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ORIGINAL ARTICLE

Peroxisome Proliferator-activated Receptor Gamma: Genetic Polymorphisms Are Not Associated With Metabolic Syndrome in Taiwan

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Background: Peroxisome proliferator-activated receptor gamma (PPARγ) is one of the transcriptional regulators of adipocyte differentiation; it was suggested to be a candidate gene modulating obesity, insulin resistance, and dyslipidemia.
Aim: This study explored the association between PPARγ genetic polymorphisms (Pro12Ala and C161T) and the risk of metabolic syndrome (MetS) in Han Taiwanese participants.
Methods: This cross-sectional study included 346 participants with MetS and 804 without MetS. The parameters for fasting serum concentrations of glucose and lipids were measured. The presence or absence of MetS was determined according to the modified criteria of the third report of the National Cholesterol Education Program's Adult Treatment Panel (NCEP ATP III). PPARγ genetic polymorphisms were genotyped with real-time polymerase chain reaction.
Results: Frequencies of the Pro12Ala Ala allele and C161T T allele among non-MetS participants were 5.2% and 26.0%, respectively. The Pro12Ala and C161T polymorphisms were not significantly associated with MetS risk (odds ratio = 0.75, 95% confidence interval = 0.47–1.21 and odds ratio = 0.92, 95% confidence interval = 0.70–1.20). No significant association was observed between haplotypes of the *PPARγ* gene and MetS risk even following stratification by sex.
Conclusion: This result suggests that PPARγ C161T and Pro12Ala genetic polymorphisms may not be associated with MetS among Han Taiwanese.

1. Introduction

Metabolic syndrome (MetS) represents a global public health problem because it leads to diabetes mellitus (DM), coronary heart disease, and cardiovascular diseases.[1,2] In Taiwan, the incidence of MetS is approximately 15.6% of the general population, with a sex predilection, leaving men (17.1%) more likely than women (13.5%) to have this problem.[3] Five of the 10 leading causes of death in Taiwan including cardiovascular accidents, coronary artery disease (CAD), DM, hypertension, and chronic renal disease are associated with MetS.[4]

Recent studies have suggested that genetic and environmental factors may play important roles in the pathogenesis of multifactorial diseases such as obesity, DM, and MetS.[5] Among the reported potential genetic determinants, the peroxisome proliferation-activated receptor (*PPAR*) gene has been extensively examined because of its involvement in adipocyte differentiation, lipid metabolism, and glucose homeostasis.[6–8] PPARs are a family of ligand-activated transcription factors with three isotypes: PPARα,

Conflicts of interest: None.

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PPARδ, and PPARγ.[9,10] PPARγ is a transcriptional regulator that is abundantly expressed in adipose tissues that regulates adipocyte differentiation as well as glucose and lipid metabolism.[11,12] The most prevalent human polymorphism in the *PPARγ* gene is Pro12Ala of exon 1.[13] The next most frequently occurring PPARγ polymorphism is a C to T substitution in exon 6 (C161T), which was first identified by Meirhaegue et al in 1998.[14]

The associations between Pro12Ala and C161T polymorphisms of the *PPARγ* gene and the risk of MetS have been demonstrated in the literature, but these results remain controversial.[15–22] In a large French population-based study, Meirhaeghe et al[17] found no association between PPARγ Pro12Ala and C161T polymorphisms and the risk of MetS. However, a recent study in Japan showed that the C161T CC genotype may increase the risk of MetS in young men with low cardiorespiratory fitness.[18] The Pro12Ala polymorphism plays no role in MetS risk among middle-aged Swedish people in a study conducted by Montagnana.[21] Passaro et al[15] found that the carriers of the Pro12Ala variant do not show an association with MetS among 364 Caucasians. A cross-sectional, population-based survey of 572 unrelated healthy Argentinian males showed that the Pro12Ala genotype is associated with a high risk for MetS.[16]

A few reports have discussed the association between these two polymorphisms of the PPARγ gene with MetS in Han populations. Liu et al[23] found no association between Pro12Ala and C161T polymorphisms and MetS among participants resident in Beijing, China. However, Yang et al[20] suggested that C161T, but not the Pro12Ala polymorphism, may be associated with MetS among 423 Chinese participants in Northern China. Furthermore, Shi et al[22] found no association of Pro12Ala and C161T polymorphisms with MetS in a Southern Chinese population. The aim of this study was to determine the prevalence of the PPARγ Pro12Ala and C161T polymorphisms, and to explore the associations of these polymorphisms with MetS in the general adult Taiwanese population.

