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RESEARCH ARTICLE

The role of the PPARG (Pro12Ala) common genetic variant on type 2 diabetes mellitus risk

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Abstract

Background Type 2 diabetes (T2DM) prevalence has been rapidly increasing in the last decades. T2DM pathogenesis is related to insulin resistance and beta-cell dysfunction. *Peroxisome proliferator-activated receptor gamma (PPARG)* is concerned about T2DM risk through the involvement in adipocyte differentiation and energy homeostasis. The present study aimed to find the risk associated with a common genetic variant (Pro12Ala) of the *PPARG* gene in the development of T2DM in a group of the Iranian population.

Methods Totally, 149 patients with T2DM and 96 healthy individuals were recruited in this case–control study. The genotyping of the genetic variant was carried out using the polymerase chain reaction (PCR) followed by Sanger sequencing.

Results No significant difference is observed between the CG and GG genotypes frequency of the *PPARG* variant ($P=0.17$) in T2DM patient and the control groups. Furthermore, the frequency of the G allele was similar between case and control groups. The Pro12Ala variant may decrease the risk of diabetic retinopathy (DR) which was not statistically significant. Furthermore, the Pro12Ala variant caused a 27% increase in the risk of diabetes nephropathy (DN) among patients with T2DM but was not significant.

Conclusions Our findings showed that the *PPARG* variant could not impact on T2DM development and its complications.

Keywords T2DM · Genetic Variant · *PPARG* · rs1801282 · Pro12Ala

Introduction

Type 2 diabetes mellitus (T2DM) is a major form of multifactorial metabolic disorder with a growing incidence among populations [1]. T2DM is characterized by hyperglycemia that has developed by deficiency in insulin resistance, insulin secretion or a combination of both from pancreatic β-cells [2]. T2DM pathogenesis results from the interaction between environmental and genetic factors that indicates strong genetic origin with roughly 30 to 70 percent genetic heritability [3]. Large-scale genetic association studies have identified more than 400 genetic signals implicating in T2DM risk [4]. *Peroxisome proliferator-activated receptors (PPARs)* as members of the nuclear hormone receptor gene superfamily are ligand-activated transcription factors [5] that regulate the glucose and lipid metabolism and also stimulate protein synthesis in a wide variety of processes (energetic metabolism, proliferation, and cellular differentiation) [6]. *Peroxisome proliferator-activated receptor gamma (PPARG)*, one of the three PPAR isoforms, is a major regulator of adipogenesis, lipid metabolism, and insulin sensitivity [5] that consider as a susceptible to T2DM loci in different ancestries [7]. Genetic variations including single nucleotide polymorphisms (SNPs) is considered as a major determinant of susceptibility to many common disese like diabetes and play an important role in genetic architecture of disese predisposition [8]. Several evidence have demonstrated that the SNPs of *PPARG* have an important role in controlling lipid and glucose metabolism. The missense Pro12Ala variant (also known as rs1801282) is the most prevalent variant in the entire coding region of *PPARG* gene

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which is located in exon B have been extensively reviewed in epidemiologic studies [9]. The impact of the Pro12Ala variant on T2DM risk has been reported firstly by Yen et al. [7] and extensively described in different studies [10–20]. The inconsistent findings emphasized the significance to study the association of *PPARG* Pro12Ala genetic variant with T2DM in different populations. Therefore, the valuable knowledge gained from polymorphic variants of PPARs in different populations and the genotypic associations between SNPs and gene–gene interactions would be helpful for the prediction and prevention of T2DM and accrodingly it might be used in the precision medicine approaches..

Accordingly, we investigated the relationship between Pro12Ala variant at the *PPARG* gene and T2DM risk in a group of Iranian patients.

