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RESEARCH ARTICLE

GENETIC POLYMORPHISMS OF SERINE RACEMASE AND PROTEIN TYROSINE PHOSPHATASE RECEPTOR TYPE D ASSOCIATED WITH TYPE 2 DIABETES IN MALAY SUBJECTS

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Abstract

Background and objectives: Serine racemase (SRR) and protein tyrosine phosphatase receptor type D (PTPRD) were suggested as Type 2 diabetes mellitus (T2DM) candidate genes by a genome-wide association study (GWAS) in the Chinese population. Associations of SRR and PTPRD with T2DM have been reported among East Asian Populations. The association of SRR and PTPRD genetic polymorphisms with T2DM still needs to be studied in Southeast Asian Populations.
Materials and Methods: This study aimed to evaluate the association of SRR and PTPRD genetic polymorphisms with T2DM in Malay subjects. The single nucleotide polymorphisms (SNPs) of SRR (rs4523957, rs391300, and rs8081273) and PTPRD (rs17584499 and rs649891) were genotyped in 440 T2DM and 398 normal Malay subjects.
Results: The recessive genetic model showed that SRR genotype GG of rs4523957 and genotype TT of rs391300 are risk factors for T2DM (OR=1.42; 1.45, *p*=0.022; 0.020, respectively), whereas the dominant and additive genetic models showed that PTPRD SNPs rs17584499 were protective for T2DM (OR=0.76; 0.77, *p*=0.033; 0.031, respectively).
Conclusion: This study replicated the association of SRR rs4523957, rs391300, and PTPRD rs17584499 genetic polymorphisms with T2DM in Malay, while more investigation in different populations is required to confirm this finding.
Keywords: Genetic polymorphism, risk factors, single-nucleotide polymorphism, type 2 diabetes mellitus.

INTRODUCTION

Diabetes is a metabolic disorder affecting 537 million people (10.5%) worldwide in 2021, and it is predicted that 783 million people will develop diabetes by 2045[1]. Type 2 diabetes mellitus (T2DM) is presented with decreased insulin secretion and is associated with insulin resistance and obesity[2]. Both environmental risk factors and genetic susceptibility may contribute to T2DM development[3]. Genome-wide association (GWAS) study identified 1,791 susceptibility loci for T2DM[4]. The serine racemase gene (SRR) is located on chromosome 17 and has been suggested to be associated with T2DM[5] and gestational diabetes in Chinese[6]. The association of the SRR genetic variations with T2DM was not replicated in another study[7]. Serine racemase enzyme is encoded by the SRR gene that synthesizes D-serine from L-serine, which is a co-agonist of glutamate signaling and thus may regulate insulin secretion in pancreatic beta cells and glucagon secretion in pancreatic alpha cells and hence may play a role in the etiology of T2DM[8].

Recently, Raza *et al.*,[9] reported that SRR gene expression is downregulated in pancreatic islands, which might be associated with metabolic disorders and T2DM. In addition, knockdown SRR has been reported to be involved in T2DM development by decreasing insulin secretion[10,11]. A recent study showed that insulin secretion is impaired by chronic supplementation with d-serine impairs[12]. PTPRD genetic variants have been suggested to be associated with T2DM in Chinese using two GWAS studies[5,8]. Another GWAS study in Mexican-Americans with 837 T2DM patients and 436 normoglycemic subjects, followed by a meta-analysis, confirmed the association of PTPRD variants with T2DM[13]. The PTPRD is a tyrosine phosphatase that may affect insulin signaling in muscle and adipose tissue[8]. Another study suggested that PTPRD genetic polymorphisms are associated with insulin resistance and the development of diabetes

in Han Chinese[5]. Furthermore, silencing the PTPRD gene by hypermethylation significantly decreased the PTPRD expression resulting in a decrease in insulin signaling[14].

The association of SRR and PTPRD genetic polymerphisms with T2DM was conducted in the Chinese population, while the Southeast Asian population remains necessary to be investigated. In addition, the association studies of SRR with T2DM are controversial. Therefore, we aimed to study the association of SRR and PTPRD polymorphisms with T2DM in Malay subjects.