2. Methods

2.1. Participants

For this cross-sectional study, we recruited 1150 healthy adult participants who underwent a comprehensive health checkup at China Medical University Hospital in 2006. The study was approved by the Human Research Ethics Committee of the hospital, and written informed consent was obtained from each participant. The 1150 participants were divided into two subgroups: the MetS group and the non-MetS group. The MetS criteria were determined according to the modified third report of the National Cholesterol Education Program's Adult Treatment Panel (NCEP ATP III). The NCEP ATP III defines MetS as the presence of at least three of the following: (1) a fasting plasma glucose of ≥110 mg/dL; (2) serum triglycerides of ≥150 mg/dL; (3) serum high-density lipoprotein-cholesterol (HDL-C) of <40 mg/dL in men and <50 mg/dL in women; (4) a blood pressure of ≥130/85 mmHg; and (5) a waist circumference (WC) of >90 cm in men and >80 cm in women.[23] Finally, 346 participants with MetS (211 males) aged 55.3 ± 11.4 years and 804 participants without MetS (465 males) aged 48.3 ± 11.4 years were studied.

2.2. Data scope and collection

Anthropometric measurements were obtained during a complete physical examination. The height and weight of the participants wearing light clothing and without shoes were measured using an autoanthropometer (Super-view, HW-666, Taipei, Taiwan). The body mass index (BMI) was derived from the formula of weight/height^2 (kg/m^2). The WC was measured at a point midway between the inferior margin of the last rib and the iliac crest in a horizontal plane with the participants in a standing position. The WC was measured to the nearest 1 mm. Blood pressure was measured at the right brachial artery using a random-zero sphygmomanometer after the participants had remained in a seated position for 20 minutes. The mean of two blood pressure recordings was used for the statistical analyses.

Data on sociodemographic characteristics, including age, sex, education level, marital status, cigarette smoking, alcohol consumption, and physical activity, were collected using a self-administered standardized questionnaire. Cigarette smoking and alcohol consumption were classified into three groups: current users, nonusers, and ex-users.

2.3. Laboratory examination

Twelve-hour overnight fasting blood samples were collected in K_2EDTA tubes and serum separator tubes (BD Vacutainer, Becton Dickinson, Plymouth, UK). Samples were taken from a puncture of the antecubital vein in the morning between 8:00 AM and 10:00 AM and were sent for analysis within 4 hours of collection. Plasma lipids were determined using an enzymatic colorimetric method (Synchron LX-20; Beckman Coulter, Brea, CA, USA) at the clinical laboratory department of the hospital. The fasting plasma glucose level was determined using a glucose oxidase method (Astra-8, Beckman Instruments, Fullerton, CA, USA). Genomic DNA was extracted from blood samples collected in the K_2EDTA tubes by using a Gentra Puregene Blood Kit (Gentra Systems, Minneapolis, MN, USA). The extracted DNA was stored in a −80°C freezer until performing the genotyping analyses.