Materials and methods

Study subjects

This case–control study was comprised a total number of 245 subjects, including 149 patients with T2DM and 96 healthy controls, who were recruited between Feb 2016 and April 2017 from a private diabetes clinic at Tehran (Iran). A structured questionnaire was completed to obtain information on specific clinical data. The inclusion criteriafor the enrolled subjects as case was according to the American Diabetes Association (ADA) guideline [21]. Individuals with fasting plasma glucose (FPG) > 126 mg/dl were considered as the case group. Based on the available information, diabetic retinopathy (DR) and diabetic nephropathy (DN) have been investigated among patients group. The diagnosis of DR ($n = 46$) was performed using an experienced ophthalmologist based on ophthalmoscopic checkup in all patients with T2DM. DN ($n = 19$) was determined by symptoms or singes according to ADA criteria [21].

Control subjects were age-matched Iranian healthy volunteers from the same area with Hemoglobin A1c (HbA1c) < 6%. Known diabetes diagnosis or any history of T2DM in their families were not disclosed.

Exclusion criteria were as follow: type 1 diabetes, gestational diabetes, pregnancy, hypo/hyperthyroidism, and cancer, autoimmune, chronic, acute, and inflammatory disease at the time of sampling.

Genomic DNA analysis

Five cc whole blood was taken using sample tubes containing EDTA form enrolled participants. The DNA extraction was performed using the standard salting-out protocol [22] and the purity of DNA was checked by Nonodrop (OD260/OD280). The purified DNA samples were stored at 4 °C for further analysis.

Genotyping of the *PPARG* rs1801282 SNP was accomplished using polymerase chain reaction (PCR) followed by Sanger sequencing.

PCR was performed using the following primers: 5′-ACA GTGCCAGCCAATTCAAG-3′ (forward) and 5′- GGGAGC CATGCACAGAGATA-3′ (reverse) to amplify a 507 bp fragment.

PCR reaction mixture were performed in 23 µl total volume containing 10 µl ddH2O, 10 µl red master mix, 1 µl of each primer (10 µM) and 200 ng DNA template.

The amplification conditions were as follows: (95 °C, 5 M) 1 cycle as predenaturation step, (95 °C, 50 S, 61 °C 50 S, 72 °C 50 S) 35 cycle, (72 °C 50 S) 1 cycle, and 4 °C permanent storage. SNP were detected using Sanger sequencing technology with a genotyping success rate and accuracy > 98%.

Statistical analysis

Frequencies of genotypes/alleles of variant were compared between case and control groups using Pearson's chi-squared test (χ^2). Crude and adjusted (controlling for ethnicity) logistic regression models were used to assess the associations between these genotypes/alleles and T2DM or its complications. The Hardy–Weinberg equilibrium (HWE) was calculated for each genotype in control group by Chi-squared test. All data were analyzed using Stata 14 software. A *P*-value of less than 0.05 was shown statistically significant.

Result

PPARG Pro12Ala variant genotyping was successfully performed in all participants ($n = 245$) with mean ± standard deviation (SD) age of 52.39 (20.58).

Characteristics of cases and controls including sex, age, and body mass index (BMI) are described in Table 1. There was not any significant difference regarding gender between case and control groups ($P = 0.35$). Patients T2DM were significantly older than control subjects ($P = 0.0001$) and showed higher BMI than non-diabetics ($P = 0.002$). Moreover, none of T2DM patients were Persian while 37.1% of controls had the Persian race ($P = 0.002$).

The genotype distributions of the rs1801282 *PPARG* variant met the HWE in the control population according to Chi-squared test ($P = 0.963$).

Genotype frequencies between the patients with and without T2DM are shown in Table 2. A significant difference was not observed for *PPARG* genotype frequencies between T2DM and normal groups (CC 87.25 vs. 80.21%; CG 12.75 vs. 18.75%; GG 0 vs. 1.04%) ($P = 0.17$). After multivariate

Table 1 Distribution of different factors among subjects with and without T2DM

Factors	Normal Subjects ($N=96$)	T2DM ($N=149$)	P-value
Gender N (%)			
Male	28 (29.17)	52 (34.9)	0.35
Female	68 (70.83)	97 (65.1)	
Age			
Mean (SD)	32.98 (13.66)	60.46 (17.33)	0.0001*
BMI			
Mean (SD)	23.78 (3.03)	28.83 (5.89)	0.002*
Ethnicity			
Non Persian	39 (62.9)	17 (100)	0.002*
Persian	23 (37.1)	0 (0)	
Not available data	34	132	

