Association between genetic variants in metabolic syndrome-related genes and risk of obstructive sleep apnea among a Chinese population

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Research

Keywords: Obstructive sleep apnea, Metabolic syndrome-related genes, Genetic variants, Targeted capture sequencing

DOI: https://doi.org/10.21203/rs.3.rs-120504/v1

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Abstract

Background

Despite the strong epidemiological association between Metabolic syndrome (MetS) and obstructive sleep apnea (OSA), the causal mechanism between the two remains not fully elucidated. We conducted a case-control study to evaluate the genetic association of twelve metabolic syndrome-related genes with OSA in Chinese subjects.

Methods

Targeted capture sequencing for twelve metabolic syndrome-related genes (EDN1, APOE, LEP, LEPR, IRS1, UCP1, ADIPOQ, PEMT, PPARG, SLC2A4, FABP2 and ADRA2A) were performed in 100 subjects including 50 patients with severe OSA and 50 non-OSA individuals. Possible associations between genetic variants and the risk of OSA were determined by logistic regression analyses.

Results

From the multiple genes studied, only the rs12486170 variant in PPARG gene was associated with OSA risk after adjusting for potential confounding factors. The PPARG rs12486170 AG/GG genotype was found to decrease the risk for OSA [dominant model: adjusted odds ratio (AOR) = 0.211, 95% confidence interval (CI) = 0.055-0.800, \( P = 0.022 \)] compared with AA genotype. Moreover, subjects with the rs12486170 AG/GG genotype had a significantly lower apnea-hypopnea index (AHI) (median: 2.50 vs. 50.90 events/h, \( P = 0.019 \)) and higher lowest oxygen saturation (LSaO\(_2\)) (median: 87\% vs. 75\%, \( P = 0.040 \)) compared with those with the AA genotype.

Conclusions

We identified a novel variant of PPARG in subjects with OSA, and specifically found an association between rs12486170 polymorphisms and OSA risk in a Chinese population.

Background

Obstructive sleep apnea (OSA) is a sleep respiratory disturbance disease characterized by nocturnal sleep snoring, apnea, and daytime sleepiness, which leads to intermittent hypoxemia, transitory hypercapnia and sleep structural disorder[1]. Over the last two decades, the prevalence of OSA has increased among the general population; nearly one billion adults aged 30–69 years are affected by OSA globally, with about 40\% of them having moderate to severe disease and 60\% mild disease[2]. This hints that the disorder is often under-diagnosed, imposing a heavy health and socioeconomic burden[3]. The main clinical risk associated with OSA is multiple organ system damage, such as cardio-cerebrovascular diseases, neurocognitive dysfunction, and metabolic syndrome[4, 5].

Metabolic syndrome (MetS), with main features including insulin resistance, dyslipidemia, obesity, and hypertension, is among the most common OSA comorbidities[6]. A meta-analysis revealed that OSA is associated with the increased risk of MetS, independently of obesity[7]. Coughlin et al. reported that MetS was over 9 times more likely to be present in patients with OSA[8]. Individuals with severe OSA [apnea-hypopnea index (AHI) > 30 event/hour] were 30\% more likely to develop diabetes in the next five to ten years[9]. There is also a particularly high incidence of hypertension and obesity in OSA patients. Several studies even reported a dose-dependent relationship between blood pressure and OSA severity[10, 11]. Although potential mechanisms relating to OSA have been identified that might predispose to metabolic disturbances, including hypoxia, oxidative stress, systemic inflammation, and sympathetic activation, in addition to imbalance of lipid synthesis and clearance, and imbalance of hormones regulating glucose and insulin, the causal association of OSA with metabolic disorders remain not fully established[12].

Strong genetic influence has been reported for OSA, with more than 1.5-fold increased risk in first-degree relatives of patients[13]. Approximately 35–40\% of variation in AHI, which measures apnea severity, can be explained by genetic factors[14]. Despite strong evidence links OSA to MetS[6–12], little is known about whether genes associated with metabolic phenotypes are also involved in OSA. Better understanding of this complex relationship may contribute to a more effective diagnostic process and personalized treatment strategy.

