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Association between *PTPN1* Single Nucleotide Polymorphisms and Type 2 Diabetes Mellitus: A Meta-analysis

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Abstract

Background: Previous studies have reported the association of *PTPN1* single nucleotide polymorphisms (SNPs) and type 2 diabetes mellitus (T2DM) incidence. But the results remain inconclusive.

Methods: We performed a meta-analysis on the association between *PTPN1* SNPs and T2DM with pooled studies available. PubMed and EMBASE databases were searched up to June 15 2015. Case-control studies on the association between PTPN1 SNPs and T2DM susceptibility were included. The pooled association strength between PTPN1 SNPs and T2DM susceptibility was measured by odds ratio (OR) with 95% confidence intervals (95% CI) using random-effects model.

Findings: rs2230605(A>G) (A vs G : OR 1.13, 95% CI 0.72-1.78; AG vs AA: 1.17, 0.72-1.91) and rs1689673(148insG) (G vs O: 1.07, 0.93-1.25) were positively associated with T2DM susceptibility, whereas rs2230604(C>T) (TT vs CC: 0.74, 0.47-1.16; CT+TT vs CC: 0.89, 0.79-1.00; TT vs CT+CC: 0.76, 0.48-1.20), rs6126033(C>T) (T vs C: 0.86, 0.64-1.16; CT vs CC: 0.87, 0.66-1.14; TT vs CC: 0.85, 0.24-3.04; CT+TT vs CC: 0.86, 0.64-1.15; TT vs CT+CC: 0.86, 0.24-3.09); and rs2426159(A>G) (GG vs AA: 0.85, 0.65-1.10; AG+GG vs AA: 0.90, 0.75-1.08; GG vs AG+AA: 0.90, 0.74-1.10) were reversely correlated with T2DM.

Conclusions: Most of the SNPs genotyped were located at non-coding regions of *PTPN1*, suggesting that intact PTPN1 protein is essential for individual survival and growth. And the frequently observed reverse correlations between T2DM susceptibility and SNPs within non-coding regions of *PTPN1* suggest that those SNPs have negative impacts on *PTPN1* gene transcription.

Keywords: Type 2 Diabetes mellitus, Insulin, Hyperglycemia

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Introduction

Type 2 Diabetes mellitus (T2DM) is a chronic disease characterized as hyperglycemia in the context of insulin resistance. Rates of T2DM have accelerated markedly since 1960, becoming a global epidemic recognized by the World Health Organization (WHO) [1,2]. With symptoms of excess thirst, frequent urination and constant hunger, T2DM is associated with a ten-year-shorter life expectancy [3]. In T2DM patients, failed response of cells to normal insulin level causes insulin resistance, which triggers liver inappropriately releases glucose into the blood [4]. Evidences have shown that deregulated insulin pathway is the major contributor in insulin resistance [5,6]. Tyrosine-protein phosphatase non-receptor type 1 (PTPN1) negatively regulates insulin signaling pathway by dephosphorylating the phosphotyrosine residues of the activated insulin receptor kinase [7,8]. PTPN1 is considered a promising therapeutic target for the treatment of T2DM [9].

Initially, Bowden et al. observed evidence for association of the PTPN1-containing chromosomal region with T2DM [10], which has led scientists to evaluate the PTPN1 gene for association with T2DM. Efforts have been made to identifying T2DM associated single nucleotide polymorphisms (SNPs) of PTPN1, whereas the inconsistent and controversial results make linkages of these SNPs with T2DM remain inconclusive [11-17]. To evaluate the correlation between PTPN1 genetic polymorphism and T2DM susceptibility, a meta-analysis was performed to systematically

review the published studies focusing on associations of PTPN1 SNPs and T2DM.

Methods

Literature searching strategy

In order to get as many relative studies as possible, extensive literature searching in PubMed and CNKI was performed without language restriction using key words "PTPN1'' or "PTPN1B " in combination with "SNP" or "Single Nucleotide Polymorphism" or/and "T2DM" or "Type 2 Diabetes". The last research was conducted on June 15, 2015. Reference list of selected citations were also checked for any eligible studies left behind.

