ASSOCIATION OF BUD13 POLYMORPHISMS WITH METABOLIC SYNDROME IN CHINESE POPULATION: A CASE-CONTROL STUDY

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Abstract

Background: BUD13 homolog (BUD13), one of substrates of the retention and splicing complex, was identified in yeast as a splicing factor that affected nuclear pre-mRNA retention. While more and more studies demonstrated that BUD13 played a potential role in the pathogenesis of metabolic syndrome (MetS). This objective was to reassess whether novel locus of BUD13 were linked to MetS and individual complements in the northeast of China.

Methods: A total of 3850 individuals were recruited in this case-control study, including 1813 MetS cases and 2037 healthy controls. The diagnostic criteria was according to the International Diabetes Federation (IDF). Metabolic complements such as waist circumference (WC), triglyceride, high-density lipoprotein cholesterol (HDL-C), systolic and diastolic blood pressure (SBP and DBP), and fasting glucose were measured. We explored the association between two novel single nucleotide polymorphism (SNPs) of BUD13 (rs7118999 and rs10488698) and MetS and its complements.

Results: Using binary logistic regression analysis we found that there were no significant associations between SNPs and MetS in different heritance models (all P > 0.05). However, novel locus of BUD13 were linked to individual complements in MetS cases. Rs7118999 conferred to risk of WC (P = 0.016) and the carrier of TT might have higher susceptibility to MetS. While rs10488698 was associated with HDL-C (P = 0.001) and the carrier of TT was significantly associated with higher level of HDL-C.

Conclusions: We concluded that novel mutations in BUD13 did not confer risk for MetS in our study population, but these mutations changed the level of metabolic complements.

Keywords: Metabolic syndrome, BUD13, Single nucleotide polymorphism

Introduction

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities, including raised triglyceride levels, low high-density lipoprotein cholesterol levels, raised blood pressure, and raised glucose levels [1]. Available evidences show that MetS is strongly increasing the risk of developing cardiovascular diseases, type 2 diabetes and all caused mortality [2–4]. Due to escalating prevalence rates and its risk for the development of several chronic diseases, MetS has become the most important health challenge at the global scale [3].

Previous studies indicated that the pathogenesis of MetS might be caused by genetics background, environmental factors and gene-environment interaction [2, 5, 6]. Furthermore, Henneman et al. [7] found that the heritability of MetS based on family study was 10.6%, indicating that gene played essential in the development of MetS. Knowledge of exact genetic factors underlying MetS development might help to explain the etiology of MetS. BUD13 was substrates of the retention and splicing complex in yeast [8], while Lin et al. [5] demonstrated that its variant significantly influenced on human development of MetS. Furthermore, Meta-analysis indicated multiple genes linking to MetS, mostly of genes involving in lipids levels, and the heritability of individual components of MetS were range from 21.9–42.9% [7, 9]. Increased studies noted

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that BUD13 involved in lipid metabolism [5, 10, 11], suggesting BUD13 might played an essential role in the pathogenesis of MetS and its traits through changing lipid levels.

To the best of our knowledge, we selected novel SNPs (rs7118999 and rs10488698) of the BUD13 to evaluate their association with MetS and MetS complements in a sample of the Jilin province, using a case-control study design.

**Materials and methods**

**Study population**

This study incorporated subjects from Jilin province in the northeast of China, in order to evaluate whether novel locus of BUD13 was linked to MetS and individual complements. The study of community-based consisted of 3850 participants, including 1813 MetS and 2037 non-MetS. MetS was diagnosed according to IDF criteria [12], Which required that subjects with three or more of the following conditions were diagnosed as MetS a) Central obesity with a waist circumference ≥ 80 cm in females and ≥ 85 cm in males b) Triglycerides ≥ 1.7 mmol/L or using drug treatment to elevate triglycerides c) HDL-C < 1.00 mmol/L in males and ≥ 1.30 mmol/L for females, or using drug treatment to elevate triglycerides d) SBP ≥ 130 mmHg and DBP ≥ 85 mmHg, or using antihypertensive drug treatment in a patient with a history of hypertension and e) fasting plasma glucose ≥5.6 mmol/L or using anti-diabetic drug therapy.

