

Targeted sequencing analysis of the adiponectin gene identifies variants associated with obstructive sleep apnoea in Chinese Han population

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Abstract

Obstructive sleep apnoea (OSA) is a prevalent sleep disorder considered as an independent risk factor for cardiovascular consequences. It has a strong genetic background and is associated with hypoadiponectinaemia.

Target sequencing of whole ADIPONQ gene was performed in 340 participants including 247 patients with OSA and 93 non-OSA participants. Polysomnography was used to diagnose OSA. The associations between variants and OSA were determined by multivariate regression analysis.

Thirteen single nucleotide polymorphisms of *ADIPOQ* were identified in all subjects. Genotype frequencies at rs4686803 ($P = .034$), rs3774262 ($P = .034$), and rs2082940 ($P = .045$) were significantly different between OSA and non-OSA groups. Individuals carrying the CT/TT genotypes of rs4686803, GA/AA genotypes of rs3774262, and CT/TT genotypes of rs1063537 were associated with 2.295-, 2.295- and 2.155-fold increased risk of OSA respectively in dominant model, after adjusting for confounding effects. The subjects with the rs2082940 CC genotype were associated with decreased risk of OSA (OR: 0.455) in recessive model. Additionally, the apnoea-hypopnea index (AHI) was significantly increased in rs3774262 (GA/AA) ($P = .001$), rs4686803 (CT/TT) ($P = .001$), and rs1063537 (CT/TT) ($P = .004$) genotype individuals than those with rs3774262 (GG), rs4686803 (CC), and rs1063537 (CC) genotypes, respectively. The AHI was significantly decreased in individuals with *ADIPOQ* rs2082940 CC genotypes than in those with the CT and TT genotype ($P = .007$). Moreover, the stratified analysis found that the genotype of rs3774262 (GA/AA), rs4686803 (CT/TT), and rs1063537 (CT/TT) variants were associated with increased risk of OSA by 2.935-, 2.935- and 2.786-fold in overweight participants. The genotype of rs2082940 CC variants was associated with decreased risk of OSA (OR: 0.373) in overweight participants compared with rs2082940 CT/TT genotypes.

ADIPOQ variants rs3774262, rs4686803, rs1063537, and rs2082940 were associated with the prevalence of OSA in Chinese Han individuals.

Abbreviations: ADIPOQ = adiponectin, AHI = apnea-hypopnea index, BMI = body mass index, DBP = diastolic blood pressure, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, LSaO₂ = lowest oxygen saturation, OSA = obstructive sleep apnea, SBP = systolic blood pressure, SNP = single nucleotide polymorphism, TC = total cholesterol, TG = triglycerides.

Keywords: Adiponectin, apnea hypopnea index, gene variants, obstructive sleep apnea, overweight, single nucleotide polymorphism

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1. Introduction

Obstructive sleep apnoea (OSA) is an increasingly common disorder involving repeated upper airway collapse during sleep. It leads to many pathological events, including recurrent reductions in oxygen saturation, hypercapnia, and sleep fragmentation.^[1,2] OSA is also emerging as a major health problem with a high disease burden associated with its own healthcare costs and its contribution as an independent risk factor for cardiovascular, metabolic, and psychiatric disorders such as hypertension, stroke, diabetes, and depression.^[1,3,4] However, the pathogenesis of OSA is unclear.