In this paper, we pooled multiple genetic variants of genes associated with MetS components such as endothelin (EDN1), apolipoprotein E (APOE), leptin and its receptor (LEP, LEPR), insulin receptor substrate 1 (IRS1), uncoupling protein 1 (UCP1), adiponectin (ADIPOQ), phospholipid methyltransferase (PEMT), peroxisome proliferator-activated receptor gamma (PPARG), solute carrier family 2 member 4 (SLC2A4), fatty acid binding protein 2 (FABP2), and adrenoceptor alpha 2A (ADRA2A), to investigate the potential links between susceptibility genes for MetS and OSA.

Methods

Ethics statement

The present study complied with the Declaration of Helsinki, and was approved by the Local Ethics Committee of People’s Hospital of Xinjiang (Xinjiang, China). Written informed consent was obtained from all subjects prior to study participation.

Subjects
Subjects referred for polysomnography (PSG) to the Hypertension Center of People's Hospital of Xinjiang for the initial investigation of OSA were recruited consecutively, from April to December 2016 (previously described in [15]). Subjects with non-OSA and severe OSA (exhibiting extreme phenotype based on AHI), were selected for an additional genomic study. In this study, we chose AHI (either very low or very high) as the extreme phenotype. Extreme phenotype sampling which selecting subjects from the extremes of trait distribution was applied, and it can increase the ability and statistical power to detect rare variants[16]. Following the inclusion and exclusion criteria as detailed in our previous study[15], while excluding smokers, a total of 100 subjects (50 non-OSA and 50 severe OSA) were enrolled in the study.

Interventions

Overnight polysomnography (PSG) monitoring, clinical data acquisition, blood sample collection and genomic DNA extraction of all subjects followed the standard techniques as previously described[15,17]. In brief, all subjects underwent overnight PSG monitoring (Compumedics E series, Australia), and were evaluated by a registered polysomnographic technologist according to the American Academy of Sleep Medicine (AASM) criteria for scoring [18]. Non-OSA was defined as an AHI < 5 events/h, and severe OSA with an AHI ≥ 30 events/h. The general demographic and clinical data were collected, mainly including age, gender, body mass index (BMI), neck circumference and abdominal circumference, as well as personal/family medical history and lifestyle habits (alcohol consumption, smoking status). Two equal samples of fasting venous blood (fasting ≥ 10hours, cubital vein blood sample) were collected from each subject in the morning after PSG. Fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), high density lipoprotein-cholesterol (HDL-C), and low density lipoprotein-cholesterol (LDL-C) levels were determined with an automatic biochemical analyzer (Beckman, CA, USA) at the central laboratory of People's Hospital of Xinjiang using standard techniques. 3ml venous blood from another sample was collected in EDTA anticoagulant tubes for all subjects. Genomic DNA was extracted from whole blood using PAXgene Blood DNA kit (Qiagen, Germany), and the purity of DNA was measured by a spectrophotometer (NanoDrop2000, MA, USA). For all samples, the total amount of DNA required was at least 2μg with the concentration of DNA ≥ 50ng/μL. Afterwards, the extracted DNA was preserved at -80℃ and sent to Genesky Biotechnologies Inc. (Shanghai, China) for targeted capture sequencing.

Targeted capture sequencing

Twelve putative genes, EDN1, APOE, LEP, LEPR, IRS1, UCP1, ADIPOQ, PEMT, PPARG, SLC2A4, FABP2 and ADRA2A, were selected from available literature[19,20] and Public Health Genomics Knowledge Base (https://phgkb.cdc.gov/PHGKB/hNHome.action) as the metabolic syndrome-related genes for the following targeted sequencing.

100 DNA samples were analyzed for targeted capture sequencing of the above genes with Agilent sureselectXT custom Kit (Agilent Technologies, CA, USA) on an Illumina HiSeq platform (Illumina, CA, USA). Sequencing reads were aligned to the human reference genome (UCSC hg38) with BWA algorithm and variant calling was carried out using GATK HaplotypeCaller. Single-nucleotide variant annotation was performed with ANNOVAR (http://annovar.openbioinformatics.org/en/latest/). Frequency of variants was evaluated based on publically available databases (1000Genomes, ESP6500, ExAC03). A combination of pathogenicity prediction softwares (SIFT[21], Polyphen V2[22], Mutation Taster[23], CADD[24], DANN[25]) was used to predict the potential impact of each genetic variant on gene function. Requiring at least two of the softwares to support the variant may be damaging.