The study was approved by the ethics committee of the School of Public Health, Jilin University. All subjects signed the approved informed consent.

**Genotyping**

The two SNPs (rs7118999 and rs10488698) of BUD13 were selected using the haploview 4.2 software (http://hapmap.ncbi.nlm.nih.gov/), and the minor allele frequency of the above two SNPs was greater than 0.05 in Chinese population.

DNA was isolated from peripheral blood samples using a commercial DNA extraction kit (Hangzhou, China). SNP genotyping was determined by MALDI-TOF-MS (Sequenom, San, Diego, CA, USA) using the Mass ARRAY system, and completed genotyping reactions were divided into a 384-well spectro CHIP. The detection rate of rs7118999 was 99.8% (1810/1813) in MetS cases, and the detection rate of rs10488698 was 93.1% (1687/1813) in MetS cases, and 85.8% (1597/1813) in non-MetS cases.

**Results**

**Characteristics of the subjects**

The characteristics of the study population, 1813 MetS cases and 2037 non-MetS subjects, were shown in Table 1. The prevalence of MetS in our cross-sectional survey was 47.1%. The distribution of age and gender were well matched. Moreover, MetS subjects showed significantly increased risk levels for all of the MetS component variables (Waist circumference, triglyceride, systolic blood pressure and diastolic blood pressure, high density lipoprotein, fasting glucose) and the habit of smoking and drinking (all P < 0.001).

**Associations with MetS risk and quantitative metabolic traits**

The distributions of rs7118999 and rs10488698 conformed to Hardy-Weinberg equilibrium among the subjects (all P > 0.05). The comparisons of genotype frequency of the above two SNPs was greater than 0.05 in Chinese population.

All statistical analyses were conducted using the SPSS program (version 21.0), and the online SNP Stats (http://bioinfo.iconcologia.net/SNPStats) program. Intergroup comparisons of means using the Student’s t-test. We conducted the chi-square test to compare the difference from two categorical data. For each SNP, Hardy-Weinberg disequilibrium was tested by χ² test with 1 degree of freedom. Binary logistic regression analysis was used to evaluate the association of the chosen SNP with MetS by adjusted age, gender, smoking and drinking. There are three inheritance models in this study, including codominant model (TT vs CT vs CC), dominant model (CT + TT vs CC) and recessive model (TT vs CT + CC). Furthermore, we estimated the association of the investigated SNP with individual components of MetS using general linear model (GLM) by adjusted age, gender, smoking and drinking. P-value ≤ 0.05 was considered statistically significant.

| Table 1 Characteristics of study subjects | Characteristic | Case | Control | t/χ² | P-value |
|------------------------------------------|---------------|------|---------|------|---------|
| No. of subjects, n                       | 1813          | 2037 |         |      |         |
| Age (years)                              | 49.5 ± 9.7    | 49.5 ± 9.4 | −0.062 | 0.950 |
| Gender                                   |               |       |         |      |         |
| Male, n (%)                              | 903(49.8)     | 1024(50.3) | 0.082  | 0.774 |
| Female, n (%)                            | 910(50.2)     | 1013(49.7) |       |       |
| Smoking                                  |               |       |         |      |         |
| Never                                    | 1077          | 1203 | 21.902  | <0.001|
| Former                                   | 199           | 144  |         |       |
| Current                                  | 537           | 690  |         |       |
| Drinking                                 |               |       |         |      |         |
| No                                       | 1172          | 1440 | 16.803  | <0.001|
| Yes                                      | 641           | 597  |         |       |
| MetS components                          |               |       |         |      |         |
| WC(cm)                                   | 914 ± 8.3     | 750 ± 7.0 | −66.045 | <0.001|
| Triglyceride (mg/dL)                     | 3.2 ± 2.6     | 1.1 ± 0.5 | −35.939 | <0.001|
| HDL-C (mg/dL)                            | 1.2 ± 0.3     | 1.6 ± 0.4 | 42.628  | <0.001|
| SBP (mm Hg)                              | 144.6 ± 19.1  | 120.2 ± 15.9 | −43.146 | <0.001|
| DBP (mm Hg)                              | 87.8 ± 11.0   | 74.6 ± 9.5 | −39.980 | <0.001|
| Fasting glucose (mg/dL)                  | 6.6 ± 2.4     | 4.8 ± 1.0 | −30.243 | <0.001|
distributions of the polymorphisms in the BUD13 between subjects with and without MetS using different model of inheritance were shown in Table 2. We then explored the association of each SNP and MetS using binary logistic regression analysis of risk factors with adjustment for age, gender, smoking and drinking. In the case and control groups, no significant associations between SNPs and MetS were observed in different heritance models.

