Original Article

Association of Protein Tyrosine Phosphatase Receptor Type D and Serine Racemase Genetic Variants with Type 2 Diabetes in Malaysian Indians

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Abstract

Introduction: Type 2 diabetes (T2D) candidate genes, protein tyrosine phosphatase receptor type D (PTPRD), and serine racemase (SRR) were suggested by a genome-wide association study (GWAS) in the Chinese population. Association studies have been replicated among East Asian populations. The association of PTPRD and SRR genetic variants with T2D in Southeast Asian populations still needs to be studied. This study aimed to investigate the association of PTPRD and SSR genetic variants with T2D in Malaysian Indian subjects. **Methods:** The single nucleotide polymorphisms (SNPs) of PTPRD (rs649891 and rs17584499) and SRR (rs4523957, rs391300, and rs8081273) were genotyped in 397 T2D and 285 normal Malaysian Indian subjects. **Results:** The homozygous dominant genotype of rs17584499 is frequent in diabetic patients (56.5%) compared to normal subjects (47.3%). In contrast, the homozygous recessive genotype of rs8081273 is more frequent among normal subjects (12.5%) than diabetic patients (5.6%). The dominant genetic model showed that PTPRD rs17584499 (CC) is a risk factor for T2D (OR = 1.42, $P = 0.029$), whereas the recessive genetic model showed that SRS SNP rs8081273 was protective for T2D (OR = 0.42, $P = 0.003$). **Conclusion:** This study confirmed the association of PTPRD rs17584499 genetic variations with T2D in Malaysian Indians. While the SRR rs8081273 (TT) genotype showed protection against T2D, more investigation in different populations is required to confirm this protection.

Keywords: Genetic variation, risk factors, single-nucleotide polymorphism, type 2 diabetes mellitus

Introduction

Diabetes is the most common metabolic disease affecting 537 million people (10.5%) worldwide in 2021, and it is predicted that the total number of people living with diabetes will increase to 783 million by 2045.[1] Type 2 diabetes (T2D) mellitus is a heterogeneous group of disorders that display relative insulin deficiency and is usually associated with obesity, insulin resistance, impaired insulin secretion, and increased hepatic glucose production.[2] Both genetic susceptibility and environmental factors likely contribute to the development of T2D.[3]

A new approach known as genome-wide association (GWAS) study has been applied to complex diseases such as T2D and resulted in the identification of 1,791 susceptibility loci for T2D.[4] Protein tyrosine phosphatase receptor type D (PTPRD) (chromosome 9) has been suggested to be associated with T2D.[5,6] Another GWAS study in Mexican-Americans with 837 T2D cases and 436 normoglycemic controls, followed by a meta-analysis, revealed such an association with PTPRD.[7] The PTPRD is a protein tyrosine phosphatase that may affect insulin signaling in its target cells.[6] In another study, the PTPRD genetic variant was suggested to be associated with progression to diabetes in Han Chinese, most likely through increased insulin resistance.[5] The levels of PTPRD were significantly decreased in patients

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with T2D, and this protein is involved in the insulin signaling pathway.[8]

The serine racemase gene (SRR) is located on chromosome 17 and has been suggested to be associated with T2D (5) and gestational diabetes in Chinese.[9] The association of SRR genetic variations with T2D was not replicated in another study.[10] The SRR encodes a serine racemase enzyme that synthesizes D-serine from L-serine. D-serine is a co-agonist of glutamate signaling, which regulate insulin and glucagon secretion in pancreatic islets and thus may play a role in the etiology of T2D.[6]

Recently, Raza *et al*.[11] reported that the downregulated expression of the SRR gene is associated with the pathophysiological development of T2D and metabolic disorders. The transcriptome of EndoC-βH1 cells with SRR knockdown has been reported to be involved in decreased insulin secretion and T2D development.[12] Decreased expression of SRR significantly affects insulin secretion from human EndoC-βH1 cells.[13] A recent study showed that chronic d-serine supplementation impairs insulin secretion.[14]

The association of PTPRD and SRR genetic variants with T2D was conducted in the Chinese population, while the Southeast Asian population still needs to be studied, as will the controversial studies on the association of SRR with T2D, thus we aimed to investigate the association of PTPRD and SSR genetic variants with T2D in Malaysian Indian subjects.