Inclusion and exclusion criteria

Eligible studies were selected according to the following criteria: full text case-control studies; investigating the association between PTPN1 SNPs and clinically diagnosed T2DM, not insulin resistance phenotypes or impaired glucose tolerance; SNPs distribution within Hardy-Winberg equilibrium (HWE); providing detail genotype frequencies. The eligibility of each citation was performed by two reviewers independently according to the inclusion criteria.

Data extraction

The following data was extracted from each eligible study: name of the first author, publication year, country where the study was carried out, ethnicity, genotyping method, origin of control, genotyped SNPs, HWE, number of cases and controls, number of different genotypes in cases and controls. Data extraction was conducted by two reviewers independently.

Statistical analysis

The association strength between PTPN1 SNPs and T2DM susceptibility was measured by odds ratio (OR) with 95% confidence intervals (95% CI). The pooled ORs were obtained by random effects meta-analysis in allele (2 vs 1), heterozygote (12 vs 11), homozygote (22 vs 11), dominant (12+22 vs 11), and recessive model (22 vs 12+11) [18], respectively (2 represents minor allele). Influence analyses were conducted to determine the effect of individual study on pooled results and test the reliability of results [19]. I-squared was used to indicate the proportion of heterogeneity between studies in total variation. Meta-regression was performed to detect the source of heterogeneity [20] For meta-regression analysis, the genotyping methods were divided into two groups: sophisticated instrument aided (SIA) (metrix-assisted laser desorptio ionization-time of flight mass spectroscopy using a sequenom platform, SNPLexTM, or SNaPshot) and non-SIA (RFLP or Bi-PASA PCR); origins of control were classified into sex and age matched and non-sex and age matched; sample size was grouped into two: <1000 and >1000 subjects. Publication bias was detected with Begg's and Egger's test [21] and $p<0.05$ was considered significant. All the statistical analysis was performed with STATA software.

Results

Characteristic of eligible studies

We identified 13 case-control datasets from 8 citations [11-18] **(Figure 1)**. Characteristics of the eligible datasets were summarized in **Table 1** and **Supplementary Table 1**. Only one study was performed in Chinese Han population, whereas the rest were studies of Caucasian. Most of the citations were published in English, the rest two were published in Chinese and Spanish. T2DM cases were diagnosed using oral glucose tolerance test (OGTT) with the criteria of WHO. Blood samples were used for DNA extraction and genotyping in all studies. HWE distribution of genotypes was tested for all SNPs and most of them were in consistent with HWE except for rs914458(C>G) reported by Cheyssac et al. [13] and rs4811078 and rs2426158 reported by Bento et al. [22] SNPs deviated from HWE were excluded from meta-analysis. Twenty two PTPN1 SNPs were studied among these datasets.

Meta-analysis results

For most of these SNPs, meta-analysis was performed in allele, heterozygote, homozygote, dominant, and recessive model, respectively, whereas only allele and/or heterozygote model were conducted for those SNPs without homozygote cases **(Supplementary Table 2)**. We observed increased risk of T2DM susceptibility to rs2230605 (A>G) (A vs G : OR 1.13, 95% CI 0.72-1.78; AG vs AA: 1.17, 0.72-1.91), and rs1689673(1484insG) (G vs O: 1.07, 0.93-1.25) **(Table 2)**. Mild positive associations with T2DM incidence were found in rs3787345(T>C), rs6020594(A>G) **(Table 2)**. Interestingly, some SNPs were found to be reversely correlated with T2DM susceptibility. Strong reverse correlation with T2DM was observed in rs2230604(T vs C: OR 0.90, 0.80-1.00; CT vs CC: OR 0.90, 0.80-1.02; TT vs CC: OR 0.74, 0.47-1.16; CT+TT vs CC: OR 0.89, 0.79-1.00; TT vs CT+CC: OR 0.76, 0.48-1.20) and rs6126033(T vs C: OR 0.86, 0.64-1.16; CT vs CC: OR 0.87, 0.66-1.14;