2.4. Genotyping

Genotypes of the PPARγ Pro12Ala (rs1801282) and the silent C161T (His447His, rs3856806) polymorphisms were determined by a 5′-exonuclease assay using allele-specific TaqMan probes. The TaqMan single-nucleotide polymorphism (SNP) genotyping assay kits were purchased from Applied Biosystems (Foster City, CA, USA) with assay IDs C_11922961_30 and C_1129864_10. A polymerase chain reaction (PCR) was conducted using an allelic discrimination assay in the StepOne Real-Time PCR System (Applied Biosystems). After the PCR cycles (initial denaturation at 60°C for 30 seconds, followed by 95°C for 10 minutes, and then 40 cycles of 92°C for 15 seconds and 60°C for 60 seconds), the genotypes were distinguished using automated sequence detection software (SDS 2.3, Applied Biosystems), resulting in the identification of three genotypes (i.e., major-allele homozygotes, heterozygotes, and minor-allele homozygotes) for each polymorphism. In addition, for quality control, 10% of the samples were randomly selected to perform repeated assays; the results were 100% concordant.

2.5. Statistical analysis

Hardy-Weinberg equilibrium and linkage disequilibrium (LD, measured by D′) of the two PPARγ polymorphisms were assessed using Testing Haplotype EffectS In Association Studies (THESIAS).[24] After excluding individuals with missing values, the haplotypes were inferred using THESIAS. Haplotype effects were tested for all possible haplotypes in an additive model and were shown as the difference from the most common haplotype. A two-sample Student *t* test was used to compare differences in continuous variables between the MetS and non-MetS groups, and Pearson chi-square test was used to compare categorical variables. Because of the relatively low allele frequency of the variant alleles for both the Pro12Ala and C161T polymorphisms, participants were also

Table 1 Demographic characteristics of the study population

Variable	MetS, *n* (%) *n* = 346	Non-MetS, *n* (%) *n* = 804
Sex		
Male	211 (61.0)	465 (57.8)
Female	135 (39.0)	339 (42.2)
Age* (mean ± SD), y	55.3 ± 11.4	48.3 ± 11.4
Years of education*		
<15	148 (48.2)	173 (23.5)
15–18	63 (20.5)	202 (27.4)
≥18	96 (31.3)	362 (49.1)
Marital status*		
Married	292 (95.7)	670 (91.0)
Unmarried	13 (4.3)	66 (9.0)
BMI*(mean ± SD), kg/m^2	27.4 ± 3.53	22.9 ± 2.96
Cigarette smoking*		
Never	209 (62.6)	537 (68.4)
Current smoker	75 (22.5)	172 (22.6)
Ex-smoker	50 (15.0)	71 (9.0)
Alcohol consumption*		
Never	197 (58.6)	523 (66.6)
Current drinker	117 (34.8)	237 (30.2)
Ex-drinker	22 (6.6)	25 (3.2)
Physical activity		
No	138 (42.1)	309 (40.0)
Yes	190 (57.9)	464 (60.0)

* $p < 0.05$; numbers might not be equal to the total number because of missing data.
BMI = body mass index; MetS = metabolic syndrome; SD = standard deviation.

classified as being either carriers or noncarriers of the variant alleles. A logistic regression model was used to calculate the odds ratios (ORs) and their 95% confidence intervals (CIs) to assess the association between each polymorphism and the risk of MetS. The MetS-associated diseases were logarithmically transformed prior to statistical analysis to meet the normality assumption. All statistical analyses were performed using the Statistical Analysis Software (SAS) package (version 9.1.3 for Windows; SAS Institute, Cary, NC, USA). Two-sided $p < 0.05$ were considered significant.

3. Results

The demographic characteristics of the participants are summarized in Table 1. Compared to the non-MetS participants, those with MetS were more likely to be older, less educated, married, cigarette smokers, and alcohol drinkers ($p < 0.05$). The MetS participants also had a substantially greater mean BMI (27.4 ± 3.53 vs. 22.9 ± 2.96 kg/m^2).

Table 2 shows the genotypic distributions of the two polymorphisms for both MetS and non-MetS groups. Frequencies of the Pro12Ala Ala allele and C161T T allele among non-MetS participants were 5.2% and 26.0%, respectively. These allelic frequencies were in Hardy-Weinberg equilibrium. After adjusting for age and sex, the Pro12Ala ProAla + AlaAla genotype was not found to be associated with MetS when compared to the Pro12Ala ProPro genotype (OR = 0.75, 95% CI = 0.47–1.21). The C161T polymorphism was also not significantly associated with MetS following adjustment for age and sex (OR = 0.92, 95% CI = 0.70–1.20).

