Associations of the hypertension-related single nucleotide polymorphism rs11191548 with high-density lipoprotein cholesterol and leptin in Chinese children

Lijun Wu 1†, Liwang Gao 1†, Xiaoyuan Zhao 1, Meixian Zhang 1, Jianxin Wu 2 and Jie Mi 1*

Abstract

Background: The genome-wide association study has founded hypertension-related single nucleotide polymorphism (SNP) rs11191548 near CYP17A1 encoding a key enzyme involved in steroid metabolism, but the molecular mechanisms are not understood and the associations of the SNP with hypertension-related traits are not fully described, especially in children. The aim of the present study is to investigate the associations between the SNP and two hypertension-related traits, lipids and leptin.

Methods: We genotyped the SNP in Beijing Child and Adolescent Metabolic Syndrome (BCAMS) study. A total of 3503 children participated in the study.

Results: The SNP rs11191548 was significantly associated with high-density lipoprotein cholesterol (HDL) (P = 0.014 and 0.028, respectively) and leptin (P = 0.011 and 0.026, respectively) under an additive model after adjustment for age, gender, and systolic blood pressure (SBP) or diastolic blood pressure (DBP). There was a statistically significant association of rs11191548 with high leptin after adjustment for age, gender, and SBP or DBP. The P-values remain significant after correction for multiple testing.

Conclusions: We demonstrate for the first time that the SNP rs11191548 near CYP17A1 is associated with HDL and leptin in Chinese children. These novel findings provide important evidence that HDL and leptin maybe possibly mediate the process of CYP17A1 involved in hypertension.

Keywords: Leptin, High-density lipoprotein cholesterol, CYP17A1, Hypertension-related single nucleotide polymorphism

Background

In recent years, the prevalence of hypertension has been increasing in most parts of the world, and hypertension is a major threat to public health [1]. Childhood hypertension is a predictor of adult hypertension and cardiovascular disease [2, 3].

Previously, multiple single nucleotide polymorphisms (SNPs) related to hypertension have been identified by genome-wide association studies [4–6]. Among those identified SNPs, the SNP rs11191548, located near the 3′ noncoding region of the gene CYP17A1 encoding the cytochrome P450 enzyme CYP17A1 as a key enzyme involved in steroid metabolism, showed a significant association with hypertension in European adults, Japanese and Chinese adults, and Chinese children [6–9]. However, the molecular mechanisms are not understood and the associations of the SNP with other hypertension-related traits are not fully described.

Dyslipidemia are recognized as a strong predictor of cardiovascular disease and several studies have suggested a positive correlation between dyslipidemia and hypertension [10, 11]. Leptin, an adipocytokine produced by adipose tissue, is associated with dyslipidemia [12], and recent study has demonstrated that leptin contributes to
hypertension through upregulation of central renin–angiotensin system and proinflammatory cytokines [13]. There has been no evidence that the SNP rs11191548 near CYP17A1 is associated with lipids and leptin. We investigated the associations between the SNP rs11191548 with lipids and leptin in the cohort. We genotyped the SNP in Chinese children who were participated in the population-based Beijing Child and Adolescent Metabolic Syndrome (BCAMS) study. The present study attempts to provide an analysis of epidemiological and genetic data towards the possible mechanism of the role of CYP17A1 in hypertension.

### Methods

#### Study population

Subjects were recruited from a cross-sectional population-based survey termed the BCAMS study in 2004. The survey included a questionnaire, anthropometric measurement, and medical examination in a representative sample (n = 19,593, 50% boys) of children in Beijing aged 6–18 years. Anthropometric measurements included weight, height, waist circumference, and fat mass percentage. Within this large group of children, 1045 children with elevating blood pressure (including pre-hypertension and hypertension) and 2458 children with normal blood pressure were randomly recruited and diagnosed by using blood pressure reference cutoffs for Chinese children and adolescents [14]. Venipuncture blood samples were collected for genotyping. The BCAMS study was approved by the ethics committees of Capital Institute of Pediatrics. We obtained written informed consent from parents or guardians.