OSA is affected by multiple factors, including environmental risk factors and genetic factors.^[5] Some genetic and epidemiological studies demonstrated that the risk of OSA is associated with multiple genes.^[6] Genetic variants contribute to an increase in OSA susceptibility through four possible pathogenic pathways: upper airway anatomy and craniofacial form, ventilation control and upper airway collapsibility, body fat distribution, and sleep-wake controlling.^[7]

Adiponectin is a protein produced predominantly by adipocytes that has pleiotropic physiological effects following binding to adiponectin receptors.^[8] Yoshikawa et al^[9] demonstrated that plasma adiponectin levels were negatively correlated with the apnoea-hypopnea index (AHI). Additionally, a clinical study by Al Mutairi et al^[10] demonstrated that plasma adiponectin is an independent marker of disease severity in patients with OSA. Human adiponectin is encoded by *ADIPOQ*, which is located at chromosomal locus 3q27.^[8] One or more *ADIPOQ* single nucleotide polymorphisms (SNPs) affect the synthesis and secretion of adiponectin, indicating that *ADIPOQ* variation may be a determinant of serum adiponectin levels.^[11] Cao et al^[12] observed a marked increase in the duration of the longest apnoea event in patients with the rs1501299 GG genotype than in those with GT/TT genotypes; another study found that the allele or genotype distributions of *ADIPOQ* rs12495941, rs182052, and rs16861205 were related to the severity of OSA.^[13] However, both of the two researchers found no *ADIPOQ* SNP association with the occurrence of OSA in Chinese Han. As these two studies only detected part of the *ADIPOQ* locus. It cannot exclude if other SNPs of *ADIPOQ* associated with the risk of OSA. Therefore, in the present study, we aimed to identify new genetic variants throughout the entire *ADIPOQ* gene using targeted sequencing analysis in unrelated Chinese Han individuals, and to investigate whether these SNPs associated with OSA.

2. Methods

2.1. Subjects

This cross-sectional study was conducted from April 2017 to October 2017 at the Otolaryngological Department of Beijing Anzhen Hospital. The study flow chart is shown in Supplemental Figure S1, <http://links.lww.com/MD/C924>. Consecutive patients were enrolled and screened for OSA with the use of the Berlin questionnaire, which consists of three categories of questions related to the risk of sleep apnoea: snoring and cessation of breathing, daytime sleepiness, and obesity or hypertension and also conduct an overnight sleep study, which was conducted using a level II portable diagnostic device (SOMNO screen; SOMNO medics GmbH, Randersacker, Germany) approved by the US Food and Drug Administration. According to the diagnostic standard, patients were considered to be control if

their Berlin questionnaire scores were less than two and the apnea hypopnea index apnoea-hypopnea index (AHI < 5). Patients are considered to be at high risk if their scores are positive in two or more categories. Eligible patients had scores of 2 or 3 on the Berlin questionnaire^[14] and AHI ≥ 5 were considered to be OSA. Subject exclusion criteria were showed in the supplemental Figure S1, <http://links.lww.com/MD/C924>. All the exclusion criteria were based on the previous study.^[15–20]

After the exclusion of these participants, 340 unrelated Chinese Han adults aged ≥ 18 years were recruited. OSA ($n=247$) and non-OSA ($n=93$). All participants gave written informed consent before enrollment. The protocol was approved by the Medicine Ethics Committee of Beijing Anzhen Hospital (2017005) and adhered to the Declaration of Helsinki. This study was registered in the Chinese Clinical Trial Registry (No. ChiCTR-ROC-17011027).

OSA was defined as an AHI of ≥ 5 events per hour according to American Academy of Sleep Medicine guidelines.^[21] The quantitative phenotypic outcomes were the AHI (defined by events associated with $\geq 3\%$ desaturation); the lowest oxygen saturation (LSaO₂) across the sleep period, excluding intermittent waking episodes; the oxygen desaturation index, defined as the number of times per hour of sleep that the blood's oxygen level dropped by a certain degree from baseline; and the mean apnoea-hypopnea duration.^[22] Anthropometric determinations and blood extractions were performed on a single day as described previously^[23] (Details are described in the supplemental Appendix S1, <http://links.lww.com/MD/C924>).

