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ORIGINAL ARTICLE

Lack of association between the $Pro_{12}Ala$ polymorphism of the PPAR-γ2 gene and type 2 diabetes mellitus in the Qatari consanguineous population

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Abstract Peroxisome proliferators-activated receptor γ (PPARγ) is a nuclear hormone receptor that serves as a master regulator for adipocytes-specific genes contributing to adipocytes differentiation, insulin sensitivity and lipid metabolism. The substitution of proline to alanine at codon 12 of the PPAR γ2 gene (Pro12Ala polymorphism) is most widely studied, and the associations with diabetes, obesity, and other clinical parameters have been reported and discussed in several ethnic groups. Among native Qatar ethnicity, however, there is no report about this polymorphism. The aim of this study was to estimate the allele frequency of the $Pro_{12}Ala$ polymorphism of PPAR γ2 gene among Qatari population and investigate the association between this polymorphism and obesity or type 2 diabetes. This is a matched case–control study. It was carried out among diabetic patients and healthy subjects at the Primary Healthcare Clinics, and the survey was conducted from February 2003 to March 2006 in Qatari male and female nationals aged 35 to 60 years. The study was based on matched age, sex, and ethnicity of 400 cases (with diabetes) and 450 controls (without diabetes). Face-to-face interviews were based on a questionnaire that included variables such as age, sex, sociodemographic status, body mass index (BMI), and obesity. Their health status was assessed by medical conditions, family history, and blood pressure measurements. The allele frequency of $Pro_{12}Ala$ polymorphism in PPAR γ2 gene among Qataris is lower than that in many Caucasian ethnic groups. No association is seen between the $Pro_{12}Ala$ and type 2 Diabetes (0.055 vs 0.059, OR = 1.1311, $P = 0.669$). Nearly half of the diabetic type 2 patients (48.5%) were obese (BMI > 30) compared to nondiabetic subjects (29.8%) ($P < 0.001$). In this study, no association is seen between the $Pro_{12}Ala$ polymorphism in PPAR γ2 gene and the type2 diabetes in Qatar.

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Introduction

Peroxisome proliferators-activated receptor gamma (PPARγ) is a nuclear hormone receptor of ligand-dependent transcription factor involved in adipogenesis and a molecular target of the insulin sensitizers, thiazolidinediones. PPARγ has been suggested to play important roles in obesity and in the development of type 2 diabetes (T2D) related with insulin sensitivity and lipid metabolism [1–3]. In an animal model, heterozygous deficiency of PPAR γ was shown to lead to the protection from high-fat diet-induced insulin resistance [4]. Barroso et al. [3], in their study of human subjects, reported that the first germ line loss-of-function mutations in the ligand binding domain of PPAR γ gene caused severe insulin resistance, early onset of T2D, and hypertension.

A more recent study has suggested that people with the Ala12 allele of the PPAR-γ2 gene could be more sensitive to insulin than those with the Pro12 allele among Brazilian Caucasians [5]. The Pro12Ala polymorphism in the PPAR γ gene has been shown to influence the risk for T2D and obesity in various ethnic populations worldwide [5–15]. A recent study in Qatar [8] revealed that obesity, consanguinity, blood pressure, total cholesterol, HDL-cholesterol, and triglyceride were more prevalent in the Qatari diabetic patients. The characterization of these factors will contribute to defining more effective and specific strategies to screen for and control diabetes and cardiovascular disease in a new developing country. The prevalence of the Pro12Ala mutation, however, varies according to the ethnic background [9–20].

In this study, we focused on the Pro12Ala polymorphism in Qatar. During this past decade, diabetes prevalence in Qatar has been dramatically increasing [8], which may be due to change of life styles such as increasing total calorie intake including fat, less exercise, and increasing level of stress under the unstable social–economic circumstances. There may, however, be genetic factors that contribute to the dramatic increase in diabetic patients under the interaction between genetic and environmental factors. Since the Pro12Ala polymorphism of the PPAR-γ2 gene has not yet been investigated in Qatar, we studied its prevalence among native Qataris and examined whether this polymorphism is associated with diabetes in Qatar.

Subjects and methods

Data collection

Data including age, sex, onset of diseases, family history of diabetes, and diabetic complications were obtained from the patients. All subjects were native Qataris, identified by themselves as being native Qataris, by at least two pedigrees (parents and grand parents). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using standard methods. The survey was based on standardized interviews performed by trained health professionals and nurses. The study was approved by the Hamad General Hospital, Hamad Medical Corporation. All human studies have been approved by the Research Ethics Committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All the persons who agreed to participate in this study gave their informed consent prior to their inclusion in the study.