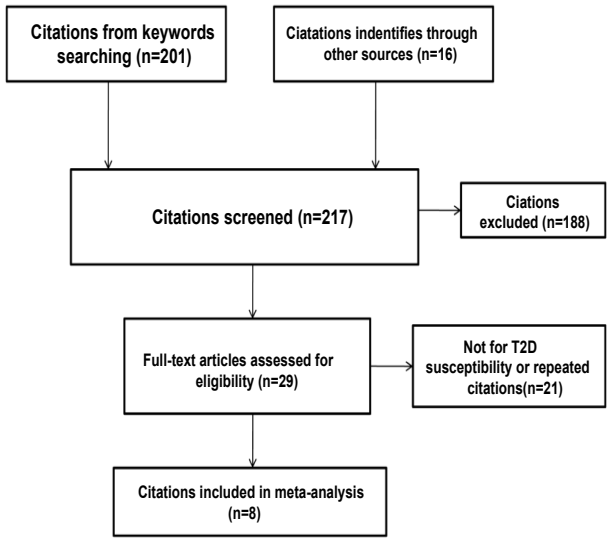

Figure 1 Changes in slow-absorbing suture durability loss and adhesion strength ingrowth with time.

Table 1 Characteristics of the eligible studies.

Author	Location/ Ethnicity	Cases/ Controls	SNPs studied	Genotyping Method	HWE	Gender	Diagnostic Method of Diabetes
Anaya et al. [16]	Peru/Peruvian	93/123	rs914458(C>G)	PCR and ABI Prism 310	Yes	Mixed	Diagnosed from hospital
Bodhini et al. [11]	India/Indian	262/249	rs941798(A>G) rs3787345(T>C) rs2230604(C>T) rs2282147(C>T) rs718049(T>C) rs718050(G>A) rs1689673(148insG)	PCR-RFLP	Yes	Mixed	Fasting plasma glucose>=7 mmol/L or 2 h postglucose value>=11.1 mmol/L
Ding et al. [17]	China/Han population	108/102	rs2230605(A>G)	Bi-PASA PCR	Yes	Mixed	Fasting blood-glucose>=7.8 mmol/L, 2h OGTT>= 11.1 mmol/L
Traurig et al. [12]	India/Pima Indian	573/464	rs3787345(T>C) rs2282147(C>T) rs718050(G>A) rs6020546(C>T) rs718630(T>G) rs3787335(T>G) rs1570179(C>T) rs754118(C>T) rs968701(A>G) rs3787348(G>T)	SNPlex	Yes	Mixed	OGTT using the criteria of the WHO
Małodobra et al. [18]	Poland/Polish	48/50	rs1689673(148insG)	PCR SNaPshot	Not mentioned	Mixed	
Cheyssac et al. [13]	France/French	325/311	rs941798(A>G) rs3787345(T>C) rs718050(G>A) rs3787335(T>G) rs1570179(C>T) rs754118(C>T) rs914458(C>G) rs6020563(T>G) rs6126033(C>T) rs2426159(A>G)	SNPlex	Yes Except rs914458	Mixed	Fasting plasma glucose>=7 mmol/L; or treatment by antidiabetic agents and IGF as as fasting plasma glucose between 6.2-6.9 mmol/L
Cheyssac et al. [13]	France/French	902/736	rs941798(A>G) rs3787345(T>C) rs718050(G>A) rs3787335(T>G) rs1570179(C>T) rs754118(C>T) rs914458(C>G) rs6020563(T>G) rs6126033(C>T) rs2426159(A>G)	SNPlex	Yes Except rs914458	Mixed	Fasting plasma glucose>=7 mmol/L; or treatment by antidiabetic agents and IGF as as fasting plasma glucose between 6.2-6.9 mmol/L
Bento et al. [14]	USA/American	575/510	rs941798(A>G) rs3787345(T>C) rs2282147(C>T) rs718049(T>C) rs718050(G>A) rs1689673(148insG) rs754118(C>T) rs3787348(G>T)		Yes except rs4811078 and rs2426158	Mixed	Not mentioned

