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The Potential Role of PTPN-22 C1858T Gene Polymorphism in the Pathogenesis of Type 1 Diabetes in Saudi Population

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ABSTRACT

Background: Recent investigations have reported an association between protein tyrosine phosphatase non-receptor type-22 (PTPN-22) gene polymorphism and susceptibility to the development of type 1 diabetes (T1D) in some populations and not in others. In this study, we aimed to investigate the association of PTPN-22 C1858T polymorphism with T1D in Saudi children.

Methods: A cohort of 372 type 1 diabetic children and 372 diabetes-free subjects was enrolled in the current investigation. The PTPN-22 C1858T polymorphism was identified using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method.

Results: Our data showed that the frequency of CT and TT genotypes of PTPN-22 C1858T was higher in T1D children (17.7% and 4.3%, respectively) compared to healthy controls (4.8% and 1.6%, respectively), and both genotypes were statistically associated with T1D patients (OR = 4.4, 95% CI: 2.55–7.58, $p < 0.001$; and OR = 3.2, 95% CI: 1.23–8.28, $p = 0.017$, respectively). Moreover, the 1858T allele was significantly associated with T1D patients compared to the C allele (OR = 3.2, 95% CI: 1.59–6.88, $p < 0.001$). In addition, the T allele was significantly associated with elevated levels of HbA1c, anti-GAD, and anti-insulin antibodies ($p < 0.001$) and a lower concentration of C-peptide ($p < 0.001$) in T1D children.

Conclusion: The data presented here suggests that the T allele of PTPN-22 C1858T polymorphism might be a risk factor for T1D development in Saudi children.

KEYWORDS
PTPN-22 gene polymorphism; Saudi population; Type 1 Diabetes

Introduction

Type 1 diabetes (T1D) is an organ-specific autoimmune disorder caused by immune destruction of β cell, leading to insulin deficiency and entire dependence on exogenously administered insulin. Previous studies have demonstrated that both multiple genetic and environmental risk factors participate in the development of T1D (Rich, 2017). Genome-wide association studies (GWAS) have identified 61 variants (so far) that are associated

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with susceptibility to T1D (Ram and Morahan, 2017). Nevertheless, the specific causative agent remains ill-defined (Ge et al., 2016). The most important genetic loci that confer risk for the disease are HLA loci, which provides about 50% of the genetic susceptibility (Noble et al., 2010); the insulin gene (Bennett et al., 1995); the CTLA-4 gene (Kavvoura and Ioannidis, 2005); the IL-2RA gene (Tang et al., 2015); and most importantly, perhaps, the protein tyrosine phosphatase non-receptor type-22 (PTPN-22) gene (Stanford and Bottini, 2014). The majority of the loci linked with T1D are involved in immune responses as well as in the maintenance of immune tolerance (Atkinson et al., 2014).

PTPN-22 is a non-receptor-type protein tyrosine phosphatase expressed in immune cells, including immature and mature T and B cells, monocytes, macrophages, natural killer (NK) cells, and dendritic cells (DCs) (Burn et al., 2011; Fousteri et al., 2013). PTPN-22 gene is located on chromosome 1p13.3-p13.1 and encodes the lymphoid-specific tyrosine phosphatase (LYP), which is composed of 807 amino acids. In physiologic conditions, LYP binds with the SH3 domain of the C-terminal Src kinase (CSK) via its P1 sequence in the non-catalytic region. The LYP/CSK complex gets anchored to the cytoplasmic side of the cell membrane and inactivates Lck, which positively regulates T-cell receptor (TCR) signaling after antigen recognition (Bottini et al., 2004). Thus, LYP has a tonic inhibitory function toward clonal expansion, T-cell differentiation, and TCR signalling (Gjorloff-Wingren et al., 1999; Hill et al., 2002). LYP function in B lymphocytes is equivalent to that of T lymphocytes (Burn et al., 2011; Rieck et al., 2007). In addition, changed LYP function may affect the functions of Treg cells and their role in suppressing autoimmune reactions (Prezioso et al., 2017). Therefore, it is possible to postulate that PTPN-22 has a pivotal role in controlling the threshold of immune cells activation and consequently the outcomes of immune responses (Bottini and Peterson, 2014; Stanford and Bottini, 2014).