Selection of diabetic subjects

Persons were classified as diabetic if they were currently taking diabetic medication. We studied Qatari diabetic subjects diagnosed for T2D in accordance with the established diagnostic criteria [21]. A total number of 400 diabetic Qatari patients aged 35–60 years selected by a simple random process from the Primary Health Care (PHC) Centers. Their health status was assessed by recording previous medical conditions, family history, and blood pressure.

Selection of control subjects

Control subjects were self-reported, aged 35–60 years with random glucose value of <6.1 mmol/l, and if had never taken any diabetic medication. Since T2D is a late onset disorder, the control subjects selected were above the age of 35. This group consisted of a random sample of 450 healthy Qatari subjects who visited the PHC Centers for any reason other than acute or chronic disease. Their health status was further assessed by recording previous medical conditions, family history, and blood pressure.

Height and weight were measured using standardized methods, and all the participants wore light clothes and no shoes for this part of the examination. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Subjects were classified into three categories: acceptable

weight, BMI < 25; overweight, BMI 25–30; and obese, BMI > 30 [8].

Blood pressure measurement was carried out by trained practical nurses according to World Health Organization (WHO) standardized criteria [22]. The mean value obtained from three readings was used in the analysis. Hypertension was defined according to WHO criteria as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or the use of antihypertensive medication. Mean blood pressure was defined as 1/3 systolic pressure + 2/3 diastolic pressure. The pulse pressure was calculated as the difference between systolic and diastolic pressures.

Procedures

Blood samples were collected by venipuncture in vacutainer EDTA tubes and used for manual DNA purification using the QiaAmp mini DNA kits. Random glucose values were determined by using the One Touch Sure Step Kit.

The single nucleotide polymorphism (SNP) detection protocol was based on a modified procedure of Ghoussaini et al. [9] and consisted of an amplification step by polymerase chain reaction (PCR) followed by mutation analysis of the PCR product by real time PCR. The PCR primer set consisted of: PGE × 1F 5′-AAT AGG ACA GTG CCA GCC-3′ and PGE × 1R 5′-TAC ATA AAT GCC CCC ACG-3′. The reaction was performed in a final volume of 25 µl and contained: 1 × GeneAmp® PCR Gold buffer; 2.5 mM $MgCl_2$, 1% DMSO, 0.25 mM each dNTP, two primers (PGE × 1F: 4.3 nM and PGE × 1R 3.58 nM), 0.75 U AmpliTaq Gold® DNA Polymerase, and 100–500 ng template DNA. The PCR cycles consisted of an initial denaturation at 95°C for 12 min followed by 35 cycles, which consisted of denaturation at 95°C for 30 s, annealing at 58°C for 30 s, elongation at 72°C for 30 s.

The $Pro_{12}Ala$ in the PPARγ*2* gene was detected on the LightCycler using two specific probes:(Sensor [G] 5′-CTC CTA TTG ACG CAG AAA GCG-FL and PPAR Anchor 5′ LC Red 640-TCC TTC ACT GAT ACA CTG TCT GCA AAC ATA TC-PH). The melting temperature profiles were interpreted as follows; wild type (CC): 54°C, mutant (GG): 60°C and heterozygous (CG): 54 and 60°C.

Sample size was calculated with 80% power at the 5% level of significance and 95% confidence interval which was found to be 410 subjects in each group. We have recruited 400 subjects and 450 controls for the current study.

Statistical analysis

Student's *t* test was used to ascertain the significance of differences between mean values of two continuous variables and confirmed by a nonparametric Mann–Whitney test. Chi-square analysis was performed to test for differences in proportions of categorical variables between two or more groups. In 2 × 2 tables, the Fisher's exact test (two-tailed) replaced the chi-square test if the assumptions underlying Chi-square violated, namely in case of small sample size and where the expected frequency is less than 5 in any of the cells. Odds Ratio (OR) and their 95% confidence intervals (CI) were calculated by using the Mantel–Haenszel test. The level $P \leq 0.05$ was considered as the cut-off value for significance.

Results

Phenotypic characteristics of the studied populations

The characteristics of the type 2 diabetic and normal control subjects are summarized in Table 1. The average age of normal subjects was (50.0 ± 12.8 years) and that of diabetic subjects was (50.3 ± 9.8 years). Nearly half of the diabetic type 2 patients (48.5%) were obese (BMI > 30) compared with nondiabetic subjects (29.8%) ($P < 0.001$). The prevalence of T2D was significantly higher among the consanguineous marriages group ($P < 0.001$). Furthermore, among first and second degrees consanguinity, the chances of diabetes were even higher. Systolic and diastolic blood pressure levels were significantly higher in diabetes patients than nondiabetics healthy subjects ($P < 0.001$).