2.2. Blood sample preparation

All blood samples were collected after the participants had fasted overnight. Blood samples were centrifuged at 3000 rpm, 2943 \times g at 4°C for 10 min. Serum and whole blood samples were then stored at -80°C prior to analysis. Serum triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and other routine serum biochemical parameters were measured in a biochemical analyzer (Hitachi-7600, Tokyo, Japan) using blinded quality control specimens in the Department of the Biochemical Laboratory at Beijing An Zhen Hospital.

2.3. DNA template preparation and amplification

Genomic DNA was extracted from 200 μl whole blood using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). A multiplex PCR amplification strategy was designed online (Ion Ampliseq Designer; <http://www.ampliseq.com>) to amplify the target region (for primer sequences, see Supplemental Table S1, <http://links.lww.com/MD/C924>). Primers were designed to provide the maximum coverage, and the ordered amplicon covered approximately 98.18% of the target sequence (Supplemental Table S2, <http://links.lww.com/MD/C924>). (Details are described in the supplemental Appendix S2, <http://links.lww.com/MD/C924>). The details of primer design referred to <https://www.ampliseq.com/help/pipelineDetails.action>.

2.4. Targeted sequencing

The *ADIPOQ* sequence was screened using Ion Torrent semiconductor sequencing (Life Technologies, Carlsbad, CA, USA). Enriched Ion Sphere Particles carrying multiple copies of the same DNA fragment were sequenced on an Ion 318 Chip to sequence pooled libraries 64 samples at a time. Sequencing was

performed using an Ion PGM Sequencing kit (Life Technologies) with the 400-bp single-end run configuration according to the manufacturer’s instructions. Primer details are given in Supplemental Table S1, <http://links.lww.com/MD/C924>. Computational analysis was in the supplemental Appendix S3, <http://links.lww.com/MD/C924>.

2.5. Statistical analysis

Continuous variables are expressed as means±standard deviations or medians (interquartile range), and categorical variables as numerals (percentages). Independent Student’s *t*-tests for normal distribution and Wilcoxon rank sum tests for asymmetric distribution were used to analyze the differences in continuous variables. Chi-squared tests and Fisher’s exact tests were used to analyze categorical variables. Deviations of genotype frequencies from the Hardy–Weinberg equilibrium (HWE) were assessed using a chi-square test. The associations between OSA and variants were determined by logistic regression analysis. All probability values were two-sided and a *P*-value < .05 was considered statistically significant. All analyses were performed with R (<http://www.R-project.org>) and EmpowerStats software (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA, USA).

3. Results

3.1. Baseline clinical characteristics of the study population

Our study included 247 patients with OSA and 93 non-OSA subjects. Clinical characteristics are shown in Table 1. There were

Table 1
Anthropometric and biochemical characteristics of the subjects included in the study.

	OSA <i>N</i> =247	Non-OSA <i>N</i> =93	<i>P</i>
Age (years)	55.59±10.64	53.20±13.93	.138
Male (<i>n</i> ,%)	212 (88.83%)	65 (69.90%)	.001*
BMI (kg/m ²)	27.29±3.62	23.88±3.53	<.001**
Obesity (<i>n</i> , %)	95 (38.46%)	14 (15.05%)	<.001**
Smoker (<i>n</i> , %)	113 (46.12%)	31 (33.70%)	.040*
Drinker (<i>n</i> , %)	102 (41.63%)	33 (35.87%)	.336
Hypertension (yes, <i>n</i> , %)	64 (25.91%)	14 (15.05%)	.034*
Diabetes (yes, <i>n</i> , %)	15 (7.28%)	5 (5.95%)	.685
Dyslipidemia (yes, <i>n</i> , %)	178 (72.06%)	54 (58.06%)	.013*
SBP (mmHg)	126.34±18.77	123.67±18.11	.237
DBP (mmHg)	77.48±12.59	74.33±11.93	.038*
FPG (mmol/L)	4.08±1.99	4.59±1.44	.037*
TG (mmol/L)	1.59 (1.09–2.22)	1.27 (0.95–1.64)	.002*
TC (mmol/L)	4.35±1.12	4.42±1.07	.607
LDL-C (mmol/L)	2.60±1.00	2.62±0.82	.806
HDL-C (mmol/L)	1.06±0.27	1.14±0.28	.015*
AHI (times/h)	26.00 (18.30–40.00)	2.50 (1.60–3.70)	<.001**
Lowest SaO ₂ (%)	82.32±8.37	90.29±2.79	<.001**
Average SaO ₂ (%)	93.50±1.851	94.42±1.795	.005