PTPN-22 is the most influential gene outside HLA loci associated with T1D susceptibility (Stanford and Bottini, 2014). A single nucleotide polymorphism (SNP) at position 1858 (rs 2476601, also known as R620W or C1858T) of the encoding sequence of PTPN-22 gene, consisting of the substitution of cytosine by thymine, results in mutation of arginine (R) to tryptophan (W) at codon 620 (R620W) of LYP. As LYP is expressed in many cell types of both innate and adaptive immunities, such mutation could affect the autoimmunity via the regulation of immune cells activation (Begovich et al., 2004). Specifically, this mutation disturbs the LYP–CSK interaction and causes alterations in BCR signal transduction as well as increased resistance to apoptosis (Habib et al., 2012; Rieck et al., 2007). Consequently, this will lead to increased survival of transitional and naive B lymphocytes (Gianchecchi et al., 2013). Indeed, asymptomatic individuals carrying the PTPN-22 1858T allele showed high frequencies of auto-reactive B lymphocytes in their blood comparable to patients with T1D, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) (Menard et al., 2011). In addition, the PTPN-22 1858T allele has been suggested to alter LYP function in Treg cells and may render it less effective in damping autoimmune response, leading to destruction of insulin-producing β cell and consequently a major loss in β-cell function in individuals carrying this allele (Bottini et al., 2006).

Recently, PTPN-22 C1858T polymorphism has received greater attention as a powerful SNP that increases susceptibility to T1D in different ethnic populations, especially European and North American populations (Blasetti et al., 2017; Bottini et al., 2004; Hermann et al., 2006; Kahles et al., 2005; Ladner et al., 2005; Saccucci et al., 2008; Santiago et al., 2007; Smyth et al., 2004; Zhernakova et al., 2005). However, many

investigations did not prove such association in other ethnicities as the majority of those tested were from Asian ethnic groups (Almasi et al., 2014; Baniasadi and Das, 2008; Giza et al., 2013; Kawasaki et al., 2006; Zheng and She, 2005). This investigation aimed to study the potential role of PTPN-22 C1858T SNP (rs2476601) in predisposing Saudi children to T1D. In addition, the association of PTPN-22 C1858T polymorphism with glycemic control, C-peptide, and autoantibodies (AAbs) levels was investigated.

Materials and methods

Subjects

This investigation included 372 T1D children who were recruited between September 2012 and January 2017 at Prince Mansour Military Hospital, Taif, Saudi Arabia. T1D patients were diagnosed according to the criteria of the American Diabetes Association (American Diabetes Association, 2015). All T1D cases were antibody positive for at least one of the three most relevant diabetes-specific AAbs [autoantibodies against insulin (IAAs), glutamic acid decarboxylase antibody (GADA), and islet cell antigen (ICA)]. All of the children recruited were newly diagnosed diabetic patients. Their AAb levels and other blood investigations were obtained at the time of diagnosis and before any treatment was started. In addition, 372 healthy control children (sex and age matched with the T1D children) who had normal glucose tolerance and no family history of autoimmune diseases were recruited as controls. Informed consent for all study participants was obtained from a parent or caretaker, and the study was approved by the Research Ethics Committee of Taif University.

Sample collection

A fresh blood sample (about 100 µL) was collected on Whatman filter paper (Sigma-Aldrich Chemical Co., St. Louis, MO, USA) for PTPN-22 gene analysis (Nasr et al., 2016). Two ml of venous blood sample was collected in EDTA Vacutainer® tubes (Becton Dickinson, Meylan, France) for estimation of glycated hemoglobin (HbA1c), C-peptide, and AAbs.

Estimation of the HbA1c percentage

The HbA1c percentage was estimated at the time of the study using the ARCHITECT/AEROSET system (Abbott Diagnostics). The percent HbA1c is the HbA1c/THb ratio, with a conversion factor to correlate the result with an NGSP-certified high-performance liquid chromatography (HPLC) method.

Quantification of C-peptide and AAbs

Fasting plasma levels of C-peptide were estimated at the time of T1D diagnosis by Biomnis laboratories (Lyon, France) using an electrochemiluminescence technique. IAAs were quantified using radioimmunoassay (RIA), GADAs were estimated using enzyme-linked immunosorbent assay (ELISA), and ICAs were analyzed using indirect immunofluorescence assay in the plasma by Biomnis laboratories (Lyon, France).

DNA preparation

The DNA was extracted from filter paper using a modified version of the Chelex-100 method and stored at −80°C, as previously mentioned in details (Nasr et al., 2013).