Statistical Analyses

Continuous data were expressed as mean±standard deviations or medians (interquartile range), while categorical data were expressed as n (%). Independent Student’s t-test or Mann-Whitney U-test was used to analyze continuous variables according to the normality of data distribution. Chi-squared test or Fisher's exact test was used for categorical variables as appropriate. Logistic regression analysis was performed to explore the association between OSA and gene variants. Hardy-Weinberg equilibrium, single-nucleotide polymorphism (SNP) association analyses and multiple comparison correction were performed using PLINK (version 1.0.7; http://pngu.mgh.harvard.edu/purcell/plink/). P-value < 0.05 was considered statistically significant.

Results

Baseline characteristics of subjects

The clinical characteristics of subjects without OSA and severe OSA patients are summarized in Table 1. There were more males, older and obese individuals in the severe OSA group compared with the non-OSA group. Patients with OSA had significantly higher BMI, neck circumference, abdominal circumference, apnea index, hypopnea index, AH1, and lower oxygen saturation than non-OSA subjects (all P < 0.001), as well as lower HDL-C level (P = 0.001), higher FBG (P < 0.001) and TG levels (P = 0.017) than non-OSA subjects. Besides, there were no significant differences in alcohol consumption (P = 0.086), systolic blood pressure (SBP; P = 0.748), diastolic blood pressure (DBP; P = 0.389), sleep efficiency (P = 0.329), total sleep time (P = 0.608), TC (P = 0.553) or LDL-C level (P = 0.773) between the two groups.

Targeted sequencing data

The target region of twelve metabolism-related genes were sequenced at average depth of 411X in this study. All variations were designated as common (MAF > 1%) or rare (MAF < 1%), according to the minor allele frequency in control group. In total, we found 98 SNPs and 14 short tandem repeat (STR) in the fragment of the twelve genes (supplemental Table S1), all of which were submitted to association analysis under additive, dominant, recessive and allele genetic models by univariate logistic regression analysis. Only SNPs with a P value ≤ 0.1 in univariate analysis under the four genetic models were taken into consideration, and were selected for subsequent multivariate logistic regression analysis to assess the association of genetic variants with OSA risk. Finally, 7 nucleotide variants remained (Table 2). In addition, we also identified 7 rare non-synonymous variants which may be potentially deleterious based on the SIFT, PolyPhen V2, Mutation Taster and DANN softwares (details in supplemental Table S2). However, further functional studies are required to validate potential role of the rare variants.
Association of genetic variants with OSA risk

Of the 7 SNPs, the genotype and allelic frequencies at rs2964, rs1511025, and rs12486170 differed statistically or nearly statistically between severe OSA and non-OSA groups (Table 2). No significant differences between the two groups were observed regarding to the other 4 SNPs. As depicted in Table 3, after adjusting for gender, age, BMI, FG, TC, TG, HDL-C and LDL-C, PPARG rs12486170 AG/GG genotype was found to decrease the risk for OSA [dominant model: multivariable-adjusted odds ratio (OR) = 0.211, 95% CI = 0.055-0.800, P = 0.022] compared with AA genotype. There were no statistically significant differences for the other 6 SNPs after adjusting for the above confounding factors.

We also performed a genotype–phenotype association analysis, which showed that subjects with the PPARG rs12486170 AG/GG genotype had a significantly lower AHI (median: 2.50 vs. 50.90 events/h, P = 0.019) and higher lowest oxygen saturation (median: 87% vs. 75%, P = 0.040) compared with those with the AA genotype, but no significant association between mean oxygen saturation level and rs12486170 was found in OSA under the dominant model (Table 4).

As obesity is common in OSA individuals and is also a significant risk factor for OSA, the association analyses above were also conducted within overweight people in this study. Our results showed that after adjusting for confounding factors, there were no statistically significant association between the genotypes at rs2964, rs1511025, and rs12486170 about risk of OSA among overweight people (Table 5).