Results are expressed as mean±standard deviation, median (interquartile range), or *n* (%). Differences between groups were analyzed by independent Student’s *t*-test, Fisher’s exact test, χ^2 test, or Wilcoxon test. AHI=apnea–hypopnea index, Average SaO₂=average saturation oxygen, BMI=body mass index, DBP=diastolic blood pressure, FPG=fasting plasma glucose, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, lowest SaO₂=lowest saturation oxygen, OSA=obstructive sleep apnea, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides.

**P* < .05.
***P* < .001.

no significant differences in age (*P* = .138), TC (*P* = .607), LDL-C (*P* = .806), or systolic blood pressure (SBP; *P* = .237) between the two groups. Patients with OSA had a significantly higher BMI compared with the non-OSA group (*P* < .001), as well as higher diastolic blood pressure (DBP; *P* = .038), TG (*P* < .002), AHI (*P* < .001), lowest saturation oxygen (LSaO₂) (*P* < .001), and average saturation oxygen (ASaO₂) (*P* = .005) compared with the non-OSA group. OSA patients also had significantly lower fasting blood glucose (FPG) levels than non-OSA subjects (*P* = .037). There were more males, obese individuals, smokers, and individuals with hypertension and dyslipidaemia in the OSA group compared with the non-OSA group.

3.2. ADPIOQ sequencing and SNP detection

We used a targeted next-generation sequencing approach to analyze the ADPIOQ sequence in 247 individuals with OSA and 93 non-OSA individuals. The fragments of ADPIOQ gene were sequenced at 327× depth in this study. 80 variants were called (details were in supplemental table S4, <http://links.lww.com/MD/C924>), after exclude the synonymous variants and intron variants, and variants not present in 1000 genomes databases, EXAC databases, dbSNP database and ESP6500 database. A total of 25 nucleotide variants were called, of which 8 were minimum allele frequency were <0.01. Only 17 variations were left. After excluding deletions and insertions, 13 SNP variants remained. We also found that there were 32 rare nonsynonymous variants (minimum allele frequency were <0.01) may be damaging variants according to the SIFT, Mutation Taster and PolyPhen-2 database (supplemental table S5, <http://links.lww.com/MD/C924>). However, further research is required to determine the functions of the rare variants.

3.3. ADIPOQ variant association with OSA

The allele frequency distribution is shown in Supplemental Table S3, <http://links.lww.com/MD/C924>. All SNPs were in accordance with the HWE. Of the 13 SNPs, genotype frequencies at rs4686803, rs2082940, and rs3774262 differed significantly (*P* < .05, Table 2) between OSA and non-OSA groups. No significant differences were observed between the two groups with respect to the other 10 SNPs. As shown in Table 3, after adjusting for age, gender, BMI, drinking, TG, TC, LDL, HDL-C, SBP, DBP, and FBG ADIPOQ rs4686803 CT/TT genotypes was still an independent detrimental factor for OSA individuals (dominant model: adjusted odds ratio (OR)=2.295, 95% CI=1.223–4.306, *P* = .010; additive model: adjusted OR=1.936, 95% CI=1.131–3.313, *P* = .016) compared with the CC genotype. ADIPOQ rs3774262 GA/AA genotypes was also an independent detrimental factor for OSA compared with the GG genotype after adjusting for the same confounding factors (dominant model: adjusted odds ratio (OR)=2.295, 95% CI=1.223–4.306, *P* = .010; additive model: adjusted OR=1.936, 95% CI=1.131–3.313, *P* = .016) as did those with rs1063537 CT/TT genotypes compared with those with the CC genotype (dominant model: adjusted odds ratio (OR)=2.155, 95% CI=1.149–4.041, *P* = .017; additive model: adjusted OR=1.842, 95% CI=1.082–3.138, *P* = .025) The ADIPOQ rs 2082940 CC genotype had decreased risk of developing OSA after adjusting for the same confounding factors (additive model: adjusted OR=0.555, 95% CI=0.330–0.935, *P* = .027; recessive model: adjusted OR=0.455, 95% CI=0.243–0.850, *P* = .014) compared with those with the CT and TT genotype. No significant