Genotyping of PTPN-22 C1858T polymorphism

The samples were genotyped for the PTPN-22 C1858T polymorphism (rs2476601) using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. A region of the PTPN-22 gene (218-bp) containing the C1858T SNP (R620W) was amplified by PCR using genomic DNA. The specific primers used were 5-ACTGATAATGTTGCTTCAACGG-3 and 5-TCACCAGCTTCCTCAACCAC-3, as mentioned elsewhere in details (Giza et al., 2013; Zheng and She, 2005). PCR products were incubated with the restriction enzyme RsaI (Fermentas, Germany) at 37°C overnight. The enzyme cuts the C allele into two fragments of 172 base pairs (bp) and 46 bp, whereas the T allele remains intact (218 bp). The products of digestion are then run through electrophoresis in 2.3% agarose gel.

Statistical analysis

The data were analyzed using statistics software (SPSS©) version 23 for Windows. The one-way analysis of variance (ANOVA) was used to compare the mean of age in years and the levels of HbA1c, GADA, ICA, IAA, and C-peptide between the study groups. The different PTPN-22 genotypes were analyzed using the ANOVA test (Table 2). Logistic regression models were used to analyze the association between the PTPN-22 C1858T gene polymorphism and T1D patients compared to healthy controls (Table 3). p values were considered significant if < 0.05. Overall, the 95% confidence intervals (CI) for odds ratio (OR) that did not cross 1.00 were taken as statistically significant. OR above 1 represents values associated with T1D patients, whereas OR less than 1 represents healthy control group.

Results

Clinical and laboratory characteristics of T1D patients

There was no statistically significant difference between the patient and control groups with respect to age (p value = 1.00). T1D patients showed significantly low fasting C-peptide levels ($p < 0.001$) compared to healthy controls (Table 1). However, levels of HbA1c, GADA, ICA, and IAA were significantly high ($p < 0.001$) in T1D patients compared to healthy controls (Table 1).

Distribution of PTPN-22 C1858T genotypes and allele frequency in the study population

The genotype frequency of PTPN-22 C1858T (rs2476601) was in agreement with the *Hardy–Weinberg equilibrium* in all study groups. The frequency of the TT and CT genotypes showed a statistically significant difference with an increased frequency in T1D patients (4.3% and

Table 1. Distribution analysis for the mean and standard deviation (SD) of age/years, HbA1c, GADA, ICA, IAA, and C-peptide between the study populations.

Type		Age/years	HbA1c	GADA[a]	ICA[b]	IAA[c]	C-peptide
Control	Mean	9.5	4.82	4.1	5.2	2.44	3.01
(n = 372)	SD	1.71	0.25	0.4	5.5	2.08	1.53
T1D	Mean	9.5	8.25	104.9	10.5	19.25	0.62
(n = 372)	SD	1.71	2.24	134.8	23.8	18.18	0.62
p value		1.00	<0.001	<0.001	<0.001	<0.001	<0.001

[a] Values of glutamic acid decarboxylase antibodies (GADA) >30 UI/mL were considered positive
[b] Data of antibodies against β-cell antigens (ICA) expressed as a titer on monkey pancreas, and values > 5 were considered as positive.
[c] Results of anti-insulin antibodies (IAA) expressed as a fixation percentage of a mono-iodine insulin tracer-A14, and concentrations greater than 5.5% were considered as positive.

Table 2. Distribution of PTPN-22 C1858T genotypes and allele frequencies in the study population.

PTPN-22 C1858T genotypes	CC	CT	TT
Healthy controls	348	18	6
(n = 372)	(93.50%)	(4.80%)	(1.60%)
T1D	290	66	16
(n = 372)	(78.00%)	(17.70%)	(4.30%)
Allele frequency	**C**	**T**[‡]	**OR, (95% CI), and *p* value**
Healthy controls	0.96	0.04	
(n = 372)			3.2, (1.59 to 6.88) and <0.001
T1D	0.87	0.13	
(n = 372)			
HWE*	0.6	6.4	

*Hardy–Weinberg equilibrium
[‡]The T allele is statistically associated with T1D patients compared to the C allele.

Table 3. Logistic regression analysis of the PTPN-22 C1858T gene polymorphism in association with T1D patients compared to healthy controls.

PTPN-22 C1858T	OR (95.0% C.I.)	p value
C/C	1.0	
C/T	4.4 (2.55–7.58)	<0.001
T/T	3.2 (1.23–8.28)	0.017

17.7%, respectively) compared to the control group (1.6% and 4.8%, respectively). The T allele frequency was significantly higher in the T1D group compared to the control group (13% versus 4%). The T allele was significantly more likely to be associated with T1D patients compared to the C allele (OR = 3.2, 95% CI: 1.59–6.88, $p < 0.001$) (Table 2).