Methods

Data sources

The Malaysian Indian patients previously diagnosed with T2D who attended the Malaya Medical Centre (UMMC) Kuala Lumpur for treatment were invited to participate in this study (case group). Malaysian Indians who enrolled for a health check-up at UMMC were approached to participate in this study (control group). All participants recruited in this study were Malaysian Indians aged 30–70 years old. Fasting venous blood (10 mL) was collected from each subject into a plain tube for biochemical analysis and a K2 EDTA tube for genetic analysis and HbA1c measurement. The blood pressure (BP) of each participant was measured by Omron IntelliSense Automatic Blood Pressure. The weight and height of all participants were measured, and BMI was calculated. The waist circumference of each participant was measured midway between the lower rib margin and the superior iliac spine in a standing position.

Genetic analyses

Genomic DNA was isolated from peripheral blood leukocytes as instructed by the manufacturer using a commercial Wizard Genomic DNA Purification Kit (Promega Corporation, Madison, WI, USA). The PTPRD (rs649891 and rs17584499) and SRR (rs4523957, rs391300, and rs8081273) SNPs were genotyped by predesign Taqman genotype assay (Applied Biosystems Inc, Foster City, USA) according to the manufacturer's protocol using the StepOnePlus Real-Time PCR system (Applied Biosystems Inc, Foster City, USA). No template control (NTC) was included in each real-time PCR run as quality control to exclude DNA contamination.

Biochemical analyses

Fasting blood glucose (FBG), glycated hemoglobin (HbA1c), triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol were measured by an automated analyzer Dimension RxL Max Integrated Chemistry System (Siemens Healthcare Diagnostics Inc. Deerfield, IL USA).

Statistical methods

The SNPs deviations from the Hardy-Weinberg equilibrium were analyzed online (http://shesisplus.bio-x.cn/SHEsis.html). The other statistical analyses were performed by IBM SPSS 22 program (SPSS, Inc, Chicago, USA). The associations of the SNPs with T2DM were evaluated by recessive, dominant, and additive genetic models using logistic regression controlled by age, gender, and body mass index.

Ethical aspects

This study was approved by the Medical Ethics Committee of the University Malaya Medical Centre (Reference No. 387.15). A written consent form was obtained from each participant.

Results

Three hundred ninety-seven T2D and 285 normal Malaysian Indian subjects signed the consent forms and donated blood. The demography and biochemical parameters of the subjects are depicted in Table 1. The T2D subjects had higher BMI, larger waist circumference, high FBG, and HbA1c, all of which were consequences of T2D. The total cholesterol, HDL-c, and LDL-c were lower in T2D patients compared to normal subjects, whereas there were no differences between normal and T2D subjects in age, triglyceride, systolic, and diastolic blood pressure.

The Hardy-Weinberg equilibrium, call rates, and SNP positions of the included SNPs in this study are depicted in Table 2. Table 3 shows the allele and genotype frequencies of PTPRD SNPs (rs649891 and rs17584499) and SRR SNPs (rs4523957, rs391300, and rs8081273) in normal subjects and diabetic patients. There were no differences in the allelic and genotype frequencies of included SNPS between the normal subjects and diabetic patients except the frequencies of rs8081273 homozygous recessive and rs17584499 homozygous dominant. The rs8081273 homozygous recessive is more frequent among normal subjects (12.5%) than diabetic patients (5.6%), whereas the rs17584499 homozygous dominant is more frequent among diabetic patients (56.5%) compared to normal subjects (47.3%).

The recessive, dominant, and additive genetic models were applied to analyze the association of rs17584499, rs649891, rs4523957, rs391300, and rs8081273 with T2D [Table 4]. The dominant genetic model showed that PTPRD rs17584499 (CC) is a risk factor for T2D (OR = 1.42, $P = 0.029$), whereas rs649891,

Table 1: Biochemical characterization of normal and type 2 diabetic Malaysian Indian subjects

	Normal subjects *n*=269 Mean±STD	Diabetic subjects *n*=362 Mean±STD	*P*
Age (years)	51.6±9.5	52.0±8.6	0.588
Body mass index (BMI)	26.5±4.4	27.5±5.3	0.014
Waist (cm)	93.1±11.5	97.8±11.8	8.05×10^{-7}
Systolic blood pressure (mmHg)	132±19	131±16	0.935
Diastolic blood pressure (mmHg)	82±11	81±10	0.409
Fasting blood glucose (mmol/l)	5.23±0.60	8.29±3.26	1.37×10^{-44}
Glycated hemoglobin (%)	5.7±0.42	8.2±1.84	6.89×10^{-51}
Total cholesterol (mmol/l)	5.21±1.0	4.73±1.09	1.82×10^{-8}
High-density lipoprotein cholesterol (mmol/l)	1.16±0.26	1.06±0.24	1.08×10^{-6}
Low-density lipoprotein cholesterol (mmol/l)	3.35±0.96	2.90±0.97	1.86×10^{-8}
Triglycerides (mmol/l)	1.60±0.80	1.70±0.99	0.1288

