesity is closely associated with low-grade inflammation (25). In view of the fact that autoimmunity and the inflammation associated with autoimmunity have been found to contribute to T2DM progression, and since autoimmunity also plays a major role in HT pathogenesis, it was decided to study the PTPN22 C1858T gene polymorphism in these diseases.
Numerous studies have been performed since Bottini et al. (17) first discovered the influence of the PTPN22 gene on autoimmune diseases (17). PTPN22 is a strong inhibitor of T cell activation and may therefore affect susceptibility to autoimmunity; it has been implicated in a number of autoimmune and inflammatory diseases (17, 27, 28).

The PTPN22 gene is on chromosome 1p13 and encodes for lymphoid-specific phosphatase (LYP), expressed in T and B lymphocytes. LYP negatively modulates T cell antigen receptor (TCR) signaling by binding to the C-terminal Src tyrosine kinase (Csk) and directly dephosphorylating the key Src family signaling molecules kinases Lck, Fyn, ZAP-70 and others (17, 27). The PTPN22 C1858T polymorphism occurs at an important nucleotide position of LYP where it binds to the SH3 domain of Csk. A tryptophan (W) to arginine (R) exchange at codon 620 of the LYP protein (C1858T SNP) impairs LYP binding to Csk, such that Csk and LYP cannot downregulate TCR signaling. Due to the fact that LYP has the capacity to inhibit TCR signaling, post-translational mechanisms are involved in regulating the function of LYP. However, in contrast to downregulating TCR signaling, this mutation makes the protein a stronger inhibitor of T cells, because of a gain-of-function mutation (27). This is surprising because the 1858T variant is expected to increase T cell activation (as in CTLA-4); however, the opposite situation is observed (29). A probable explanation for this may be that a reduced T cell receptor signal may promote the evasion of self-reactive T cells from thymic deletion and thereby allow them to persist in the periphery (30).

In vitro studies suggest that the PTPN22 1858T allele provides less effective binding to Csk than the C allele and decreases the activation of T cell signals; as a result, carriers of the T allele are prone to autoimmune diseases (17). A correlation has been found between the PTPN22 C1858T gene polymorphism with T1DM in a meta-analysis of 11 European populations, with T2DM in an Estonian population, with HT in a German population and with several other autoimmune diseases (16, 17, 30, 31). Thyroid dysfunction is more common in T1DM patients than in T2DM patients (7). In recent publications, this frequency in T1DM has been reported as equal to that in an elderly group of T2DM patients (6, 7). There have been previous studies in which the T2DM and HT groups were examined separately, but to our knowledge no study has examined the PTPN22 C1858T gene polymorphism in a group with coexisting T2DM and HT; this is the first study performed in this group. We found that the frequency of the PTPN22 1858T allele was markedly lower in out Turkish cohort than the frequency in European populations in Finland, Estonia, Germany and Sweden. In the T2DM group in this study, the CT genotype and T allele frequencies were lower than in Estonian (17), Finnish (15, 16) and Swedish (16) T2DM groups. In these T2DM patients, the frequency of the C1858T gene polymorphism was found to be statistically significantly different (15-17). Also, in the HT group in this study, we found that the frequencies of the CT genotype and T allele were lower than in European populations (30, 31). In contrast to this study, Criswell et al. (32) reported that the second highest frequency of the T allele was 14.2% (27 patients) in 194 HT cases of Caucasian origin in America; as a result of the statistical analysis performed by comparing with the control group, the association between HT and the C1858T gene polymorphism was emphasized. In contrast to this, Dolts et al. (30) showed that T allele carriers were more frequent in the T1DM+HT group than in the T1DM group. Similarly, this study detected that T allele carriers were more frequent in the T2DM+HT group than in the T2DM; however, in the present study, T allele carriers and CT genotype frequencies were more frequent in the HT group than in the T2DM+HT group. Therefore, the combination of T2DM and HT is associated with T allele carriage in comparison to the T2DM group. We cannot make this association with the HT group.

Despite the existence of the TT genotype in Caucasian population studies, this genotype was not detected in any of the groups in this study. However, both the TT genotype and the T1858 allele are almost absent in African American and Asian populations. In some published papers, the T allele has been reported to be virtually absent in Japanese, Korean and Chinese populations (27). Recently, a meta-analysis suggested that the PTPN22 C1858T polymorphism is associated with AITD risk, especially in Caucasians than Asian and African American populations (33). These studies performed in different regions and populations have revealed the existence of ethnic differences in connection with the founder effect. A selection advantage in European populations and in individuals with Northern European origins is a possible reason for the T1858 variant distribution in the world; this evidence shows that host genetic factors are important (12, 27). Considering these results, it can be stated that the Turkish population is a transitional group between the populations of Asia and Europe regarding the frequency of distribution of the PTPN22 C1858T single nucleotide polymorphism.

The present study is the first to examine the association between the PTPN22 C1858T gene polymorphism and the T2DM+HT group. Although there were no statistically significant differences between the patient and control groups with regards to genotypes and allele frequencies (p>0.05), the data of this study show that a statistically significant association exists between both the CT genotype and the T allele in female patients with coexistent T2DM+HT and that a statistically significant association exists between the CT genotype and the mean values of BMI and FT3 in the coexistent T2DM+HT patient group. So, the PTPN22 C1858T gene polymorphism is associated with female T2DM+HT patients, which may contribute to increased BMI and FT3 levels. The results of this study suggest that T allele carriers are more common in the T2DM+HT group and in females than in the T2DM group.
and males. Therefore, the coexistence of T2DM and HT and female gender are associated with increased T allele carriage in comparison to the T2DM and male groups.

As a limitation, the sample sizes of the experimental groups in this study were not large enough to evaluate a small impact from very low penetrance genes or SNPs. Further studies with larger cohorts of Turks and other ethnic populations are needed to clarify the etiopathophysiological and functional role of PTPN22 gene expression on T2DM, HT and coexistent T2D+HT.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Firat University (vide No. 05 dated: 24.06.2010)

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.


Conflict of Interest: No conflict of interest was declared by the authors.

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