Discussion

OSA is known to be heritable, with approximately 40% of variation in AHI can be attributable to genetic factors[14]. Over the last years, prospective observational and therapy studies have shown that the association between metabolic disorders and OSA is feedforward and bidirectional [26, 27]. The interrelationships among OSA, MetS, insulin resistance, dyslipidemia, and obesity were complicated and multifaceted. In this study, we hypothesized that genes associated with MetS components may be relevant to the genetics of OSA because both disorders share common epidemiological and clinical features. Hence, we sought to evaluate the genetic association of OSA with 12 genes linked to MetS. We finally detected a novel genetic variant in the PPARG gene that is independently associated with OSA. The mutant genotype GA/GG in PPARG rs12486170 was associated with a decreased risk of OSA in dominant genetic carriers with this mutant genotype had a significantly lower AHI and higher lowest oxygen saturation.

PPARG, peroxisome proliferator-activated receptor gamma, belongs to the nuclear receptor family of ligand-activated transcription factors that heterodimerize with the retinoic X receptor (RXR) to regulate gene expression[28]. As a master regulator of adipocyte differentiation, PPARG plays a crucial role in the accumulation, phenotype and function of adipose tissue resident regulatory T (Treg) cells, which is associated with improved insulin sensitivity[29]. PPARG has been reportedly involved in the pathology of various diseases including obesity, diabetes, lipodystrophy, atherosclerosis and cancer[28]. Additionally, a study reported that the progresses of myogenesis was regulated by altered intracellular PPARG levels[30]. PPARG polymorphisms may involve the growth hormone/STAT5B signaling pathway which regulates energy metabolism in muscles and adipose tissue[31], and mice deficient for members of the pathway also developed craniofacial abnormalities[32]. As we know, obesity increases the risk of OSA by 10 to 14-fold, and is expected to explain up to 40% of AHI variation[14]. Craniofacial abnormalities and metabolic dysfunction of muscles and adipose tissue can cause upper airway obstruction, which are also risk factors for OSA[1, 14]. PPARG may affect obesity, craniofacial abnormalities, and dysregulated metabolism thereby causing OSA[33]. Gharib et al. have observed the association of PPARG signaling and PPARG expression with OSA. They found that most members of PPARG signaling cascade were down-regulated in the adipose tissue of patients with OSA, including the PPARG expression, which was confirmed using qPCR[34].

Prior genome-wide association and linkage studies have revealed multiple loci/genes related to OSA, including the PPARG. The potential associations between several variants of PPARG gene and OSA have been investigated in different populations with inconsistent results[33, 35, 36]. The PPARG rs1801282 polymorphism has raised some concern owing to its correlation with various metabolic disorders such as obesity, dyslipidemia and diabetes[33]. For the Chinese population, Jiao et al. reported subjects carrying the CC genotype of rs1801282 had decreased risk of developing OSA compared to individuals carrying the CC genotype (OR = 0.318)[33], whereas these associations were not observed in Guan et al.’s study[36]. Also, we did not find an association of rs1801282 with OSA. The differences in study design, sample size, or the study populations among these different studies may cause discrepant results.

Differed from previous researches mainly focusing on specific predefined SNPs, we used targeted multiple gene sequencing to detect genetic susceptibility loci without prior knowledge about position or functionality within the genome. After sequencing of 12 metabolism-related genes, we finally identified a novel association at rs12486170 of the PPARG gene with OSA. Available evidence has indicated that male gender, age, obesity, and smoking are major risk factors that increase vulnerability to OSA [1, 5]. We therefore excluded smokers, and adjusted for gender, age, and BMI in order to avoid confounding effects. Besides, as PPARG is a known regulator of glucose, lipid metabolism[29], we also adjusted for FG, TC, TG, HDL-C and LDL-C. After adjustment for the above confounders, PPARG rs12486170 remained significantly associated with OSA.

- Our study does have several limitations. First, the sample size for targeted sequencing was relatively small due to financial constrains. Consequently, it cannot be completely ruled out that a lack of statistical power influences our results; replication studies in future with a large sample size are warranted. Second, the enrolled severe OSA patients may not be fully representative of the general OSA population; some false positives may still remain in spite of multiple corrections, so it necessitates larger prospective cohort studies to confirm our results. Third, we did not investigate the interaction between gene and environmental exposure, which underlies the pathogenesis of many complex diseases. Finally, the exact mechanisms of the identified common or rare variants are still not clear and require further functional studies.