STD, standard deviation of the mean

Table 2: Hardy-Weinberg equilibrium, call rate, and SNP position

PTPRD SNPs	*P* value in diabetic patients	*P* value in normal control	Call rate	SNP Position Chromosome 9*
rs17584499	0.004	0.618	0.966	8,869,118
rs649891	0.98	0.555	0.95	10,420,602
SSR SNPs	***P* value in case**	***P* value in control**	**Call rate**	**SNP Position Chromosome 17***
rs4523957	0.004	0.042	0.963	2,155,649
rs391300	0.534	0.554	0.969	2,163,008
rs8081273	0.00014	0.872	0.951	2,169,075

*Location on chromosome based on dbSNP Hap-Map (forward strand at NCBI build 36). PTPRD, protein tyrosine phosphatase receptor type D gene; SSR, serine racemase gene

Table 3: Frequencies SSR and PTPRD single nucleotide polymorphisms among normal and diabetic subjects

	Normal *n*=285				Diabetic *n*=397			
	Minor allele (frequency %)	Homozygous recessive *n* (%frequency)	Heterozygous *n* (%frequency)	Homozygous dominant *n* (%frequency)	Minor allele (%frequency)	Homozygous recessive *n* (%frequency)	Heterozygous *n* (%frequency)	Homozygous dominant *n* (%frequency)
PTPRD SNPs								
rs17584499	T (28.3)	TT 11 (4.0)	CT 134 (48.7)	CC 130 (47.3)	T (24.2)	TT 19 (4.9)	CT 148 (38.5)	CC 217 (56.5)
rs649891	A (48.3)	AA 63 (23.1)	AG 138 (50.5)	GG 72 (26.4)	A (49.7)	AA 98 (26.1	AG 177 (47.2)	GG 100 (26.7)
SSR SNPs								
rs4523957	T (43.9)	TT 66 (24.3)	GT 107 (39.3)	GG 99 (36.4)	T (43.5)	TT 85 (22.1)	GT 165 (42.9)	GG 135 (35.1)
rs391300	G (42.7)	GG 55 (19.9)	AG 126 (45.7)	AA 95 (34.4)	G (41.0)	GG 70 (18.2)	AG 176 (45.7)	AA 139 (36.1)
rs8081273	T (27.3)	TT 34 (12.5)	CT 80 (29.5)	CC 157 (57.9)	T (24.6)	TT 21 (5.6)	CT 144 (38.1)	CC 213 (56.3)

SSR, serine racemase gene; PTPRD, protein tyrosine phosphatase receptor type D gene; SNPs, single nucleotide polymorphisms

rs4523957, rs391300, and rs8081273 were not associated with T2D (P = 0.96; 0.73; 0.66; 0.69, respectively). The recessive genetic model showed that SRS rs8081273 was protective against T2D (OR = 0.42, P = 0.003), while rs17584499, rs649891, rs4523957, and rs391300 were not associated with T2D (P = 0.505; 0.34; 0.55; 0.612, respectively). The additive genetic model showed no association of rs17584499, rs649891, rs4523957, rs391300, and rs8081273 with T2D (P = 0.103; 0.59; 0.91; 0.57; 0.31, respectively).

Discussion

The associations of PTPRD SNPs rs649891 and rs17584499 as well as SSR SNPs rs391300, rs4523957, and rs8081273

Table 4: Association of SSR and PTPRD S single nucleotide polymorphisms with type 2 diabetes among Malaysian Indian subjects

	Normal number of genotypes 11/12/22	Type 2 diabetes number of genotypes 11/12/22	Recessive OR (95% CI) *P*	Dominant OR (95% CI) *P*	Additive OR (95% CI) *P*
PTPRD SNPs					
rs17584499	111/118/40	193/106/63	1.3 (0.60–2.8) 0.505	1.42 (1.04–1.95) 0.029	0.80 (0.61–1.05) 0.103
rs649891	71/135/63	96/174/92	1.2 (0.83–1.72) 0.34	1.01 (0.71–1.44) 0.96	1.06 (0.85–1.32) 0.59
SSR SNPS					
rs4523957	99/107/66	135/165/85	0.89 (0.62–1.29) 0.55	0.94 (0.68–1.31) 0.73	0.99 (0.80–1.22) 0.91
rs391300	95/126/55	139/176/70	0.90 (0.0.61–1.34) 0.612	1.08 (0.79–1.49) 0.66	0.94 (0.76–1.17) 0.57
rs8081273	157/80/34	213/144/21	0.41 (0.23–0.73) 0.003	0.94 (0.68–1.29) 0.69	0.88 (0.69–1.12) 0.31