T2DM type 2 diabetes mellitus

*P-value < 0.05 is significant

Table 2 Association between genotypes of *PPARG* rs1801282 variant and T2DM risk

Genotypes	Normal Subjects	T2DM	Crude OR (P-value)	Adjusted* OR (P-value)
CC	77 (80.21%)	130 (87.25%)	1	1
CG	18 (18.75%)	19 (12.75%)	0.63 (0.26)	0.28 (0.43)
GG	1 (1.04%)	0 (0%)	0.60 (0.75)	2 (0.99)

T2DM type 2 diabetes mellitus, *OR* odds ratio

*Adjusted for gender

Table 3 Association between alleles of *PPARG* rs1891282 variant and T2DM risk

Alleles	Normal Subjects	T2DM	P-value	OR (P-value)
C	89.58%	93.62%	0.11	1
G	10.42%	6.37%		0.58 (0.11)

T2DM type 2 diabetes mellitus, *OR* odds ratio

analysis for gender using regression test the *P*-value still remained non-significant.

It was not indicated a difference in the frequency of the G allele (mutant) among T2DM and normal subjects (6.37% vs. 10.42%) ($P=0.11$) (Table 3).

After merging heterozygous and homozygous mutant genotypes, T2DM patients with ophthalmic complication did not have significantly higher frequency of *PPARG* variant than those without ($P=0.96$; OR = 0.97, 95%CI: 0.34–2.79). The frequency of CG + GG genotype was not significantly difference among patients with and without renal complication ($P=0.72$; OR = 1.27, 95%CI: 0.33–4.90) (Table 4).

Discussion

There are huge genetic variations in the Iranian population and performing genetic studies in diverse ethnic groups may indicate valuable results in genetic susceptibility to T2DM [23]. A locus that is associated with disease in one ethnic group but not in another may indicate ethnic differences in risk allele frequency. So, genetic association studies in the complex disease needs to perform in every population.

In this study, we observed similar genotypes and alleles frequency of *PPARG* variant between T2DM and healthy groups. The crude regression model showed that homozygote and heterozygote genotypes of *PPARG* variant decreased by approximately 40% the risk of T2DM. Controlling for ethnicity, the odds of T2DM was increased by two folds in the presence of homozygote genotype and decreased around 30% in the presence of heterozygote genotype. However, none of these observed associations were significant. Therefore, *PPARG* variant cannot be a risk factor or protective factor for T2DM.

A recent comprehensive meta-analysis with 62,250 cases and 69,613 controls conducted by Sarhangi et.al suggested that the Pro12Ala variant could impact on decrease risk of T2DM in different ancestries including East Asian, South East Asian, and European [8].

There are many contradictions in assessing the effect of the Pro12Ala variant on T2DM risk in diverse ethnicity.

Table 4 Association between genotypes of *PPARG* rs1801282 variant and T2DM complications risk

Genotypes	No Complication N (%)	Diabetic Retinopathy N (%)	P-value	OR (P-value)	95% CI
CC	78 (86.67)	40 (86.96)	0.96	1	
CG + GG	12 (13.33)	6 (13.04)		0.97(0.96)	0.34–2.79
	No Complications N (%)	Diabetic Nephropathy N (%)	P-value	OR (P-value)	95% CI
CC	102 (87.18)	16 (84.21)	0.72	1	
CG + GG	15 (12.82)	3 (15.79)		1.27(0.72)	0.33–4.90

T2DM type 2 diabetes mellitus, *OR* odds ratio, *CI* confidence interval

The results of the present study are consistent with previous case–control reports on Asian and European different populations in recent years [15, 16, 24] where they did not report any association of rs1801282 with T2DM susceptibility.

Our observation is also supported by previous reports; a study by Bener and colleagues indicated that there is no association between Pro12Ala genetic variant and T2DM development. Finding of the study did not support the role of the Pro12Ala variant as the genetic risk factor for diabetes in the Qatari diabetic population [25].

Despite the previously known role of the *PRAPG* gene, Kommoju et.al could not replicate the biological association of *PRARG* with T2DM in a population of Hyderabad, India [26].