Florez et al. [15]	USA/ Scandinavia	471/471	rs2230605(A>G) rs941798(A>G) rs3787345(T>C) rs2230604(C>T) rs2282147(C>T) rs718049(T>C) rs718050(G>A) rs6020546(C>T) rs718630(T>G) rs754118(C>T) rs968701(>-G) rs3787348(G>T) rs914458(C>G) rs6067484(A>G) rs6020594(A>G) P387L(T>C) 1484insG(O>G)	metrix-assisted laser desorptio ionization-time of flight mass spectroscopy using a sequenom platform	Yes	Mixed	OGTT
Florez et al. [15]	USA/Sweden	514/514	Same as above	Same as above	Yes	Mixed	OGTT
Florez et al. [15]	USA/GCI U.S.	1226/1226	Same as above	Same as above	Yes	Mixed	OGTT
Florez et al. [15]	USA/GCI Poland	1009/1009	Same as above	Same as above	Yes	Mixed	OGTT
Florez et al. [15]	USA/Canada	127/127	Same as above	Same as above	Yes	Mixed	OGTT
Total		6233/5892					

Table 2 Meta-analysis results for SNPs prone to T2DM.

SNP	Model type	Number of datasets	OR	95% CI	I-squared	p_h
rs2230605(A>G)	Allele (G/A)	4	1.13	[0.72-1.78]	58.00%	0.067
	Heterozygote (AG/AA)		1.17	[0.72-1.91]	55.10%	0.083
rs1689673(148insG)	Allele (G/O)	8	1.07	[0.93-1.25]	26.20%	0.22
	Heterozygote(OG/OO)		1.02	[0.89-1.17]	0.00%	0.693
rs6020594(A>G)	Allele (G/A)	5	1.03	[0.67-1.58]	56.20%	0.058
	Heterozygote (AG/AA)		1.03	[0.68-1.56]	53.20%	0.074
rs3787345(T>C)	Allele (C/T)	10	1.03	[0.95-1.11]	40.60%	0.087
	Heterozygote (TC/TT)		1.01	[0.92-1.10]	0.00%	0.504
	Homozygote (CC/TT)		1.05	[0.92-1.21]	30.70%	0.163
	Dominant (TC+CC/TT)		1.02	[0.92-1.13]	26.40%	0.201
	Recessive (CC/TC+TT)		1.05	[0.96-1.14]	0%	0.444

TT vs CC: OR 0.85, 0.24-3.04; CT+TT vs CC: OR 0.86, 0.64-1.15; TT vs CT+CC: OR 0.86, 0.24-3.09) **(Table 3)**. Relatively mild reverse associations with T2DM incidence were found for rs718049(T>C), rs718050(G>A), rs6020546(C>T), and rs718630(T>G) **(Table 2).** No obvious associations with T2DM susceptibility were observed for the rest SNPs.

Heterogeneity

Heterogeneity between studies was low for most of SNPs concerned. For those comparisons with greater than 40% I-squared values, we investigated the source of heterogeneity by genotyping method, source of control, and sample size with meta-regression analysis. Meta-regression results revealed sample size and source of control, rather than genotyping method, contributed to the source of heterogeneity. Sample size could explain 8%, 12%, 11%, 12%, and 9% of the between studies variance for rs941798(A>G) (allele model), rs941798(A>G) (homozygote model), rs2282147(C>T) (allele model), rs2282147(C>T) (homozygote model), and rs754118(C>T) (allele model), respectively **(Table 4)**. Source of control could explain 32% and 100% of the variance for rs3787345(T>C) (allele model) and rs718049(T>C) (allele model) **(Table 4)**.

Sensitivity analysis and publication bias

For SNPs with at least 7 datasets, sensitivity analysis was performed to explore influence of individual study on the pooled results. The results showed that no individual study affected the pooled OR significantly for the SNPs studied (Data not shown). Publication bias was evaluated by Begg's and Egger's test. No significant bias was observed (p>0.05) **(Table 5)**.

Discussion

In this meta-analysis, 13 eligible datasets containing 6233 T2DM cases and 5892 control subjects, were included and analyzed. Overall 22 SNPs of PTPN1 were investigated. Most of *PTPN1* SNPs genotyped are located within non-coding regions. Our meta-analysis confirmed limited number of *PTPN1* SNPs associated with T2DM susceptibility. rs1689673(148insG) and rs2230605(A>G)

Table 3 Meta-analysis results for SNPs reversely correlated to T2DM.