As shown in Table 3, we also explored to association between novel SNPs and metabolism complements in with MetS subjects. Rs7118999 associated with WC in MetS cases ($P = 0.016$) and the carrier of TT was significantly associated with higher WC. However, rs10488698 was associated with HDL-C in MetS cases ($P = 0.001$) and the carrier of TT was significantly associated with higher level of HDL-C. However, our results did not exhibit association between the two SNPs with the rest of MetS components ($P>0.05$).

### Table 2 BUD13 association with MetS

| SNP       | Inheritance model | genotype | case | control | Adjusted OR(95%CI) | P-value |
|-----------|-------------------|----------|------|---------|--------------------|---------|
| rs7118999 | Codominant        | CC       | 725  | 825     | 1.00               |         |
|           |                   | CT       | 771  | 840     | 1.03(0.90–1.19)    | 0.656   |
|           |                   | TT       | 191  | 254     | 0.84(0.68–1.04)    | 0.101   |
|           | Dominant          | CC       | 725  | 825     | 1.00               |         |
|           |                   | CT/TT    | 962  | 1094    | 0.99(0.86–1.13)    | 0.845   |
|           | Recessive         | CC/CT    | 1496 | 1665    | 1.00               |         |
|           |                   | TT       | 191  | 254     | 0.82(0.67–1.01)    | 0.058   |
| rs10488698| Codominant        | CC       | 1543 | 1733    | 1.00               |         |
|           |                   | CT       | 254  | 288     | 0.98(0.82–1.18)    | 0.823   |
|           |                   | TT       | 13   | 11      | 1.33(0.59–3.00)    | 0.491   |
|           | Dominant          | CC       | 1543 | 1733    | 1.00               |         |
|           |                   | CT/TT    | 267  | 299     | 0.99(0.83–1.19)    | 0.931   |
|           | Recessive         | CC/CT    | 1797 | 2021    | 1.00               |         |
|           |                   | TT       | 13   | 11      | 1.33(0.59–3.00)    | 0.486   |

OR was adjusted for age, gender, smoking and drinking

### Discussion
This study incorporated subjects from community-based cross-sectional study with a sample of Jilin province in the northeast of China. According to the IDF diagnostic criteria [12], the prevalence of MetS was 47.1% in Jilin province in 2012. This prevalence was higher than the prevalence reported in China in 2010 (33.9%) [13]. Here, we demonstrated that novel mutations in BUD13 did not

### Table 3 Association between BUD13 with complements

| characteristics | CC   | CT      | TT      | $t/\chi^2$ | P-value |
|-----------------|------|---------|---------|------------|---------|
| rs7118999       |      |         |         |            |         |
| WC(cm)          | 91.8 ± 7.9 | 90.9 ± 8.8 | 92.3 ± 8.1 | 4.139     | 0.016   |
| Triglyceride (mg/mL) | 3.2 ± 2.6 | 3.3 ± 2.6 | 3.3 ± 3.0 | 0.337     | 0.714   |
| HDL-C (mg/dL)   | 1.16 ± 0.28 | 1.16 ± 0.30 | 1.16 ± 0.30 | 0.114     | 0.892   |
| SBP (mm Hg)     | 145.4 ± 19.6 | 143.6 ± 18.8 | 144.8 ± 18.8 | 1.820     | 0.162   |
| DBP (mm Hg)     | 88.1 ± 10.9 | 87.7 ± 11.0 | 87.4 ± 10.8 | 0.826     | 0.438   |
| Fasting glucose (mg/dL) | 6.6 ± 2.3 | 6.6 ± 2.4 | 6.8 ± 3.3 | 0.693     | 0.500   |
| rs10488698      |      |         |         |            |         |
| WC(cm)          | 91.4 ± 8.0 | 91.5 ± 8.3 | 90.3 ± 5.1 | 0.132     | 0.876   |
| Triglyceride (mg/mL) | 3.3 ± 2.6 | 3.2 ± 2.7 | 2.6 ± 2.5 | 0.687     | 0.503   |
| HDL-C (mg/dL)   | 1.21 ± 0.33 | 1.22 ± 0.33 | 1.27 ± 0.30 | 6.721     | 0.001   |
| SBP (mm Hg)     | 144.5 ± 19.1 | 144.9 ± 19.2 | 147.2 ± 19.2 | 0.018     | 0.982   |
| DBP (mm Hg)     | 87.7 ± 10.9 | 88.3 ± 11.2 | 83.7 ± 12.1 | 1.221     | 0.295   |
| Fasting glucose (mg/dL) | 6.6 ± 2.4 | 6.7 ± 2.7 | 7.2 ± 3.2 | 0.432     | 0.649   |