#### Measurement of biochemical analyses and genotyping

Total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides (TG), were analyzed by an automatic biochemical analyzer (Hitachi 7060) using a kit assay (SEKISUI medical technology Ltd., Tokyo, Japan). The levels of adipocytokines (including pre-hypertension and hypertension) and genetic data towards the possible mechanism of the role of CYP17A1 in hypertension.

| Additive model | HDL Mean ± SD | P-value<sup>a</sup> | Power | P-value<sup>b</sup> | Power | P-value<sup>c</sup> | Power | Leptin Mean ± SD | P-value<sup>a</sup> | Power | P-value<sup>b</sup> | Power | P-value<sup>c</sup> | Power |
|---------------|---------------|---------------------|-------|---------------------|-------|---------------------|-------|-----------------|---------------------|-------|---------------------|-------|---------------------|-------|
| CC            | 1.36 ± 0.32   | 10.71 ± 12.72       | 0.043 | 0.690               | 0.281 | 0.060               | 0.700 | 0.945           | 0.004               | 0.811 | 0.749–0.945         | 0.004 | 0.848               | 0.281 |
| CT            | 1.40 ± 0.32   | 10.42 ± 11.63       | 0.043 | 0.690               | 0.281 | 0.060               | 0.700 | 0.945           | 0.004               | 0.811 | 0.749–0.945         | 0.004 | 0.848               | 0.281 |
| TT            | 1.41 ± 0.32   | 9.70 ± 11.14        | 0.043 | 0.690               | 0.281 | 0.060               | 0.700 | 0.945           | 0.004               | 0.811 | 0.749–0.945         | 0.004 | 0.848               | 0.281 |

**Table 1** Associations of rs11191548 with HDL and leptin

**Table 2** Association of rs11191548 with high leptin under the additive model

#### Statistical analysis

Categorical variables were presented as percentages and continuous variables were presented as mean ± standard deviation (SD). Hardy-Weinberg equilibrium was assessed using the chi-square test. Adjusted odds ratios (ORs) for high leptin were performed by logistic regression with genotypes, age, gender, and systolic blood pressure (SBP) or diastolic blood pressure (DBP) as the independent variables. The data were analysed using SPSS statistical software. P < 0.05 was used to indicate statistically significant differences. False discovery rate (FDR) approach was used to correct for multiple testing. In brief, the stringent p-value was considered statistically significant only if it was less than 0.05. Power calculation was performed using Quanto software according to the assumed effect size and allele frequency (http://hydra.usc.edu/gxe/).

#### Results

The basic characteristics of the study participants are summarized in Table S1 (Additional file 1). We genotyped the SNP rs11191548 near CYP17A1 in the cohort, and the genotype of the SNP was tested to be in Hardy–Weinberg equilibrium (P = 0.795). The minor allele frequency (MAF) of the SNP was 0.277 in the cohort. The associations of the SNP rs11191548 with HDL and leptin are shown in Table 1. As the SNP was associated with blood
pressure, we also adjusted SBP or DBP besides age and gender. The SNP rs11191548 was significantly associated with HDL under an additive model ($P = 0.014$ and 0.028, respectively) after adjustment for age, gender, and SBP or DBP. The SNP was also significantly associated with leptin under an additive model ($P = 0.011$ and 0.026, respectively) after adjustment for age, gender, and SBP or DBP.

Table 2 shows the association of rs11191548 with high leptin defined as leptin$\geq75$ percentile of the participant with same age and gender. The SNP rs11191548 was significantly associated with high leptin under an additive model after adjustment for age, gender, and SBP or DBP. The $P$-values remain significant after correction for multiple testing.

