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Associations of *PPAR-γ*, *APM1* and *APOC1* gene polymorphisms with metabolic syndrome in children: A case-control study

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ABSTRACT

Objectives: We aimed to evaluate the association of genes of peroxisome proliferator-activated receptor-γ (*PPARγ*), adiponectin (*APM1*) and apolipoprotein E (*APOC1*) polymorphisms with metabolic syndrome (MS) in children.
Methods: A matched case-control study was conducted with 114 MS cases and 114 controls. Anthropometric measurements and a questionnaire survey were conducted in all subjects. The polymerase chain reaction method and DNA sequencing were used for genotyping of single nucleotide polymorphism for *PPARγ* (rs1801282), *APM1* (rs266729) and *APOC1* (rs4420638).
Results: After adjustments for sex, age, educational level of parents, physical activity, dietary patterns, pubertal development and household income, there were significant associations between rs266729 (OR = 1.91, 95% CI: 1.01–3.62), rs4420638 (OR = 2.21, 95%CI: 1.19–4.10) polymorphisms and the risk of MS in children. However, no association was found between rs1801282 polymorphism and MS.
Conclusion: The results showed that the genetic variants of the *APM1* and the *APOC1* were associated with MS in children.

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1. Introduction

The metabolic syndrome (MS) is characterized by the clustering of metabolic abnormalities including abdominal obesity, dyslipidemia [high triglycerides (TG) or low level of high-density lipoprotein cholesterol (HDL-C)], insulin resistance and high blood pressure (BP), which raises the risk for cardiovascular disease, diabetes and stroke (Vega, 2001; Air & Kissela, 2007; Isomaa et al., 2001). With socio-economic development and the changes of lifestyle, MS in children is growing worldwide (Weiss et al., 2004). The prevalence rates of MS in children vary from 2.6 to12.8% in different populations or regions (Miller et al., 2014; Li et al., 2014; Dias Pitangueira et al., 2014; Fadzlina et al., 2014).

The etiology of MS is complicated, which involves genetic susceptibility, environmental factors and lifestyles. Genetic factors account for the inter-individual differences in susceptibility to MS (Cornier et al., 2008). Previous studies reported that the main components of MS such as high BP, obesity, disorders of glucose and lipid metabolism are influenced by multiple gene loci (Bosy-Westphal et al., 2007; Pankow et al., 2004; Rich et al., 2005). Each involved gene locus may influence the development of MS in children by its pathway.

Peroxisome proliferator-activated receptor gamma (PPARγ) is a nuclear transcription factor whose metabolic pathways are involved in fat synthesis and promoting the storage of triglycerides in fat cells (Auwerx et al., 1996; Spiegelman & Flier, 1996). PPARγ plays a positive role in control of fat storage and release to maintain energy balance and promoting adipocyte gene expression, and the *PPARγ* is therefore a promising candidate gene for the predisposition to MS. Pro12Ala polymorphism, located in the exon 2 of the *PPARγ* gene, commonly results in a Proline(Pro) to Alanine(Ala) substitution at codon12, which can modulate the transcriptional activity of the *PPARγ* gene (Deeb et al., 1998; Masugi et al., 2000). Several studies had conducted on the association of *PPARγ* Pro12Ala (rs1801282) single nucleotide polymorphisms (SNPs) with MS in adults, however, contradictory results were reported from these studies (Rooki et al., 2014; Passaro et al., 2011; Tellechea et al., 2009; Montagnana et al., 2008). Up to date, there is no report about the association between *PPARγ* gene and MS in children.

Abbreviations: MS, metabolic syndrome; PPARγ, peroxisome proliferator-activated receptor-γ; APM1, adiponectin; APOC1, apolipoprotein C; SNP, single nucleotide polymorphism; PCR, polymerase chain reaction; OR, odds ratio; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; Pro, Proline; Ala, Alanine; T2DM, type II diabetes mellitus; CNY, China Yuan; LDL-C, low-density lipoprotein cholesterol; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; BMI, body mass index; HWE, Hardy - Weinberg genetic equilibrium.

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Adiponectin (APM1) is an adipocytokines secreted by mature fat cells which is linked to relieve insulin-resistance, have anti-inflammatory and anti-atherosclerotic effects and be involved in pathogenesis of MS (Li et al., 2011). Variability of APM1 may lead to this cytokine deficiency. About 30–70% variability in APM1 can be attributed to genetic factors (Comuzzie et al., 2001). Previous study reported that -11377C/G (rs266729) is a common SNP in the *APM1* promotor and has been shown to be associated with serum APM1 levels (Vasseur et al., 2002).

Apolipoprotein C1 (APOC1) plays an important role in the metabolism of in high density lipoprotein and very low density lipoprotein, which is associated with elevated plasma glucose, atherogenic dyslipidemia, vascular inflammation and central obesity (Avery et al., 2011; Anoop et al., 2010). Previous studies found that the *APOC1* rs4420638 SNP was associated with lower plasma HDL-C level, higher total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels and higher total cholesterol/HDL-C and LDL-C/HDL-C ratios (Kathiresan et al., 2008; Teslovich et al., 2010; Willer et al., 2009; Liu et al., 2011). However, the association between *APOC1* rs4420638 SNP and MS in children remains not clear.