Table 3 Association between haplotypes in peroxisome proliferator-activated receptor gamma (*PPARγ*) gene and the risk of metabolic syndrome (MetS)

Haplotype*				
Pro12Ala (C > G)	C161 T (C > T)	MetS (%)	Non-MetS (%)	OR (95% CI)†
C	C	0.749	0.727	1.00
C	T	0.209	0.220	0.95 (0.76–1.19)
G	C	0.011	0.013	0.86 (0.33–2.25)
G	T	0.031	0.039	0.73 (0.43–1.27)

* The linkage disequilibrium (LD, measured by D′) values for the Pro12Ala G allele and C161T T allele was 0.66 ($p < 0.01$)
† Adjusted for age and sex.
CI = confidence interval; OR = odds ratio.

Four haplotypes were observed among the four possible haplotypes defined by the two PPARγ polymorphisms in our study population (Table 3). Linkage analysis showed a significant association between the Pro12Ala Ala allele and the C161T T allele pairwise combination (D′ = 0.66, $p < 0.01$). The most common CC haplotype, which is severed as the reference haplotype in our analyses, was present in 72.7% of the non-MetS group. We did not find any of the haplotypes to be associated with MetS.

To investigate the pathological mechanisms of how polymorphisms in the *PPARγ* gene may influence the risk of MetS, we tested both PPARγ polymorphisms for associations with the individual associated disease of MetS among our study participants (Table 4). Neither the Pro12Ala nor the C161T genotype was associated with any of the individual associated diseases of MetS in the current study population. We also failed to detect any association between the haplotypes of Pro12Ala and C161T genotypes and the individual components of MetS after stratifying by sex (Table 5).

4. Discussion

This investigation of the possible association between PPARγ polymorphisms and MetS and its associated diseases was conducted in an ethnic Taiwanese population. In our sample, the allele

Table 2 Association between polymorphisms in peroxisome proliferator-activated receptor gamma (*PPARγ*) gene and the risk of metabolic syndrome (MetS)

Polymorphism	All		Male		Female	
	MetS/Non-MetS	OR (95% CI)†	MetS/Non-MetS	OR (95% CI)‡	MetS/Non-MetS	OR (95% CI)‡
Pro12Ala (C > G)						
ProPro	318/722	1.00	194/409	1.00	124/313	1.00
ProAla	27/80	0.74 (0.46–1.19)	16/54	0.62 (0.34–1.12)	11/26	1.07 (0.48–2.40)
AlaAla	1/2	1.29 (0.11–15.6)	1/2	1.18 (0.10–13.6)		—
ProPro	318/722	1.00	194/409	1.00	124/313	1.00
ProAla + AlaAla	28/82	0.75 (0.47–1.21)	17/56	0.64 (0.36–1.14)	11/26	1.07 (0.48–2.40)
C161 T (C > T)						
CC	200/444	1.00	112/250	1.00	88/194	1.00
CT	126/302	0.94 (0.71–1.24)	82/184	0.99 (0.70–1.40)	44/118	0.92 (0.57–1.48)
TT	20/58	0.82 (0.47–1.43)	17/31	1.30 (0.69–2.47)	3/27	0.23 (0.07–0.84)*
CC	200/444	1.00	112/250	1.00	88/194	1.00
CT + TT	146/360	0.92 (0.70–1.20)	99/215	1.03 (0.74–1.43)	47/145	0.78 (0.49–1.23)

* $p < 0.05$
† Adjusted for age and sex
‡ Adjusted for age.
CI = confidence interval; MetS = metabolic syndrome; OR = odds ratio.