Logistic regression analysis of the PTPN-22 C1858T gene polymorphism in association with T1D compared to healthy controls

The logistic regression analysis of the PTPN-22 C1858T gene polymorphism showed that the CT genotype was significantly increased in T1D patients compared to the control subjects, specially when we used the CC genotype as reference value (OR = 4.4, 95% CI: 2.55–7.58, $p < 0.001$) (Table 3). In addition, the TT genotype was significantly associated with T1D patients compared to the control group (OR = 3.2, 95% CI: 1.23–8.28, $p = 0.017$) (Table 3).

Table 4. Median, range, and logistic regression analysis of the up normal levels of HbA1c, GADA, ICA, IAA, and C-peptide in association with the T1D patients carrying the T allele compared with other patients carrying non-T allele.

Variables		Median (Range)	OR (95% Confidence Interval)	*p* value
Non-T carrier	HbA1c	5.2 (4.3–8.7)	1.00	
T carrier		11.45 (4.7–19.9)	162 (18.93–386.43)	<0.001
Non-T carrier	GADA	4.19 (1–19)	1.00	
T carrier		4.7 (1–63)	6.25 (2.12–18.44)	0.001
Non-T carrier	ICA	4.34 (1–160)	1.00	
T carrier		4.63 (1–164)	2.16 (0.86–5.43)	0.102
Non-T carrier	IAA	3.9 (1–77)	1.00	
T carrier		6.39 (0.02–77)	36.47 (7.85–169.41)	<0.001
Non-T carrier	C-peptide	1.7 (0.01–7.7)	1.00	
T carrier		0.61 (0.01–7.7)	0.02 (0.00–0.06)	<0.001

The median, range, and logistic regression analysis of the abnormal levels of HbA1c, GADA, ICA, IAA, and C-peptide in association with T1D patients carrying the T allele compared with other T1D patients who are non-T allele carriers

The medians of HbA1c, GADA, and IAA were statistically significantly higher in T1D patients carrying the T allele ($p < 0.001$) compared to non-T allele carriers (Table 4). Furthermore, the median of C-peptide was statistically significantly lower in T1D patients carrying the T allele compared to non-T allele carriers ($p < 0.001$). However, the median of ICA did not show any statistically significant difference between T1D patients carrying the T allele and patients carrying the non-T allele ($p = 0.102$) (Table 4).

Discussion

Recently, PTPN-22 C1858T polymorphism has received great interest as a risk factor for the development of T1D in several populations. However, there is a paucity of data in the Arab and Middle Eastern populations. To the best of our knowledge, the current investigation is the first one addressing the role of PTPN-22 C1858T SNP in susceptibility to T1D in the Saudi population.

Our data showed that the frequencies of CT and TT genotypes of PTPN-22 C1858T SNP are higher in T1D patients (17.7% and 4.3%, respectively) compared to control subjects (4.8% and 1.6%, respectively; Table 2), and both genotypes are significantly associated with T1D patients (Table 3). In concordance with our data, a previous study has demonstrated that the frequency of CT-TT genotypes was 18.7% in Brazilian T1D patients versus 10.6% in the control group (Mainardi-Novo et al., 2013). Recently, Gloria-Bottini et al. have showed an association between the T allele carriers of PTPN-22 and T1D in Italian patients (13.6% in T1D patients versus 6.7% in controls) (Gloria-Bottini et al., 2014). In addition, the frequency of PTPN-22 CT and TT genotypes was high in German children with T1D (Kordonouri et al., 2010). A more recent investigation conducted in a cohort of Caucasian population demonstrated a 17.7% frequency of the PTPN-22 C1858T polymorphism in T1D patients, higher than the frequency in healthy subjects (Blasetti et al., 2017). Moreover, it has been reported that the CT + TT genotypes of PTPN-22 C1858T were more prevalent in T1D patients (19%) compared to control subjects (10.6%) (Gomes et al., 2017). Furthermore, CT and TT genotypes of PTPN-22

C1858T have been found more frequently in T1D patients (10.8% and 5.8%, respectively) compared to the controls (5.9% and 3.0%, respectively) (Giza et al., 2013).