In this study, we conducted a case-control study to investigate the relationships between three SNPs (*PPARγ* Pro12Ala rs1801282, *APM1* rs266729 and *APOC1* rs4420638) and MS in school students in Guangzhou City, aiming to provide novel knowledge on genetic predisposition in the development of MS in children.

2. Materials and methods

2.1. Study subjects

School children were screened for MS by Guangzhou Center for Disease Control and Prevention between April and June in 2009 in Guangzhou City. Epidemiological Information and blood samples were obtained. MS was diagnosed by de Ferranti et al. (2004) standard [if they met three or more of the following criteria: waist circumference(WC) ≥ the age-specific and gender-specific 75th percentile; systolic blood pressure (SBP)/diastolic blood pressure (DBP) ≥ the age-specific and gender-specific 90th percentile; Serum TG ≥ 100 mg/dl; Serum HDL-C ≤ 50 mg/dl; Fasting plasma glucose(FPG) ≥ 110 mg/dl]. The criteria of case inclusion were: 1) 7–10 years old school children; 2) diagnosed as MS. Those who did not suffer from MS, with normal body mass index, waist-to-hip ratio, blood pressure, blood sugar, cholesterol and other metabolic indicators were randomly selected as the controls. Children with heart, liver, endocrine, genetic, metabolic, kidney diseases or children using drugs for regulating blood pressure, blood lipids were excluded.

There were 114 pairs of eligible subjects, including 114 MS cases and 114 control subjects matched by age and sex.

2.2. Anthropometric measurement

Anthropometrics parameters, including body weight, height, waist circumference, hip circumference, waist/hip ratio, SBP and DBP were measured by using standard methods. The body mass index (BMI) was obtained from the ratio of weight (kg) to height squared (m^2). Fasting serum lipid profile and fasting blood glucose were measured with standard enzymatic techniques.

2.3. Demographic characteristic and lifestyle

Information about usual dietary patterns, pubertal development, physical activity levels, educational levels of parents and family income was collected by using a standard questionnaire. The dietary pattern was identified by a cluster analysis with the factor scores reflecting patterns of consumption of food categories which had been identified by an exploratory factor analysis firstly as Salameh et al. (2014) described. Firstly, the KMO statistic and the *p* value for Bartlett's Test of Sphericity were calculated. KMO statistic was 0.701 and *p* value for Bartlett's Test of Sphericity was <0.001, which indicated the samples can be used for factor analysis. Secondly, 7 factors accounting for 60.20% of dietary variation were selected for cluster analysis. Thirdly, the dietary pattern was classified into three patterns by a cluster analysis (Liu, 2011). We classified physical activity levels according to the formula presented by America Medical Association (Trumbo et al., 2002). Briefly, we first valued each physical activity by using a questionnaire with metabolic equivalent (METs) which was the energy per weight per hour for a physical activity. Then we calculated the physical activity level (PAL) according to the formula: male, $\Delta PAL = [(A\ METs\text{-}1) \times 1.34 \times (B\ min)]/1440\ min$ (A METs, METs for physical activity A; B, the time for this physical activity); female, $\Delta PAL = [(A\ METs\text{-}1) \times 1.42 \times (B\ min)]/1440\ min$, $PAL = 1.0 + \Delta PAL$. When a PAL value was ≥1.7, it was defined as sufficient. When a PAL value was <1.7, it was defined as insufficient.

2.4. SNP genotyping

Genomic DNA was extracted from peripheral blood using a DNeasy tissue kit (Qiagen) according to the manufacturer's protocol. The polymerase chain reaction (PCR) was performed in a 25 μl reaction mixture containing 12.5 μl GoTaq Green Master Mix (2×), 1 μl primer, 2 μl DNA and 10 μl nuclease-free water. The PCR condition were 95 °C for 2 min, followed by 35 cycles of 30 s at 95 °C, 30 s at 53 °C for rs1801282, 30 s at 55 °C for rs266729, 30 s at 62 °C for rs4420638, respectively. Then 30 s at 72 °C with a final step at 72 °C for 5 min. PCR products were verified on a 1.0% agarose gel and photographs were taken. Genotyping was carried out by direct sequencing. For genotyping quality control, 5% of the samples were measured in duplicates and nuclease-free water was used as negative control.

2.5. Statistical analysis

Allele frequency and genotype distribution of polymorphism of each SNP were tested for Hardy-Weinberg equilibrium among controls. The association of genotypes with MS was estimated by computing the odds ratios (ORs) and their 95% confidence intervals (CIs). Multivariate logistic regression analysis was used for controlling potential confounders, such demographic factors and lifestyle factors. All statistical tests were performed using SPSS 19.0. A two-tailed *p* value <0.05 was considered statistically significant.

2.6. Ethics

The study was approved by the Ethical Committee of the National Institute for Nutrition and Food Safety, Chinese Center for Disease Control and Prevention. Written informed consent was obtained from subjects and their parents.

3. Results

3.1. Demographic characteristics of study subjects

The demographic characteristics of the study participants with (n = 114) MS and without (n = 114) MS are shown in Table 1. There were no significant differences for sex, age, educational levels of their parents, household income per capita, pubertal development and dietary patterns between the cases and the controls. But significant difference was found for physical activity in the two groups ($p = 0.001$).

3.2. Distribution of individual components of MS

In 114 control children, BP, WC, TG, HDL-C, BMI and FPG were normal. In 114 children of cases, high WC was 92.1% with the highest frequency among individual components of MS, followed by high TG

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