$P$-value was adjusted for age, gender, smoking and drinking
confers risk for MetS among Jilin population, but these mutations changed the level of metabolic complements.

In this literature, we for the first time explored association between novel SNPs in BUD13 and MetS. It has been noted that genetic variants are linking to the development of MetS in different populations. Previous literatures showed that SNPs of rs10790162 [10, 14, 15], rs11216129 [5] and rs623908 [5] contributed to the susceptibility for MetS in Chinese [1, 2], India [3] and Taiwanese population [5]. In this study, the distribution of genotype frequencies of rs7118999 and rs10488698 was no difference between subjects with and without MetS in different model of inheritance ($P > 0.05$).

Furthermore, novel locus of BUD13 were linked to individual complements in MetS cases. The carrier of TT in rs7118999 conferred to risk of MetS by increasing the level of WC. While rs10488698 might a protected factor by increasing the level of HDL-C. Similarly, many studies also investigated that BUD13 variants associated with triglyceride [5, 10, 14, 16, 17], LDL [14], total cholesterol [17] and HDL-C [5], but not discovered rs12286037 and rs28927680 with HDL in Finish [18]. Therefore, the correlation of BUD13 variants with serum lipid levels was not yet clear. Firstly, factors like age, gender, ethnicity, lifestyle and genetic background influenced the association between SNPs with serum lipid levels [19]. Secondly, inter-genetic variant might play an important role in the level of serum lipid [20]. The gene regions of APOA1/C3/A4/A5/BUD13 and BUD13/ZNF were significantly influencing the association with lipid metabolism [10, 16, 21–23].

There are certain limitations to our study. Firstly, our studies subjects were coming from the cross-sectional study, which might limit its ability to detect association between BUD13 and MetS, largely because of bias [24]. Secondly, the etiology of MetS might be caused by multiple factors, such as genetics background, nutritional status and environmental factors. Our study only discussed associations between gene and MetS in the north-east of China, so we could not evaluate the same association in other population. Lastly, the detection rate of SNPs might influence the distribution of MetS and its complements. Therefore, these peculiar characteristics might be contributing factors to the findings of our study.

Conclusion
We indicated that novel mutations in BUD13 did not confer risk for MetS in our study population, but these mutations changed the level of metabolic complements. The carrier of TT in rs7118999 conferred to risk of MetS by increasing the level of WC. While the carrier of TT in rs10488698 might be protective factor for MetS, who had high level of HDL-C. Considering the complex environment and genetic disease complex mechanism, independent replication studies are needed to provide further insights into the role of the BUD13.

Abbreviations
DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; MetS: metabolic syndrome; SBP: systolic blood pressure; SNP: single nucleotide polymorphism; WC: waist circumference

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Availability of data and materials
Not applicable.

Authors’ contributions
LZ, YY, YW, YZ, and CK designed and performed the study. LZ, YW, YZ, and YY analyzed the data. LZ drafted the manuscript. YY, MW, YS and XL participated in revising draft of the manuscript. All authors approved the final version of the manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The study was approved by the ethics committee of the School of Public Health, Jilin University. All subject signed the approved informed consent.

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