Table 4 Association of polymorphisms in the peroxisome proliferator-activated receptor gamma (*PPARγ*) gene with components of metabolic syndrome (MetS) *

Component	Pro12Ala (C > G)		C161 T (C > T)	
	ProPro	ProAla + AlaAla	CC	CT+TT
Waist circumference (cm)	82.4 ± 10.8	82.6 ± 10.3	82.3 ± 10.7	82.5 ± 10.9
Serum HDL-C (mg/dL)	43.8 ± 14.7	43.5 ± 12.8	43.8 ± 14.4	43.7 ± 14.7
Serum triglyceride (mg/dL)	118.9 ± 91.0	115.9 ± 108.4	119.4 ± 92.3	117.5 ± 93.5
SBP (mm Hg)	119.1 ± 16.3	117.5 ± 14.7	119.7 ± 16.2	118.0 ± 16.0
DBP (mm Hg)	76.0 ± 9.7	75.1 ± 9.1	75.8 ± 9.6	76.0 ± 9.6
Plasma glucose (mg/dL)	97.6 ± 25.6	94.6 ± 17.2	98.1 ± 25.6	96.2 ± 24.0

* All data are expressed as the mean value ± standard deviation.
DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure.

frequencies of Pro12Ala (Pro: 0.951; Ala: 0.049) and C161T (C: 0.75 and T: 0.25) of the *PPARγ* gene were comparable to those reported in other Asian populations.[19,20,25–27] We did not detect a significant association between the PPARγ Pro12Ala and C161T genotypes and MetS risk in the general Taiwanese population. In addition, we did not observe any significant associations between the two PPARγ polymorphisms and any of the individual components of MetS.

Although some studies have suggested that there is an association between the PPARγ Pro12Ala polymorphism and MetS, others have reported negative associations leaving the results in conflict.[15–21,28] The lack of an association between the Pro12Ala polymorphism and MetS risk in our study is in agreement with previous studies conducted in Han Chinese populations[19,20] and a study on an Italian population.[29]

Because C161T was first identified among French patients, several reports have been published concerning its MetS risk.[17–20,26] However, these prior studies yielded inconsistent results.[17–20,26] Although there are reports of an association between C161T and MetS in the literature,[18,20] we did not observe any significant differences between either MetS or its individual components and the C161T polymorphisms investigated in the current study. This lack of consistency in reported results may stem from ethnic effects, which also seems to play a role in the association between C161T polymorphisms and other metabolically related conditions. For example, in Caucasian women, the C161T polymorphism of the human *PPARγ* gene was found to be associated with insulin resistance and was considered to be a stronger predictor of fasting insulin levels and insulin resistance than the Pro12Ala polymorphism.[30] In contrast, reports from a Brazilian population and a Chinese population showed that PPARγ C161T is not associated with insulin sensitivity or blood glucose levels.[31,32]

The prevalence of the homozygous C161T TT genotype is low in Caucasian populations (average 1.6–2.5%).[14,33] In contrast, we observed a higher frequency of the TT genotype in our Han population (7.2%), as did previous reports investigating a Han population (4.3–9.2%).[19,20,27,34] Thus, it is possible that genetic variation across the ethnic groups studied in the literature played an important role in the lack of continuity of the findings. Previous reports have suggested the possibility that there are haplotype effects influencing the association between Pro12Ala and C161T polymorphisms and MetS risk.[35,36] Therefore, we subdivided participants into four groups according to the different combinations of the two polymorphisms. However, we found no association between any of these combinations and MetS among our Taiwanese participants.