Conclusions

In conclusion, we identified a novel variant of PPARG associated with OSA in a Chinese population. Subjects with the PPARG rs12486170 GA/GG genotype have a decreased risk of developing OSA, a significantly lower AHI and higher lowest oxygen saturation compared with those with AA genotype after...
adjustment for potential confounders. But again these findings need to be confirmed in further functional studies and independent validations in larger populations, leading to a more holistic understanding of the association between PPARG polymorphisms and OSA risk, which may be helpful for personalized diagnosis and treatment in OSA.

Abbreviations

EDN1: Endothelin; APOE: Apolipoprotein E; LEP: Leptin; LEPR: Leptin receptor; IRS1: Insulin receptor substrate 1; UCP1: Uncoupling protein 1; ADIPOQ: Adiponectin; PEMT: Phospholipid methyltransferase; PPARG: Peroxisome proliferator-activated receptor gamma; SLC2A4: Solute carrier family 2 member 4; FABP2: Fatty acid binding protein 2; ADRA2A: Adrenoceptor alpha 2A; OSA: Obstructive sleep apnea; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; TC: Total cholesterol; TG: Triglyceride; HDL-C: High density lipoprotein-cholesterol; LDL-C: Low density lipoprotein-cholesterol; AHI: Apnea hypopnea index; LSaO₂: lowest oxygen saturation; SNPs: Single nucleotide polymorphisms; MAF: Minor allele frequency

Declarations

Ethics approval and consent to participate

The present study complied with the Declaration of Helsinki, and was approved by the Local Ethics Committee of People's Hospital of Xinjiang (Xinjiang, China). Written informed consent was obtained from all subjects prior to study participation.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the National Health Committee Key Laboratory of Hypertension Clinical Research of China.

Authors' contributions

YYC and NFL conceived and designed the study; YYC and XTC performed the data processing and analyses; YYC wrote and revised the manuscript; QZ and TW contributed to discussion, analyses and reviewed the manuscript; XA, AA and SSL helped to collect the samples and provide technical support. All authors read and approved the final manuscript.

Acknowledgements

This study was supported by the National Health Committee Key Laboratory of Hypertension Clinical Research of China.

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Table S2. Summary of detected rare variants by targeted sequencing.

Tables

| Variables                  | Non OSA (n=50) | Severe OSA (n=50) | P-value |
|---------------------------|----------------|-------------------|---------|
| Gender (male, %)          | 29(58.0%)      | 40(80.0%)         | 0.017   |
| Age (years)               | 44.96±11.44    | 51.20±10.53       | 0.006   |
| BMI (kg/m²)               | 24.96(22.96, 26.66) | 30.06(27.45, 31.68) | <0.001 |
| Neck circumference (cm)   | 38.88±3.62     | 43.34±3.41        | <0.001  |
| Abdominal circumference (cm) | 97.78±9.53    | 110.36±7.83       | <0.001  |
| Alcohol history (n, %)    | 14(28.0%)      | 7(14.0%)          | 0.086   |
| SBP (mmHg)                | 150.80±21.32   | 149.44±20.95      | 0.748   |
| DBP (mmHg)                | 94.86±15.64    | 92.16±15.58       | 0.389   |
| FBG (mmol/L)              | 4.54(4.09, 4.88)| 5.19(4.48, 5.89)  | <0.001  |
| TC (mmol/L)               | 4.39±0.90      | 4.50±1.04         | 0.553   |
| TG (mmol/L)               | 1.42(1.01, 2.01)| 1.84(1.35,2.86)  | 0.017   |
| HDL-C (mmol/L)            | 1.06 (0.89, 1.33)| 0.92(0.78,1.01)  | 0.001   |
| LDL-C (mmol/L)            | 2.63±0.78      | 2.68±0.94         | 0.773   |
| AHI (events/h)            | 0.80(0.40, 2.13)| 59.05(53.85, 70.60)| <0.001 |
| AI (events/h)             | 0.00(0.00, 0.30)| 43.25(32.45, 57.90)| <0.001 |
| HI (events/h)             | 0.75(0.38, 1.90)| 14.75(9.65, 27.70)| <0.001 |
| LSaO₂ (%)                 | 89.0(87.0, 91.0)| 68.0(61.0, 74.0)  | <0.001  |
| MSaO₂ (%)                 | 94.00(93.00, 95.25)| 91.00(88.75, 92.00)| <0.001  |
| Sleep efficiency (%)      | 68.20(63.20, 74.75)| 72.35(61.10, 78.18)| 0.329   |
| Total sleep time (min)    | 413.25(379.00, 449.13)| 421.50(387.38,453.38)| 0.608   |