Association with T2D

Table 2 shows the distribution of the $Pro_{12}Ala$ polymorphism in 400 diabetic and 450 nondiabetic subjects. The distribution of the genotypes both in the diabetic and nondiabetic groups was in agreement with the Hardy–Weinberg equilibrium. The table also shows the calculated frequency of the Ala_{12} frequency of the PPAR γ gene in both groups. There was however no significant difference in the allelic frequency of the Ala_{12} variant between the type 2 diabetic subjects and the controls (0.055 vs 0.059, $P = 0.669$), indicating the absence of association between the $Pro_{12}Ala$ polymorphism and the T2D in the Qatar.

Comparison of the clinical characteristics

Tables 3 and 4 show a comparison of the clinical profiles between the Pro/Ala heterozygotes and the homozygous normal genotype (Pro/Pro) with and without diabetes

Table 1 Characteristics of the type 2 Diabetic and normal control subjects

Characteristics	Type 2 diabetic	Normal control	*P*-value
Number of subjects	400	450	
M/F	142/258	180/270	NS
Age (years) (Mean ± SD)	50.3 ± 9.8	50.0 ± 12.8	NS
Age (years)			
Male (Mean ± SD)	49.7 ± 10.8	50.8 ± 12.4	NS
Female (Mean ± SD)	50.6 ± 9.2	49.4 ± 13.1	NS
BMI group			
<25	64(16.0)	118(26.2)	
25–30	142(35.5)	198(44.0)	<0.001
>30	194(48.5)	134(29.8)	
BMI (kg/m^2) Mean ± SD	30.6 ± 5.1	27.5 ± 4.4	<0.001
Consanguinity			
None	211(52.7)	279(61.9)	
Second degree	57(14.3)	62(13.8)	<0.001
First degree	132(33.0)	109(24.3)	
Systolic blood pressure (mmHg)	134.2 ± 16.9	126.1 ± 12.7	<0.001
Diastolic blood pressure (mmHg)	83.9 ± 10.3	80.7 ± 6.9	<0.001

Data are *n* (%), or means ± SD

NS Not significant

Table 2 Allele frequencies of the Pro12Ala polymorphism of PPAR γ 2 in type 2 diabetic patients and control subjects

Subjects	Total (*N*)	Genotype				
		Pro/Pro	Pro/Ala	Ala/Ala	Ala frequency	*P*-value
Diabetic	400	361(90.2)	34 (8.5)	5 (1.3)	0.055	0.669[a]
Nondiabetic	450	401(89.1)	45 (10)	4 (0.9)	0.059	

Odds ratio 95% CI

Dominant (Pro/Pro - Pro/Ala + Ala/Ala)1.1311 0.7256 to 1.7633

Recessive (Pro/Pro + Pro/Ala - Ala/Ala)0.7085 0.1889 to 2.6569

[a] *P*-value for differences between diabetic subjects versus nondiabetic subjects was obtained by Chi square test

concerning the Ala_{12} variant of the PPAR γ gene in relation to age, BMI, and blood pressure.

Discussion

T2D is a chronic condition in Qatar with an estimated prevalence rate of 11–15% affected and a further 11% showing impaired glucose tolerance [8].

Among the candidate genes known for T2D, the Pro12Ala polymorphism of the *PPARγ* gene has been widely implicated in the T2D in various ethnic populations. *PPARγ* gene codes for a transcription factor that is activated by certain fatty acids and the insulin-sensitizing antidiabetic thiazolidiones. The activated form of the factor binds specific DNA sites and facilitates transcription of a wide range of target genes [23]. The *PPARγ-2* isoform is expressed predominantly in adipose tissues and is critical in adipogenesis and insulin action. The rs number for the studied polymorphism is 1805192.

The $Pro_{12}Ala$ allele frequencies in the *PPAR γ2* gene in diabetic subjects or nondiabetic subjects vary among ethnic communities. Frequencies among Caucasians are generally higher than those of the other ethnic groups. Several studies of the Caucasians in different countries have indicated that their $Pro_{12}Ala$ polymorphism was greater than 10% [11, 15, 19]. In contrast, Asian populations have less prevalence of this polymorphism. A Japanese multicenter study involving a large number of samples demonstrated that the Ala_{12} allele frequencies of diabetic and nondiabetic subjects were 2.39 and 4.13%, respectively [12]. In both Chinese and Korean studies, their allele frequencies were less than 5% [16, 17]. A recent publication from the 1998 Singapore National Health Survey reported that the Ala_{12} allele frequency for Malaysians was also less than 5% [16]. Our study with native Qataris have also indicated rather low incidence of this polymorphism (5.5% for diabetic and 5.9% for nondiabetics) as compared to the previous reports in various Caucasians suggesting a common tendency of the Qataris with Asian populations.

