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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