Values are expressed as mean±standard deviation, median (interquartile range), or n (%)

Differences between groups were analyzed by independent Student t test, Fisher’s exact test, χ² test, or Wilcoxon test

OSA obstructive sleep apnea, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, FBG fasting blood glucose, TC total cholesterol, TG triglyceride, HDL-C high density lipoprotein-cholesterol, LDL-C low density lipoprotein-cholesterol, AHI apnea hypopnea index, AI apnea index, HI hypopnea index, LSaO₂ lowest oxygen saturation, MSaO₂ Mean oxygen saturation
### Table 2 Results from univariate logistic regression analyses under the four genetic models

| Gene    | SNP ID  | Ref Allele | Alt Allele | Freq_Alt (1000g) | Additive OR(95%CI) | P     | Dominant OR(95%CI) | P     | Recessive OR(95%CI) | P     | Allele OR(95%CI) | P     |
|---------|---------|------------|------------|------------------|-------------------|-------|-------------------|-------|-------------------|-------|-------------------|-------|
| FABP2   | rs2964  | T          | C          | 0.333            | 2.388(1.133-5.031) | 0.022 | 2.198(0.774-6.244) | 0.139 | 5.087(1.249-20.724) | 0.023 | 2.149(1.104-4.183) | 0.024 |
| FABP2   | rs1511025 | T       | C          | 0.333            | 1.996(0.929-4.289) | 0.077 | 1.625(0.547-4.831) | 0.382 | 4.533(1.077-19.082) | 0.039 | 1.870(0.923-3.789) | 0.082 |
| PPARG   | rs17036160 | C     | T          | 0.068            | 0.284(0.072-1.120) | 0.072 | 0.284(0.072-1.120) | 0.072 | -                 | -     | 0.306(0.080-1.166) | 0.083 |
| PPARG   | rs12486170 | A    | G          | 0.169            | 0.596(0.301-1.180) | 0.138 | 0.436(0.185-1.029) | 0.058 | 1.000(0.182-5.487) | 0.999 | 0.559(0.273-1.143) | 0.111 |
| UCP1    | rs3811790 | C     | A          | 0.286            | 1.555(0.884-2.735) | 0.126 | 1.494(0.679-3.286) | 0.318 | 2.875(0.837-9.881) | 0.094 | 1.657(0.911-3.014) | 0.098 |
| UCP1    | rs3811877 | T     | G          | 0.462            | 1.496(0.826-2.709) | 0.184 | 2.173(0.902-5.237) | 0.084 | 1.152(0.405-3.277) | 0.790 | 1.444(0.823-2.532) | 0.199 |
| ADRA2A  | rs1800545 | G     | A          | 0.178            | 0.625(0.308-1.266) | 0.192 | 0.437(0.172-1.107) | 0.081 | 1.022(0.196-5.326) | 0.979 | 0.558(0.256-1.215) | 0.142 |

FABP2 fatty acid binding protein 2, PPARG peroxisome proliferator-activated receptor gamma, UCP1 uncoupling protein 1, ADRA2A adrenoceptor alpha 2A, SNP single nucleotide polymorphism, Ref reference, Alt alternate, Freq_Alt (1000g) the frequency of alternative allele in 1000 Genomes Project, OR odds ratio, CI confidence interval