SNP	Model type	Number of datasets	OR	95% CI	I-squared	p
rs2230604(C>T)	Allele (T/C)	6	0.90	[0.80-1.00]	0.00%	0.857
	Heterozygote (CT/CC)		0.90	[0.80-1.02]	0.00%	0.893
	Homozygote (TT/CC)		0.74	[0.47-1.16]	0.00%	0.99
	Dominant (CT+TT/CC)		0.89	[0.79-1.00]	0.00%	0.848
	Recessive (TT/CT+CC)		0.76	[0.48-1.20]	0%	0.994
rs718049(T>C)	Allele (C/T)	7	0.92	[0.84-1.00]	41.40%	0.115
	Heterozygote (TC/TT)		0.93	[0.84-1.02]	0.00%	0.603
	Homozygote (CC/TT)		0.84	[0.71-1.01]	36.70%	0.149
	Dominant (TC+CC/TT)		0.90	[0.81-1.01]	24.90%	0.239
	Recessive (CC/TC+TT)		0.95	[0.84-1.06]	0%	0.943
rs718050(G>A)	Allele (A/G)	10	0.94	[0.88-1.00]	22.70%	0.234
	Heterozygote (GA/GG)		0.94	[0.87-1.02]	0.00%	0.841
	Homozygote (AA/GG)		0.89	[0.79-1.01]	9.90%	0.352
	Dominant (GA+AA/GG)		0.93	[0.86-1.01]	0.00%	0.514
	Recessive (AA/GA+GG)		0.93	[0.84-1.02]	0%	0.54
rs6020546(C>T)	Allele (T/C)	6	0.89	[0.74-1.08]	73.80%	0.002
	Heterozygote (CT/CC)		0.90	[0.74-1.09]	66.10%	0.012
	Homozygote (TT/CC)		0.95	[0.66-1.36]	32.70%	0.203
	Dominant (CT+TT/CC)		0.89	[0.72-1.09]	71.90%	0.003
	Recessive (TT/CT+CC)		0.99	[0.73-1.32]	7%	0.367
rs718630(T>G)	Allele (G/T)	6	0.95	[0.90-1.03]	0.00%	0.776
	Heterozygote (TG/TT)		0.96	[0.86-1.06]	0.00%	0.96
	Homozygote (GG/TT)		0.93	[0.82-1.06]	0.00%	0.8
	Dominant (TG+GG/TT)		0.95	[0.85-1.05]	0.00%	0.875
	Recessive (GG/TG+TT)		0.96	[0.86-1.08]	0%	0.891

Table 4 Meta-regression analysis.

SNP	Model	I-squared	Tau-squared	Genotyping		Source of control		Sample size	
				Tau-squared	p	Tau-squared	p	Tau-squared	p
rs941798(A>G)	Allele	47.10%	0.0064	0.008	0.406	0.010	0.889	0.006	0.181
	Homozygote	44.50%	0.0239	0.028	0.378	0.036	0.920	0.021	0.173
rs3787345(T>C)	Allele	40.60%	0.0052	0.006	0.482	0.004	0.168	0.007	0.963
rs2282147(C>T)	Allele	46.40%	0.0067	0.009	0.564	0.007	0.366	0.006	0.193
	Homozygote	40.00%	0.0239	0.028	0.430	0.021	0.372	0.021	0.188
rs718049(T>C)	Allele	41.40%	0.0054	0.008	0.646	0.000	0.060	0.006	0.339
rs6020546(C>T)	Allele	73.80%	0.0369	0.034	0.309	0.034	0.309	0.049	0.962
	Heterozygote	66.10%	0.0353	0.031	0.267	0.031	0.267	0.050	0.993
	Dominant	71.90%	0.0435	0.040	0.301	0.040	0.301	0.058	0.995
rs754118(C>T)	Allele	43.20%	0.0055	0.008	0.570	0.007	0.447	0.005	0.218
rs3787348(G>T)	Allele	50.70%	0.0071	0.010	0.508	0.008	0.395	0.009	0.498
	Homozygote	47.90%	0.0263	0.038	0.563	0.025	0.340	0.032	0.464

were positively associated with T2DM susceptibility, whereas rs2230604 (C>T), rs6126033(C>T), and rs2426159(A>G) were reversely associated with T2DM susceptibility.