One limitation of this study is that our participants were recruited from a single tertiary medical center. Therefore, the results may mainly refer to this local population. However, because this medical center is the primary point of care for medical services in a large metropolitan area in central Taiwan, our findings may

Table 5 Age- and sex-adjusted odds ratio and 95% confidence interval for the association of peroxisome proliferator-activated receptor gamma (*PPARγ*) gene with components of metabolic syndrome (MetS) *

	Abdominal obesity	Decreased HDL-C	Hypertriglyceridemia	High blood pressure	Impaired fasting glucose
Pro12Ala (C>G) ProAla+AlaAla vs. ProPro					
All	1.14 (0.74–1.75)	0.97 (0.65–1.45)	0.75 (0.46–1.23)	0.83 (0.53–1.29)	1.05 (0.61–1.80)
Male	1.04 (0.61–1.76)	0.79 (0.49–1.29)	0.63 (0.35–1.14)	0.69 (0.41–1.18)	1.25 (0.67–2.33)
Female	1.36 (0.65–2.86)	1.45 (0.71–2.97)	1.16 (0.48–2.78)	1.23 (0.56–2.69)	0.66 (0.21–2.02)
C161T (C>T) CT+TT vs. CC					
All	1.11 (0.86–1.44)	0.86 (0.68–1.09)	0.93 (0.70–1.23)	0.90 (0.70–1.16)	0.86 (0.62–1.19)
Male	1.24 (0.89–1.72)	0.91 (0.67–1.24)	0.82 (0.59–1.15)	1.08 (0.79–1.49)	1.02 (0.68–1.52)
Female	0.97 (0.64–1.49)	0.80 (0.55–1.17)	1.27 (0.77–2.09)	0.65 (0.42–1.03)	0.63 (0.35–1.13)
Haplotype (Pro12Ala/C161T)					
All					
CT vs. CC	1.08 (0.87–1.35)	0.95 (0.77–1.16)	0.98 (0.77–1.24)	0.91 (0.73–1.13)	0.86 (0.65–1.14)
GC vs. CC	1.39 (0.56–3.45)	1.62 (0.67–3.95)	1.27 (0.48–3.33)	0.98 (0.39–2.44)	0.50 (0.11–2.23)
GT vs. CC	1.08 (0.64–1.82)	0.83 (0.53–1.31)	0.64 (0.34–1.18)	0.77 (0.46–1.29)	1.14 (0.60–2.18)
Male					
CT vs. CC	1.27 (0.96–1.67)	1.02 (0.78–1.33)	0.93 (0.70–1.24)	1.04 (0.80–1.37)	1.02 (0.73–1.42)
GC vs. CC	1.04 (0.26–4.12)	1.36 (0.40–4.67)	1.35 (0.40–4.63)	0.36 (0.07–1.75)	0.52 (0.07–4.03)
GT vs. CC	1.13 (0.62–2.03)	0.75 (0.45–1.26)	0.53 (0.25–1.10)	0.83 (0.47–1.48)	1.33 (0.67–2.67)
Female					
CT vs. CC	0.85 (0.59–1.23)	0.85 (0.62–1.17)	1.11 (0.72–1.72)	0.70 (0.46–1.05)	0.63 (0.36–1.11)
GC vs. CC	1.64 (0.48–5.67)	1.79 (0.44–7.23)	1.09 (0.23–5.18)	1.99 (0.55–7.19)	0.45 (0.05–4.22)
GT vs. CC	1.11 (0.38–3.27)	1.23 (0.48–3.14)	1.20 (0.37–3.87)	0.73 (0.22–2.36)	0.72 (0.14–3.76)

* Abdominal obesity: waist circumference >90 cm in men and >80 cm in women; decreased HDL-C: serum HDL-C <40 mg/dL in men and <50 mg/dL in women; hypertriglyceridemia: serum triglyceride ≥150 mg/dL; high blood pressure: blood pressure of ≥130/85 mmHg; impaired fasting glucose: plasma glucose ≥110 mg/dL.
HDL-C = high-density lipoprotein cholesterol.

reflect conditions similar to that of the general population. Although it is also possible that this study suffered from recall bias, we think that its effect would have been mitigated because our cases would most likely not have known that they had MetS prior to filling out the questionnaire administered during the health checkup when the condition was diagnosed. In conclusion, we confirmed a higher frequency of PPARγ C161T in our Han Taiwanese population than that has been reported in Caucasian populations. The PPARγ Pro12Ala and C161T polymorphisms were apparently not significantly associated with MetS or its individual components even after stratifying by sex.

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