Genetic models of recessive (22 versus 12+11), dominant (22+12 versus 11), and additive (22 versus 12 versus 11), with adjustment for gender, age and body mass index. 11, homozygous of major allele; 12, heterozygous; 22, homozygous of minor allele; SSR, serine racemase gene; PTPRD, protein tyrosine phosphatase receptor type D gene; SNPs, single nucleotide polymorphisms

with T2D, were investigated in Malaysian Indians. The present study found that the PTPRD rs17584499 was associated with T2D, which agreed with previous studies[5,6,15,16] but disagreed with two other studies on the Chinese[17] and the Japanese populations.[18] The difference between our study and the Chinese study[17] might be due to the low number of subjects in their study (136 T2D and 136 control subjects). While in the Japanese study,[18] they included control participants with fasting plasma glucose <7 mmol/L instead of <6.1 mmol/L, which means they included prediabetic subjects (fasting plasma glucose ≥6.1 to <7 mmol/L), which may have contributed to a higher minor allele frequency in controls in the Japanese study.

In our study, rs649891 showed no association with T2D, which agreed with the previous report on Japanese[18] and differed from previous findings on the American population.[7] The controversial data might be attributed to gene-environmental and gene-gene interactions that may have contributed to many of the reported differences in gene-disease association studies between racial or ethnic groups.[19] Another opinion attributed this to ethnic differences and linkage disequilibrium patterns, compounded by the contribution of non-genetic factors and lifestyle changes that can modify the risk of T2D.[20]

The present study showed that the SRR rs8081273 genotype (TT) was protective against T2D. To the best of our knowledge, no published data on the association of this SNP with T2D in other populations. However, the SRR rs391300 and rs4523957 were not associated with T2D among Malaysian Indian subjects, which agreed with the previous meta-analysis for six studies that included 21,305 Chinese Han individuals (10,213 T2D and 11,092 controls)[10] and on the Japanese population, which included SRR rs391300.[18] On the other hand, our findings were not in agreement with previous studies on Chinese.[6] We believe this difference might be due to the control subjects in the Chinese study who were obtained from the Han Chinese Cell and Genome Bank, who were diagnosed according to HbA1c instead of FBG or oral glucose tolerance test.[21] It is possible that the patients with T2D were included in the control group,[22] which might contribute to a higher minor allele frequency in controls in the Chinese study. Furthermore, the association of the SRR rs391300 with impaired glucose metabolism, fasting insulin level, or insulin resistance was not significant.[23]

PTPRD gene is widely expressed in tissues, including skeletal muscle and pancreas, which belongs to the receptor type IIA (R2A) subfamily of protein tyrosine phosphatase D (PTPD).[24] PTPRD-expressed protein was reported to be implicated in neural development, cancer, and diabetes.[25] The genetic variations of PTPRD may modulate the blood glucose homeostasis, insulin sensitivity, and insulin resistance to cause T2D.[5,26] The SRR gene encodes a serine racemase that synthesizes D-serine from L-serine,[27] which is widely expressed in the tissue, including the pancreas.[28] D-serine is a physiological co-agonist of the N-methyl D-aspartate (NMDA) class of glutamate receptors. Glutamate signaling functions in peripheral tissues, including the pancreas, and positively modulates glucagon and insulin secretion in pancreatic islets.[29] Dysregulation of D-serine could alter glutamate signaling and affect insulin or glucagon secretion in T2D pathogenesis.[6] A recent study found a significant downregulation of SSR with significant fold change values among diabetes compared to controls.[11]

This study is hospital-based, and the sampling method is non-probability; thus, the sampling for this study has limited its generalization to the whole Indian population. In conclusion, this study confirmed the association of PTPRD rs17584499 with T2D in Malaysian Indians. While SRR rs8081273 genotype (TT) showed protection against T2D, more investigations in different populations are required to confirm this protection. PTPRD is implicated in insulin sensitivity,

which may participate in the regulation of insulin action on its target cells, while SRR variants may alter glutamate signaling in the pancreas, thus regulating insulin and or glucagon secretion.

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Conflicts of interest

There are no conflicts of interest.

Author contributions

Saif-Ali Riyadh: Conceptualization, Design, Literature search, Data analysis, Statistical analysis, Validation and Manuscript preparation.
Al-Hamodi Zaid and Salem Sameer D: Data Acquisition, Data analysis and Methodology.
AL-Habori Molham: Editing and review the manuscript.
Al-Dubai Sami A: Statistical analysis and Manuscript review.
Ismail Ikram S: Supervision, Validation, Editing and review the manuscript.

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