Our results confirmed the associations of rs1689673(148insG) with T2DM susceptibility, which are consistent with several case-control studies. Paola et al. identified 1484insG(a variation in 3'UTR of *PTPN1*) in two Italian populations, and 1484insG was further found to be associated with several features of insulin resistance [23]. Subjects carrying 1484insG showed over-expressed *PTPN1* mRNA in skeletal muscle. As PTPN1 is a negative regulator of the insulin signaling pathway, elevated expression of PTPN1 caused by 1484insG would lead to insulin resistance and T2DM susceptibility. Our pooled meta-analysis found no association of T2DM susceptibility with rs941798, rs754118, rs2282147, and rs3787348, which were reported as T2DM associated SNPs in the study of two independently ascertained collections of Caucasian subjects [22].

Our results showed that several SNPs [rs2230604(C>T), rs6126033(C>T), rs718049(T>C), rs2426159(A>G), rs718050 (G>A), rs6020546(C>T), and rs718630(T>G)] displayed reverse correlations with T2DM, indicating those SNPs are protective. Interestingly, rs6126033(C>T), rs718049(T>C), rs2426159(A>G),

Table 5 Begg's and Egger's test.

SNP	Number of datasets	p values for Begg's Test					p values for Egger's Test				
		Allele	Heterozygote	Homozygote	Dominant	Recessive	Allele	Heterozygote	Homozygote	Dominant	Recessive
rs941798(A>G)	9	0.75	0.92	0.45	0.75	0.92	0.99	1.00	0.98	0.98	0.98
rs3787345(T>C)	10	0.37	1.00	0.28	0.59	0.59	0.39	0.74	0.39	0.53	0.45
rs2282147(C>T)	8	0.90	1.00	0.90	1.00	0.90	0.91	0.85	0.95	0.88	0.87
rs718049(T>C)	7	1.00	0.55	1.00	0.55	0.76	0.40	0.21	0.45	0.22	0.83
rs718050(G>A)	10	0.59	0.59	0.47	0.37	0.86	0.33	0.07	0.38	0.10	0.85
rs754118(C>T)	9	1.00	1.00	0.75	1.00	0.75	0.72	0.78	0.70	0.74	0.68
rs3787348(G>T)	7	0.76	1.00	1.00	1.00	1.00	0.57	0.51	0.59	0.58	0.51
rs914458(C>G)	8	0.54	0.17	0.90	0.39	0.90	0.65	0.24	0.77	0.42	0.57

Only SNPs with at least 7 datasets were included for Begg's and Egger's test.

and rs718050(G>A) are intron variants, while rs6020546(C>T) and rs718630(T>G) are promoter variants. Intron variants might lead to impaired intron splicing followed by translation of PTPN1 mutant proteins. Reports have shown that some introns also possess transcriptional regulation activity [24-27], so both intron and promoter variants of *PTPN1* might suppress the transcription of *PTPN1* gene, resulting in active insulin signaling. Future investigations are needed to validate these hypotheses.

Due to limited number of datasets, we didn't stratify the datasets by ethnic group, genotyping method, source of control, or sample size. So any potential OR differences caused by these influential factors could not be distinguished. For most SNPs investigated, we didn't observed high heterogeneity between studies. Our meta-regression analysis indicates that different genotyping methods didn't contribute into the heterogeneity between studies, whereas the source of control and sample size were the influential factors to the pooled estimates. Adoption of sex- and age-matched control could partially avoid inclusion of unnecessary heterogeneity, and bigger sample size could make the statistics more authentic and convincing.

Of the 22 SNPs investigated, 19 SNPs are located in the non-coding regions of *PTPN1* **(Supplementary Table 2)**. Of the 3 SNPs located in exons, only one SNPs leads to amino acid substitution. The disequilibrium distributions of SNPs between coding and non-coding region indicates that intact PTPN1 protein is essential for individual survival and growth. We hypothesized that, compared with SNPs in non-coding regions, individuals carrying SNPs in coding regions tended to be eliminated during evolution. So we suggest that underlying mechanism of *PTPN1* SNPs with T2DM susceptibility is more likely at gene transcription level.

In conclusion, our pooled meta-analysis produced more authentic and convincing results on T2DM associated *PTPN1* SNPs. More genetic studies are needed to validate the biological effects of those *PTPN1* SNPs at molecular level. The T2DM associated SNPs also have great guiding significance for therapeutic strategy development in clinical T2DM treatment.

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