MATERIALS AND METHODS

University Malaya Medical Ethics Committee approved this study (Reference No. 387.15). The purpose and nature of the study were explained to each participant, and written consent forms were provided to all participants.

Data sources

Malay normal subjects who engaged in a health check-up at UMMC were invited to join this study (control group). The previously diagnosed Malay patients with T2DM who attended the UMMC, Kuala Lumpur, for treatment, were recruited (case group). The age of all participants was 30-70 years old. Fasting venous blood (5 ml) was withdrawn from each subject into a K2EDTA tube (for glycated hemoglobin measurement and genetic analysis) and a plain blood tube (for biochemical analysis). The participant's waist circumference (WC) was measured midway between the superior iliac spine and the lower rib margin. The height and weight were measured for each included subject, and BMI was calculated. Automatic Digital Blood Pressure Omron IntelliSense (Omron Healthcare Co. Ltd. Kyoto Japan) was used to measure the participant's blood pressure (BP).

Genetic analysis

Wizard Genomic DNA Purification Kit (Promega Corporation, Madison, WI, USA) was used to extract peripheral blood leukocyte DNA according to the manufacturer's instructions. The predesign TaqMan genotype assay (Applied Biosystems Inc, Foster City, USA) was used for genotyping the SNPs of SRR (rs4523957, rs391300, and rs8081273) and PTPRD (rs649891 and rs17584499) according to the manufacturer's instruction 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 and to exclude DNA contamination.

Biochemical analysis

Dimension® RxL Max® (Fully automated analyzer) Integrated Chemistry System (Siemens Healthcare Diagnostics Inc. Deerfield, IL USA) was used to measure diabetic parameters, glucose and HbA1c and lipid profile, triglyceride (TG), total cholesterol, and high-density lipoprotein cholesterol (HDL-c).

Statistical analysis

The statistical analyses were executed by IBM SPSS 22 program (SPSS, Inc, Chicago, USA). Logistic regression controlling for age, gender, and body mass index was used to analyze the association of each SNP recessive, dominant, and additive genetic model with T2DM. The SNPs deviations from the Hardy-Weinberg equilibrium were evaluated online (*http://shesisplus.bio-x.cn/SHEsis.html*).

RESULTS

Eight hundred thirty-eight Malay subjects signed the consent forms and donated blood, 440 T2DM, and 398 normal subjects. The anthropometric measurement and biochemical analytes of the subjects were depicted in Table 1. As a consequence of T2DM, the diabetic patients had larger waist circumferences, higher BMI, high FBG, HbA1c, and TG compared to normal subjects. The total cholesterol and HDL-c levels were lower in T2DM patients compared to normal individuals, whereas there were no differences between normal and T2DM subjects in systolic and diastolic blood pressure. In addition, the diabetic patients were significantly older than normal subjects. Table 2 shows the Hardy-Weinberg equilibrium (HWE), call rates, and SNP positions of the included SNPs in this study. The included SNPs in this study did not deviate from HWE in normal subjects, and all SNPs were further analyzed. The results found that homozygous genotype GG of rs4523957 and genotype TT of rs391300 were frequent in diabetic patients (34.6%; 31.3) compared to normal subjects (27.7%; 25.2), respectively.

Table 1: Biochemical characterization of normal and type 2 diabetic Malay subjects.

	Normal subjects n=398	Diabetic subjects n=440	*p* value
	Mean±SD	Mean±SD	
Age (years)	47.55±10.03	50.28±8.68	$2.8x10^{-5}$
Body mass index (BMI)	27.35±5.38	28.66±5.17	$3.3x10^{-04}$
Waist (cm)	90.12±14.36	96.54±11.78	$8.9x10^{-12}$
Systolic blood pressure (mmHg)	135±18.98	137±18.07	0.14
Diastolic blood pressure (mmHg)	83.33±10.63	82.66±9.83	0.14
Fasting blood glucose (mmol/l)	5.12±0.58	8.98±3.76	$1.5x10^{-74}$
Glycated hemoglobin (%)	5.65±0.53	8.5±2.09	$2.5x10^{-100}$
Total cholesterol (mmol/l)	5.37±1.01	5.04±1.34	$5.1x10^{-05}$
High-density lipoprotein Cholesterol (mmol/l)	1.31±0.33	1.15±0.27	$4.5x10^{-15}$
Triglycerides (mmol/l)	1.56±0.86	1.91±1.23	$2.5x10^{-06}$

