Studyof the Association of Protein Tyrosine Phosphatase Non Receptor Type 22 (PTPN22) C1858T Gene Polymorphism with Type 1 Diabetes Mellitus

Thesis

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Abstract

Background: The protein tyrosine phosphatase non receptor 22 gene (PTPN22) is an important negative regulator of signal transduction through the T-cell receptors (TCR). A single-nucleotide polymorphism (SNP) C1858T within this gene was shown to be a risk factor for several autoimmune diseases.**Objectives:** The aim of this study was to analyze a possible association between C1858T SNP of protein tyrosine phosphatase non receptor type 22 (PTPN22) and T1DM.**Subjects and Methods:** The current study evaluated the PTPN22 C1858T polymorphism in 50 previously diagnosed T1DM subjects and 30 healthy age and sex matched subjects with no family history of T1DM or any other types of autoimmune disease. Genotyping was performed by polymerase chain reaction-restriction fragment length polymorphism, HbA1c is determined at the time of the study. **Results:** Statistical comparisons for the distribution of genotypes and allele frequency for the PTPN22 C1858T polymorphism between T1DM patients and controls showed no statistically significant difference. There was a statistically non-significant association between the PTPN22 genotypes and HbA1c, body mass index, and age at onset of T1DM among the patients' group where the *P* values were: 0.951, 0.11 and 0.801 respectively. **Conclusion:** No statistically significant association was found between the PTPN22 C1858T polymorphism and T1DM.

Key words: Type 1 diabetes mellitus, PTPN22, Single-nucleotide polymorphism.

List of Abbreviations

ADA	**:**	American Diabetes Association
APC	**:**	Antigen presenting cell
BCR	**:**	B cell receptor
BMI	**:**	Body Mass Index
CD3ε	**:**	CD3 epsilon
Csk	**:**	C-terminal Src kinase
CTLA4	**:**	Cytotoxic T-lymphocyte-associated protein 4 gene
CYP27B1	**:**	Cytochrome P450, subfamily XXVIIB, polypeptide 1 gene
DM	**:**	Diabetes Mellitus
DSPs	**:**	Dual specific phosphatases
FPG	**:**	Fasting blood glucose
GAD	**:**	Glutamic acid decarboxylase
Grb2	**:**	Growth factor receptor-bound protein 2
HePTP	**:**	Hematopoietic protein tyrosine phosphatase
HLA	**:**	Human leukocyte antigen
HNF	**:**	Hepato nuclear transcription factor
IAA	**:**	Insulin autoantibodies
IFG	**:**	Impaired fasting glucose
IFIH1	**:**	Interferon induced with helicase C domain 1 gene
IFN-γ	**:**	Interferon gamma
IGT	**:**	Impaired glucose tolerance
IL2	**:**	Interleukin-2
IL2RA	**:**	Interleukin-2 receptor alpha gene
INS	**:**	Insulin gene
ITAM	**:**	Immunoreceptor tyrosine activation motif
LADA	**:**	Latent Autoimmune Diabetes in Adults
LAT	**:**	Linker for activation of T cells
LCK	**:**	Lymphocyte protein tyrosine kinase
LMPTP	**:**	Low molecular weight protein tyrosine phosphatase
Lyp	**:**	Lymphoid phosphatase
MAPK	**:**	Mitogen activated protein kinase
MHC	**:**	Major histocompatibility complex