**Discussion**

*CYP17A1* encodes the cytochrome P450 enzyme CYP17A1 and has a key role in the biosynthesis of steroid hormones [16]. CYP17A1 deficiency caused by a mutation in the gene usually results in severe hypertension and hypokalemia in males [17]. The SNP rs11191548 near *CYP17A1* showed a significant association with hypertension [6–9], but the molecular mechanisms are not understood.

In this study, we examined the SNP rs11191548 near *CYP17A1* with lipids and leptin in Chinese children. Our results indicated that the SNP rs11191548 was significantly associated with HDL and leptin after adjustment for age, gender, and SBP or DBP, and there was statistically significant association of the SNP rs11191548 with high leptin under an additive model adjusted for age, gender, and SBP or DBP, after correction for multiple testing. No significant associations of the SNP with TC, TG and LDL were found in the population for multiple testing. No significant associations of the SNP with high leptin defined as leptin$\geq$75 percentile of the participant with same age and gender. The SNP was also significantly associated with HDL and leptin that contribute to hypertension.

**Conclusion**

We demonstrate for the first time that the SNP rs11191548 near *CYP17A1* is associated with HDL and leptin in Chinese children. These novel findings provide important evidence that HDL and leptin maybe possibly mediate the process of CYP17A1 involved in hypertension.

**Additional file**

**Additional file 1: Table S1.** Basic characteristics of study participants (DOC 42 kb)
8. Liu C, Li H, Qi Q, Lu L, Gan W, et al. Common variants in or near FGF5, CYP17A1 and MTHFR genes are associated with blood pressure and hypertension in Chinese Hans. J Hypertens. 2011;29:70–5.
9. Wu L, Xi B, Zhang M, Shen Y, Zhao X, et al. A sex-specific effect of the CYP17A1 SNP rs11191548 on blood pressure in Chinese children. J Hum Hypertens. 2012;26:731–6.
10. Otsuka T, Takada H, Nishiyma Y, Kodani E, Saki Y, et al. Dyslipidemia and the risk of developing hypertension in a working-age male population. J Am Heart Assoc. 2016;5:e003053.
11. Borghi C, Rodriguez-Artalejo F, De Backer G, Dallongeville J, Medina J, et al. The association between blood pressure and lipid levels in Europe: European study on cardiovascular Risk Prevention and Management in Usual Daily Practice. J Hypertens. 2016;34:2155–63.
12. de Haro MC, Figueiredo VN, de Faria AP, Barbaro NR, Sabbatini AR, et al. High-circulating leptin levels are associated with increased blood pressure in uncontrolled resistant hypertension. J Hum Hypertens. 2013;27:225–30.
13. Xue B, Yu Y, Zhang Z, Guo F, Beltz TG, et al. Leptin mediates high-fat diet sensitization of Angiotensin II elicited hypertension by Upregulating the Brain-Renin-Angiotensin system and inflammation. Hypertension. 2016;67:970–6.
14. Xue B, Zong X, Kelishadi R, Hong YM, Khadilkar A, et al. Establishing international blood pressure references among nonoverweight children and adolescents aged 6 to 17 years. Circulation. 2016;133:398–408.
15. Araki S, Dobashi K, Kubo K, Asayama K, Shirahata A. High molecular weight, rather than total, adiponectin levels better reflect metabolic abnormalities associated with childhood obesity. J Clin Endocrinol Metab. 2006;91:5113–6.
16. Dhir V, Ivison HE, Krone N, Shackleton CH, Doherty AJ, et al. Differential inhibition of CYP17A1 and CYP21A2 activities by the P450 oxidoreductase mutant A287P. Mol Endocrinol. 2007;21:1958–68.
17. Yang J, Cui B, Sun S, Shi T, Zheng S, et al. Phenotype-genotype correlation in eight Chinese 17alpha-hydroxylase/17,20 lyase-deficiency patients with five novel mutations of CYP17A1 gene. J Clin Endocrinol Metab. 2006;91:3619–25.

Submit your next manuscript to BioMed Central and we will help you at every step:

- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at www.biomedcentral.com/submit