In this case-control study, we found that the PTPN-22 1858T allele is associated with T1D in Saudi children (Table 2). In keeping with this result, the PTPN-22 1858T allele has been confirmed to be associated with T1D in different populations, as shown in Table 5. On the other hand, some investigations have reported no significant association between the 1858T allele and T1D in Greek (Giza et al., 2013), Colombians (Gomez et al., 2005), Hispanics from Colorado (Steck et al., 2006), Iranian (Almasi et al., 2014), Indian (Baniasadi and Das, 2008), Chinese (Zheng and She, 2005), Japanese, and Korean (Kawasaki et al., 2006) populations. These discrepancies may likely be due to either low frequency of the 1858T allele in these populations (Blasetti et al., 2017) or limitations in the design of some studies. However, such conflicted results reflect a wide variation in the C1858T polymorphism among various racial populations.

The mechanism linking PTPN-22 C1858T SNP with the risk for T1D is not fully understood. However, the C1858T variant changes the amino acid at position 620 from an arginine (R) to a tryptophan (W) and disrupts the interaction between LYP and CSK, thus not forming the correct complex (Almasi et al., 2014). Therefore, it has been postulated that this SNP disrupts the mechanism of T lymphocytes deactivation, modifies the thresholds of thymic selection, affects the development and selection of B cells, and immune tolerance, leading to an expansion of auto-reactive T and B lymphocytes (Blasetti et al., 2017; Metzler et al., 2017). In vitro experiments have shown that the 1858T allele binds less efficiently to CSK than the C allele does. Therefore, assuming that T lymphocytes expressing the 1858T allele could be hyper-responsive, carriers of this allele may be prone to autoimmunity (Bottini et al., 2004). In addition, macrophages from the PTPN-22 1858T allele knock-in mouse showed altered morphology, higher expression of MHC class II and B7 molecules, and increased phagocytic ability, which further leads to a potent T-cell activation (Li et al., 2017). Moreover, this PTPN-22 variant alters B-cell-tolerance mechanisms and increased resistance to apoptosis (Habib et al., 2012; Metzler et al., 2017).

Table 5. The frequency of the PTPN22 1858T allele in Saudi population and other different populations.

Population	Controls Subjects (%)	T1D patients (%)	OR at 95% CI	*p* value	Reference
Saudis	4	13	3.2 (1.59–6.88)	< 0.001	Data of this study
Germans	11.3	19.3	1.88 (1.3–2.7)	0.0009	(Kahles et al., 2005)
Dutch	8.7	18.0	2.3 (1.7–3.1)	2×10^{-7}	(Zhernakova et al., 2005)
British	10.4	17.0	1.78 (1.54–2.06)	1.17×10^{-14}	(Smyth et al., 2004)
Finnish	13.9	23.9	Undefined	8×10^{-6}	(Hermann et al., 2006)
Danish	9.0	16.0	1.89 (1.3–2.7)	0.0003	(Nielsen et al., 2007)
Spanish	6.7	10.9	1.71 (1.20–2.45)	0.002	(Santiago et al., 2007)
Italians (Rome)	5.9	11.6	2.09 (1.04–4.22)	< 0.03	(Saccucci et al., 2008)
Italians (Chieti)	5.6	14.6	2.91 (0.89–10.03)	< 0.05	(Saccucci et al., 2008)
Croatians	11.7	28.9	3.06 (1.98–4.7)	< 0.0001	(Korolija et al., 2009)
Polish	11.7	18.6	1.73 (1.19–2.51)	0.004	(Fichna et al., 2010)
Ukrainian	14.1	21.1	1.6 (1.2–2.3)	0.003	(Fedetz et al., 2006)
non-Hispanic whites from Colorado	9.0	16.2	1.94 (1.50–2.51)	< 0.0001	(Steck et al., 2006)
Chinese Han	4.0	10.0	2.81 (1.59–4.95)	< 0.001	(Liu et al., 2015)
North Indians	0.5	2.76	5.93 (1.4–24.8)	0.027	(Kumar et al., 2014)
Iranians	0.0	6.1	Undefined	< 0.001	(Abbasi et al., 2017)
Egyptians	4.8	10.0	2.2 (1.2–4.1)	< 0.01	(Abdelrahman et al., 2016)

The PTPN-22 1858T variant promotes self-reactivity into the naive B-cell repertoire and, consequently, is likely to increase the probability of triggering auto-reactive B-cell response in at-risk subjects (Metzler et al., 2017). It has been suggested that the PTPN-22 1858T allele inhibits TCR signaling, resulting in expansion of auto-reactive T lymphocytes, enhancing hyper-responsive auto-reactive B lymphocytes to produce AAbs, and increasing susceptibility to T1D (Schickel et al., 2016). These findings could explain the association of the 1858T allele with T1D.