Table 3 Comparison of clinical characteristics between diabetic subjects with and without the Pro12Ala variant of PPAR γ

Characteristics	Pro/Pro	Pro/Ala	Ala/Ala	Pro/Ala+Ala/Ala
N (M/F)	129/232	10/24	3/2	13/26
Age (years)	50.2 ± 9.8	52.1 ± 10.5	46.8 ± 6.0	51.4 ± 10.1
Body mass index (kg/m^2)	30.6 ± 5.0	31.2 ± 6.2	30.8 ± 3.3	31.1 ± 5.8
Systolic blood pressure (mmHg)	133.9 ± 16.9	136.5 ± 17.2	137.0 ± 21.7	136.6 ± 17.5
Diastolic blood pressure (mmHg)	84.1 ± 10.5	82.1 ± 9.6	85.6 ± 5.3	82.6 ± 9.1

Characteristics when compared with Pro/Pro vs. Pro/Ala; Pro/Pro vs. Ala/Ala; Pro/Ala vs. Ala/Ala and Pro/Pro vs. Pro/Ala + Ala/Ala revealed no statistical differences

Table 4 Comparison of clinical characteristics between nondiabetic subjects with and without the Pro12Ala variant of PPAR γ

Characteristics	Pro/Pro	Pro/Ala	Ala/Ala	Pro/Ala + Ala/Ala
N (M/F)	157/244	23/22	0/4	23/26
Age (years)	50.9 ± 12.4	43.2 ± 13.5*	33.8 ± 16.2	42.4 ± 13.8†
BMI (kg/m^2)	27.4 ± 4.3	28.4 ± 4.5	29.9 ± 13.6	28.4 ± 4.9
Systolic blood pressure (mmHg)	126.0 ± 12.8	126.7 ± 12.1	–	126.7 ± 12.1
Diastolic blood pressure (mmHg)	80.8 ± 6.9	80.10 ± 7.5	–	80.1 ± 7.5

* Pro/Pro vs. Pro/Ala; *P*-value < 0.001

† Pro/Pro vs. (Pro/Ala + Ala/Ala); *P*-value < 0.001

Several studies have demonstrated that the $Pro_{12}Ala$ substitution in the *PPAR* γ gene is associated with protection against diabetes in both Caucasians and Asians [12, 13, 24–30]. The most extensive study was a meta-analysis involving 3000 individuals that found 1.25-fold ($P = 0.002$) increase in the diabetes risk associated with the Pro_{12} allele (85% frequency) [13]. The reduced frequency of the Ala_{12} allele among Qataris, relative to many Caucasian populations, potentially indicates that a larger number of the Qatari population is at risk of T2D. Furthermore, the controls in our study were self-reported and were only checked for diabetes by random glucose measurement. A better selection procedure for diabetes would require oral glucose tolerance test. Future studies should also include detailed patient and control characterization based on laboratory data such as triglycerides, total cholesterol, HDL, LDL, and glycated haemoglobin (HbA_{1c}) measurements.

Our result is consistent with several previous studies, which reported an absence of association between the $Pro_{12}Ala$ polymorphism of the PPARγ gene and the T2D. However, a meta-analysis from 30 independent studies with a total number of 19,136 subjects demonstrated that the Pro12Ala carriers had significantly higher BMI than the noncarriers, particularly in those with the higher BMI (BMI > 27) [14].

There are some possible explanations for the effects of this polymorphism on BMI. Lindi et al. [25] reported an interesting finding in their 10-year follow-up study that the $Pro_{12}Ala$ carriers have a tendency to gain weight over time. They speculated that higher insulin sensitivity could explain why the subjects with the $Pro_{12}Ala$ allele gained more weight during follow-up. In our study, the association of $Pro_{12}Ala$ allele with higher BMI in nondiabetic controls was more prominent than in diabetic subjects. Accordingly to this, the controls with $Pro_{12}Ala$ may have higher insulin sensitivity and gain weight without developing diabetes.

The study by Luan et al. [27] suggested that when the ratio of dietary polyunsaturated fat and saturated fat is low, the BMI in $Pro_{12}Ala$ carriers is greater than that in Pro_{12} homozygotes, but when the ratio is high, the opposite is seen. In general, Qatari population consumes a high-carbohydrate and high-fat diet from many sources. Furthermore, in the most recent study, the impact of high consanguinity on the prevalence of common adult diseases in the Qatari population was investigated [31, 32], the rate of consanguinity in the present generation was 51% (95% CI = 47.7–54.4) with a coefficient of inbreeding 0.023724.

Similar to the observations from several groups [24, 26], among other parameters studied, blood pressures, especially the systolic blood pressure in $Pro_{12}Ala$ carriers, were significantly higher than Pro/Pro homozygotes in diabetic subjects. Although the small number of Pro/Ala carriers might restrict our interpretation, this observed phenomenon might be related to the notion that once diabetes has developed, the protective effect of Ala_{12} allele may be lost [2].

In summary, this is the first study on $Pro_{12}Ala$ polymorphism performed in Qatar, and in this population, we

failed to find an association between this polymorphism and T2D, but found no association with obesity.

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