In contrast to our present results, Chauhan et.al reported a significant association of the common genetic variant of *PPARG* (Pro12Ala) with T2DM risk in a large scale case–control study on Indo-European ethnicity [27]. Also, the role of the Pro12Ala variant as a genetic risk factor for insulin resistance and T2DM risk have been confirmed in the Malaysian population [14]. The same association has also been identified in another study on Indian population [10]. The Ala allele may influence progressed insulin secretory capacity and can protect from T2D susceptibility in the Chinese population [28]. The protective effect of the Ala allele on T2DM was confirmed in a recent meta-analysis by Li et.al [29].

Some evidence indicates that the progression of diabetes complications is slightly influenced by genetic factors [30, 31]. Consequently, concerning the role of *PPARG*, as a mediator in diabetes complications, investigation of the Pro12Ala variant in a case–control survey will be beneficial for knowing the influence of genetic factors on the advancement of diabetes complications including diabetic nephropathy and retinopathy.

Although the presence of *PPARG* variant slightly decreased the odds of developing diabetic retinopathy complications, the observed association was not statistically significant. A report inconsistent with our results, showed that the 12Ala genetic variant protects against diabetic retinopathy in T2DM patients of the Pakistan population [32].

In addition, presence of this variant caused 27% increase in the risk of DN complication, but this association was not significant. Previous reports have shown that the Pro12Ala variant of *PPARG* is not significantly associated with better renal function in Chinese T2D patients with and without DN [33].

No significant associations of a common genetic variant (Pro12Ala) in *PPARG* and diabetic retinopathy or proliferative diabetic retinopathy (PDR) were also found in a group of Chines patients [34].

In a meta-analysis of 18 studies with 3,361 DN cases and 5,825 control subjects the Pro12Ala variant was significantly related to the decreased risk of DN [31].

Further, a comment on mentioned meta-analysis suggested a significant association between the Pro/Pro genotype and risk of DN that genotype has synergistic effects with smoking [35]. The protective role of the *PPARG2* Pro12Ala variant in the development of nephropathy and decay of renal function among T2DM patients have been shown in a cross-sectional study with an average 5-year follow-up [30]. This result is slightly in contrast to our findings, however given the difference in the ethnicity and background of the sample groups, this discrepancy can be expected.

We had to report the above results with cautious, because the exposure and outcome associations were investigating cross-sectionally. Accordingly, the potential relationships cannot be evaluated.

In conclusion, it seems that the Pro12Ala variant of *PPARG* gene was not associated with T2DM and its renal and ophthalmic complications among a group of the Iranian population. Most of these genomics variants either do not indicate noticeable differences or basically make us look different. Some genetic variations can cause diseases or susceptibility to some phenotype. Genetic variants will make precision medicine possible for better prediction and prevention Non-significant findings of the present study may be due to the small sample size. Thus, longitudinal studies with larger sample sizes are needed to show the precise effect of this variant on developing T2DM.

Abbreviations T2DM: Type 2 diabetes mellitus; PPARs: Peroxisome proliferator-activated receptors; PPARG: Peroxisome proliferator-activated receptor gamma; ADA: American diabetes association; FPG: Fasting plasma glucose; DR: Diabetic retinopathy; DN: Diabetic nephropathy; HbA1c: Hemoglobin A1c; SNP: Single nocleutide polymorphism; PCR: Polymerase chain reaction; $\chi 2$: Chi-squared test; HWE: Hardy–weinberg equilibrium; SD: Standard deviation; BMI: Body mass index

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Author contributions MH managed the project and provided guidance to the research; LH and NS drafted the manuscript and performed lab genotyping; MA performed the statistical analysis; HRAM: provided clinical guidance to the research.

All authors contributed to and approved the final version of the manuscript.

Data availability Data from this project will be available to share.

Declarations

Consent for publication Written informed consent was obtained from all the subjects and the present study was approved by ethical committee by the ethics code of IR.IAU.TMU.REC.1395.110.

Competing of interest The authors declare that there is no conflict of interest.

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