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

	p value in case	*p* value in control	Call rate	SNP Position
SRR SNPs				
rs4523957	0.0007	0.378	0.962	Chromosome 17* (2,155,649)
rs391300	0.217	0.961	0.974	Chromosome 17* (2,163,008)
rs8081273	0.257	0.386	0.958	Chromosome 17* (2,169,075)
PTPRD SNPs				
rs17584499	0.041	0.142	0.975	Chromosome 9*(8,869,118)
rs649891	0.887	0.996	0.974	Chromosome 9*(10,420,602)

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

In contrast, the homozygous genotype CC of rs17584499 is more frequent among normal individuals (50.9%) than diabetic patients (57.4%) (Table 3). There were no differences in genotype frequencies of SRR SNP (rs8081273) and PTPRD SNP (rs649891 between normal subjects and diabetic patients. The recessive, dominant, and additive genetic models were applied to analyze the association of SRR SNPs, rs4523957, rs391300, and rs8081273 and PTPRD SNPs, rs17584499, rs649891 with T2DM (Table 4).

Table 3: Frequencies SRR and PTPRD single nucleotide polymorphisms among normal and diabetic Malay subjects.

	N (%frequency) in Normal n=398			N (%frequency) in Diabetic n=440		
	HR	**Hetero**	**HD**	**HR**	**Hetero**	**HD**
SRR SNPs						
rs4523957	TT	GT	GG	TT	GT	GG
	98 (25.3)	182 (47.0)	107 (27.7)	107 (24.9)	174 (40.5)	149 (34.6)
rs391300	GG	AG	AA	GG	AG	AA
	91 (23.5)	199 (51.3)	98 (25.2)	100 (23.4)	194 (45.3)	134 (31.3)
rs8081273	CC	CT	TT	CC	CT	TT
	51 (13.2)	166 (43.0)	169 (43.8)	69 (16.4)	178 (42.4)	173 (41.2)
PTPRD SNPs						
rs17584499	TT	CT	CC	TT	CT	CC
	22 (5.6)	170 (43.5)	199 (50.9)	14 (3.3)	167 (39.3)	244 (57.4)
rs649891	AA	AG	GG	AA	AG	GG
	18 (7.2)	151 (39.5)	206 (52.2)	35 (8.4)	165 (39.5)	218(52.1)

SRR, serine racemase gene; PTPRD, protein tyrosine phosphatase receptor type D gene; SNPs, single nucleotide polymorphisms; HR, Homozygous recessive; Hetero, Heterozygous; HD, Homozygous dominant

Table 4: Association of PTPRD and SRR single nucleotide polymorphisms with type 2 diabetes among Malay subjects.

	Normal Number of Genotypes 11/12/22	Type 2 Diabetes Number of Genotypes 11/12/22	Recessive OR (95% CI) *p* -Value	Dominant OR (95% CI) *p* -Value	Additive OR (95% CI) *p* -Value
SRR SNPS					
rs4523957	107/182/98	149/174/107	**1.42**	1.07	1.2
			(1.05-1.93)	(0.78-1.48)	(0.97-1.41)
			0.022	0.67	0.10
rs391300	98/199/91	134/194/100	**1.45**	1.02	1.16
			(1.06-1.98)	(0.73-1.41)	(0.96-1.41)
			0.020	0.91	0.13
rs8081273	169/166/51	173/178/69	1.27	1.10	1.11
			(0.86-1.89)	(0.83-1.45)	(0.91-1.35)
			0.236	0.53	0.30
PTPRD SNPs					
rs17584499	199/170/22	244/167/14	0.54	**0.77**	**0.77**
			(0.27-1.08)	**(0.58-0.95)**	**(0.64-0.98)**
			0.083	**0.033**	**0.031**
rs649891	206/151/18	218/165/35	1.18	1.04	1.05
			(0.70-1.99)	(0.78-1.37)	(0.85-1.31)
			0.54	0.80	0.64