Auto-reactive B lymphocytes may play a role in the autoimmune destruction of β cell via the presentation of β-cell antigens to auto-reactive T lymphocytes, which in turn activate B cell to produce AAbs (Marrack and Kappler, 2012). ICA, IAA, and GADA are the most reliable predictive biomarkers of T1D. The appearance of AAbs could precede clinical manifestations of the disease by years (Steck et al., 2016). However, we still lack biomarkers that will reliably indicate the dynamic loss of β cell and predict the emergence of the disease (Galvani and Fousteri, 2017). In this study, T1D patients showed highly significant levels ($p < 0.001$) of GADA, ICA, and IAA compared to control subjects (Table 1). Moreover, the PTPN-22 1858T allele was significantly associated ($p < 0.001$) with elevated levels of both GADA and IAA in T1D patients. However, high levels of ICA were not significantly ($p > 0.05$) correlated with this variant (Table 4). In line with our results, Mainardi-Novo et al. have reported an association between the 1858T allele and increased frequency of GAD AAbs when both T1D patients and healthy controls were taken together (Mainardi-Novo et al., 2013). Similarly, Petrone et al. showed increased levels of GAD AAbs in the 1858T carriers (Petrone et al., 2008b). Another study revealed an association between the 1858T allele and elevated levels of IAA (Hermann et al., 2006), and further studies supported this result (Blasetti et al., 2017; Kumar et al., 2014; Maziarz et al., 2010). These findings indicate that the PTPN-22 1858T allele might be an important marker of disease progression. However, further studies will be needed to elucidate the underlying mechanisms by which PTPN-22 regulates the acquisition and persistence of AAbs (Kumar et al., 2014).

The HbA1c% in our T1D patients was significantly higher ($p < 0.001$) than that of nondiabetic controls. At the same time, C-peptide levels of T1D patients were significantly decreased ($p < 0.001$) compared to controls (Table 1). This result indicates that endogenous insulin secretion is largely reduced due to the progressive destruction of β cell. Indeed, C-peptide secretion could be found at onset, during the so-called remission phase. This endogenous insulin secretion could completely disappear soon after diagnosis or persist over a long period of time (Scholin et al., 2004). Our data showed that the PTPN-22 1858T allele is significantly associated with low levels of C-peptide and high levels of HbA1c in T1D patients (Table 4). Our results are supported by the findings of Petrone et al., who reported that the 1858T allele is significantly associated with low C-peptide levels and worse glycemic control in T1D patients with long duration of the disease (Petrone et al., 2008a). However, these results are in conflict with the findings of other studies, where one demonstrated that the proinsulin/C-peptide ratio was higher in T1D patients carrying CT and TT genotypes with a borderline significance (Nielsen et al., 2011) and the other reported high C-peptide levels at diabetes onset in the 1858T allele carriers (Blasetti et al., 2017). The exact explanation for such discrepant results in not clear and needs further investigation. A possible explanation for these discrepancies is that the 1858T variant has an influence on autoimmunity, which may result from a complex interplay with other genetic loci that regulate the immune responses such as HLA regions and cytokine genes (Allam et al., 2017).

One of the limitations of this study is that it only included children with a positive GADA and IAA AAbs in association with PTPN22 1858T genotypes among the Saudi population (mainly of Arab ethnicity), so our findings may not be generalizable to all children clinically diagnosed with T1D. As such, future studies are needed to clarify this point.

Conclusion

In summary, results of the present study demonstrated an association between the PTPN-22 1858T variant and susceptibility to T1D in Saudi subjects. The data presented here showed a clear association between the T allele and elevated levels of HbA1c, GADA, and IAA in T1D patients. Therefore, we can speculate that the 1858T allele is considered a potential risk factor for T1D development in Saudi children. More investigations are needed to explore the mechanism by which PTPN-22 gene polymorphism contributes in the autoimmune destruction of insulin-producing β cell. This will help in understanding the role of this SNP in the pathogenesis of T1D, early prediction of the disease, and may exploit it as a potential therapeutic target to prevent T1D and other autoimmune diseases.

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Declaration of interest

The authors declare no conflict of interest.

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