### Table 3 Multivariate logistic regression analyses of 7 SNPs with the risk of OSA

| Gene    | SNP ID  | Additive P0 | P1 | P2 | OR(95%CI)P0 | P1 | P2 | OR(95%CI)P0 | P1 | P2 | OR(95%CI)P0 |
|---------|---------|-------------|----|----|-------------|----|----|-------------|----|----|-------------|
| FABP2   | rs2964  | 0.022       | 0.176 | 0.165 | 2.242(0.717-7.011) | 0.139 | 0.522 | 0.583 | 1.555(0.321-7.524) | 0.023 | 0.110 | 0.055 | 8.610(0.959-77.342) |
| FABP2   | rs1511025 | 0.077 | 0.830 | 0.344 | 1.704(0.565-5.138) | 0.382 | 0.858 | 0.569 | 1.637(0.300-8.924) | 0.039 | 0.536 | 0.296 | 2.845(0.401-20.200) |
| PPARG   | rs17036160 | 0.072 | 0.190 | 0.185 | 0.241(0.029-1.976) | 0.072 | 0.190 | 0.185 | 0.241(0.029-1.976) | -     | -     | -     | -     |
| PPARG   | rs12486170 | 0.138 | 0.149 | 0.148 | 0.471(0.170-1.306) | 0.058 | 0.026 | 0.022 | 0.211(0.055-0.800) | 0.999 | 0.387 | 0.268 | 4.315(0.324-57.389) |
| UCP1    | rs3811790 | 0.126 | 0.174 | 0.344 | 1.488(0.653-3.392) | 0.318 | 0.315 | 0.493 | 1.510(0.465-4.902) | 0.094 | 0.162 | 0.316 | 2.488(0.418-14.800) |
| UCP1    | rs3811877 | 0.184 | 0.180 | 0.565 | 1.271(0.562-2.875) | 0.084 | 0.377 | 0.763 | 1.210(0.351-4.179) | 0.790 | 0.170 | 0.504 | 1.645(0.381-7.092) |
| ADRA2A  | rs1800545 | 0.192 | 0.439 | 0.158 | 0.418(0.124-1.404) | 0.081 | 0.305 | 0.132 | 0.292(0.059-1.447) | 0.979 | 0.994 | 0.696 | 0.521(0.020-13.791) |

P0 no adjust
P1 adjusted for gender, age, BMI
P2 adjusted for Model 1 + FBG, TC, TG, HDL-C and LDL-C
OR adjusted for Model 1 + FBG, TC, TG, HDL-C and LDL-C

FABP2 fatty acid binding protein 2, PPARG peroxisome proliferator-activated receptor gamma, UCP1 uncoupling protein 1, ADRA2A adrenoceptor alpha 2A, SNP single nucleotide polymorphism, BMI body mass index, FBG fasting blood glucose, TC total cholesterol, TG triglyceride, HDL-C high density lipoprotein-cholesterol, LDL-C low density lipoprotein-cholesterol
Table 4 Association of gene polymorphisms with clinical features of OSA

| SNP   | Genotype       | Univariate logistic | Multivariate logistic |
|-------|----------------|---------------------|-----------------------|
|       | Univariate OR(95%CI) | P     | Multivariate OR(95%CI) | P     |
| rs2964 | Recessive CC/TT+TC | 5.727 (1.121, 29.253) | 0.036 | 6.246 (0.674, 57.896) | 0.107 |
| rs2964 | Additive CC/TT   | 2.739 (1.191, 6.300)  | 0.018 | 2.388 (0.741, 7.698)  | 0.145 |
| rs1511025 | Recessive CC/TT+TC | 3.509 (0.819, 15.031) | 0.091 | 2.189 (0.295, 16.232) | 0.444 |
| rs1511025 | Additive CC/TT   | 2.010 (0.897, 4.506)  | 0.090 | 1.578 (0.496, 5.015)  | 0.440 |
| rs12486170 | Dominant AG+GG/AA | 0.333 (0.132, 0.840)  | 0.020 | 0.304 (0.079, 1.170)  | 0.083 |
| rs12486170 | Additive GG/AG/AA | 0.507 (0.242, 1.065)  | 0.073 | 0.620 (0.225, 1.711)  | 0.356 |

Multivariate adjusted for Model 1 + FBG, TC, TG, HDL-C and LDL-C

SNP single nucleotide polymorphism, BMI body mass index, FBG fasting blood glucose, TC total cholesterol, TG triglyceride, HDL-C high density lipoprotein-cholesterol, LDL-C low density lipoprotein-cholesterol, AHI apnea hypopnea index, LSaO\textsubscript{2} lowest oxygen saturation, MSaO\textsubscript{2} Mean oxygen saturation"
- SupplementaryMaterial.doc
- SupplementaryMaterial.doc
- SupplementaryMaterial.doc
- SupplementaryMaterial.doc