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

The recessive genetic model showed that SRR rs4523957 genotype GG and rs391300 genotype TT were risk factors for T2DM (OR=1.42; 1.45, *p*=0.022; 0.020, respectively), while rs8081273 and rs649891 were not associated with T2DM (*p*=0.236; 0.54, respectively). In addition, the dominant genetic model showed that PTPRD SNPs rs17584499 were associated with T2DM (OR=0.76, *p*=0.033), whereas rs4523957, rs391300, and rs8081273, and rs649891 were not associated with T2DM (*p*=0.67; 0.91; 0.53; 0.80, respectively). The additive genetic model showed that SNPs rs17584499 associated with T2DM (OR=0.77, *p*=0.031), whereas rs4523957, rs391300, and rs80812 73, and rs649891, were not associated with T2DM (*p*=0.10; 0.31; 0.30; 0.64, respectively).

DISCUSSION

The associations of SRR SNPs rs4523957, rs391300, and rs8081273, as well as PTPRD SNPs rs649891 and rs17584499 with T2DM, were investigated in Malay subjects. This study showed that SRR rs4523957 and rs391300 were associated with T2DM among Malay subjects, which agreed with previous studies on Chinese[8]. However, this finding disagreed with previous studies on Chinese Han individuals[7] and the Japanese population[15]. The controversial data might be attributed to gene-environmental and gene-gene interactions that may contribute to the differences in the reported gene-disease association between ethnic or racial groups[16]. Another opinion imputed this to linkage disequilibrium patterns and ethnic differences, combined with the involvement of lifestyle changes and non-genetic factors that can modulate the risk of T2DM[17]. The presented study showed that the SRR rs8081273 was not associated with T2DM. To the best of our knowledge, no published data on the association of this SNP with T2DM in other populations.

The present study found that the PTPRD rs17584499 was associated with T2DM, which agreed with previous studies[5,8,18,19] but disagreed with two other studies on the Chinese[20] and the Japanese populations[15]. The difference between our study and the Chinese study[20] might be due to the low number of subjects in their study (136 T2DM and 136 control subjects). While in the Japanese study[15], 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 T2DM, which agreed with the previous report on Japanese[15].

PTPRD encodes a protein belonging to the receptor type IIA (R2A) subfamily of protein tyrosine phosphatase D (PTPD) and is expressed in the pancreas and skeletal muscle[21] and reported to be implicated in diabetes[22]. The genetic variations of PTPRD may modulate insulin resistance to develop T2DM[5,19]. The SRR gene encodes SRR enzymes, is widely expressed in the tissue, including the pancreas[23], and synthesizes D-serine from L-serine[24]. D-serine is a co-agonist of glutamate receptors[25], and thus glutamate signaling may positively modulate insulin and glucagon secretion in beta cells[26]. Dysregulation of D-serine could alter glutamate signaling and affect insulin or glucagon secretion in T2DM[8]. A recent study found that SRR significantly downregulated in diabetes compared to controls[9].

Limitations of the study

The sampling method of this study is non-probability and is hospital-based, and thus the results of this study cannot generalize to the whole population.

CONCLUSIONS

This study replicated the association of SRR SNPs rs4523957, rs391300, and PTPRD rs17584499 with T2DM in Malay. However, more investigations in different populations are required to confirm this association. PTPRD protein is involved in insulin sensitivity, and its genetic variants may participate in the dysregulation of insulin action in muscle and adipose tissues, while SRR genetic variants may disturb insulin secretion through glutamate signaling transduction.

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AUTHOR'S CONTRIBUTION

Saif-Ali R: Writing original draft, review, methodology, data curation, literature survey, editing.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

None to declare.

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