miR-181a	**:**	MicroRNA-181a
MODY	**:**	Maturity-onset diabetes of the young
NEUROD1	**:**	Neurogenic differentiation 1 gene
NK	**:**	Natural killer cell
NRPTP	**:**	Non-receptor like protein tyrosine phosphatase
N-SH2	**:**	Amino-terminal SH2
P value	**:**	Probability value
PEP	**:**	PEST-enriched phosphatase
PEST PTPs	**:**	Proline glutamic acid serine and threonine rich PTPs
PLCγ	**:**	Phospholipase C gamma
PTK	**:**	Protein tyrosine kinase
PTP	**:**	Protein tyrosine phosphatase
PTP-HSCF/BDP1	**:**	PTP hematopoietic stem cell fraction (PTP-HSCF) [also termed brain-derived phosphatase
PTPN22	**:**	Protein tyrosine phosphatase, nonreceptor type 22 gene
RPTP	**:**	Receptor-like protein tyrosine phosphatase
S35	**:**	Serine 35
Ser	**:**	Serine
SES	**:**	Socioeconomic status
SH2	**:**	Src homology 2 domain
SH2B3	**:**	SH2B adaptor protein 3, also known as LNK, lymphocyte adaptor protein gene
SLP-76	**:**	SH2 domain-containing leukocyte protein of 76 kDa
SNP	**:**	Single-nucleotide polymorphism
SSH1	**:**	Slingshot 1
T1DM	**:**	Type 1 diabetes mellitus
TCR	**:**	T cell antigen receptor
TCR-ζ	**:**	T cell receptor zeta chain
Thr	**:**	Threonine
Treg	**:**	Regulatory T cell
Tyr	**:**	Tyrosine
VH-1	**:**	Vaccinia H1 related
VNTR	**:**	Variable number of tandem repeat
ZAP-70	**:**	Zeta-associated protein 70 kDa

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Introduction

Type 1 diabetes Mellitus (T1DM) is an autoimmune disease characterized by autoimmune destruction of the insulin-producing pancreatic β-cells, resulting in a lack or absence of insulin production and disturbed glucose homeostasis ***(American Diabetes Association, 2011).***

Type 1 diabetes mellitus appears to be precipitated by a complex interplay between inherited traits as well as poorly understood environmental factors, although the precipitating factors remain incompletely understood ***(Vang et al., 2007).***

It is clear that genetic predisposition plays a major role and a number of co-inherited susceptibility alleles interspersed throughout the genome have been identified, notably in the HLA class II locus and the genes for insulin (INS), cytotoxic T lymphocyte antigen-4 (CTLA4), and lymphoid tyrosine phosphatase (PTPN22). In addition to these major predisposing genes, numerous minor loci add to the overall risk of T1DM ***(Maier and Wicker, 2005)***.

The most relevant non-HLA genes identified as susceptible for T1DM are those connected with the T-cell mediated immune response. T-cells activity level and their effectors functions are determined by intracellular signaling pathways and related genes, like PTPN22 and CTLA-4, both of which prevent spontaneous activation of auto-reactive cells and development of autoimmunity ***(Bottini, et al.,2006).***

The PTPN22 gene located on chromosome 1p13, encodes the lymphoid tyrosine phosphatase (Lyp), which is expressed exclusively in hemopoietic cells ***(Cohen et al., 1999).***

In T cells, LYP is an important negative regulator of signal transduction through the T-cell receptor (TCR) and forms a complex with the negative regulatory kinase C-SRC kinase (Csk) ***(Cloutier and Veillette, 1999)***. The C1858T variation causes the substitution of an Arg with a Trp in position 620 (R620W), which is located in the LYP–Csk interaction motif. The Arg620Trp substitution strongly reduces the affinity of LYP for Csk ***(Begovich et al., 2004)***. LYP-W620 is a gain-of function form of the enzyme, and carriers of 1858T show reduced signal transduction through the TCR receptor ***(Vang et al., 2005)***.

An association of PTPN22 (R620W) polymorphism was reported first with T1DM ***(Bottini, et al., 2004)***, rheumatoid arthritis ***(Bottini et al., 2004),*** systemic lupus erythematosus ***(Reddy et al., 2005)***, graves' disease ***(Skorka et al., 2005)***, generalized vitiligo ***(Canton et al., 2005)*** and many other autoimmune diseases.

Aim of the Work

Aim of the work was to study the association of protein tyrosine phosphatase non receptor type 22 (PTPN22) C1858T gene polymorphism with type 1 diabetes mellitus.

CHAPTER 1
Diabetes Mellitus