Table 2
Genotype frequencies in OSA and non-OSA subjects.

SNP	Genotype	OSA (n/%)	Non-OSA (n/%)	χ^2	P
rs4686803	CC	115 (46.56%)	58 (62.37%)	6.768	.034*
	CT	112 (45.34%)	30 (32.26%)		
	TT	20 (8.10%)	5 (5.38%)		
rs3774262	GG	115 (46.56%)	58 (62.37%)	6.768	.034*
	GA	112 (45.34%)	30 (32.26%)		
	AA	20 (8.10%)	5 (5.38%)		
rs1063537	CC	118 (47.77%)	58 (62.37%)	5.788	.055
	CT	109 (44.13%)	30 (32.26%)		
	TT	20 (8.10%)	5 (5.38%)		
rs6414520	AA	127 (51.42%)	39 (41.94%)	2.431	.297
	AG	100 (40.49%)	45 (48.39%)		
	GG	20 (8.10%)	9 (9.68%)		
rs6773957	AA	80 (32.39%)	27 (29.63%)	1.247	.536
	AG	124 (50.20%)	45 (48.39%)		
	GG	43 (17.41%)	21 (22.58%)		
rs17846872	GG	227 (91.90%)	6 (6.45%)	0.259	.611
	GT	20 (8.10%)	20 (21.51%)		
	TT	0	0		
rs2082940	TT	22 (8.91%)	6 (6.45%)	6.192	.045*
	TC	111 (44.94%)	30 (32.26%)		
	CC	114 (46.15%)	57 (61.29%)		
rs1063538	TT	82 (33.20%)	27 (29.03%)	1.527	.466
	TC	123 (49.80%)	45 (48.36%)		
	CC	42 (17.00%)	21 (22.58%)		
rs35469083	CC	238 (96.36%)	89 (95.70%)	.757	
	CT	9 (3.64%)	4 (4.30%)		
	TT	0	0		
rs4686804	GG	86 (34.82%)	31 (33.33%)	0.848	.654
	GA	121 (48.99%)	43 (46.24%)		
	AA	40 (16.19%)	19 (20.43%)		
rs1063539	GG	127 (51.52%)	56 (60.22%)	2.399	.301
	GC	99 (40.08%)	32 (34.41%)		
	CC	21 (8.50%)	5 (5.38%)		
rs17846865	TT	208 (84.21%)	79 (84.95%)	0.61	.737
	TC	38 (15.38%)	13 (13.98%)		
	CC	1 (0.4%)	1 (1.07%)		
rs2241766	TT	136 (55.06%)	44 (47.31%)	1.629	.443
	TG	95 (38.46%)	42 (45.16%)		
	GG	16 (6.48%)	7 (7.53%)		

OSA = obstructive sleep apnea, SNP = single nucleotide polymorphism.

* $P < .05$.

differences were observed with respect to other SNPs after adjustment.

3.4. ADIPOQ genotype significantly increased the AHI and LSAO₂

As shown in Table 4, the AHI in individuals with ADIPOQ rs4686803 CT/TT genotypes was significantly higher than in those with the CC genotype (23.30 (10.50–36.70) vs. 17.00 (3.60–30.20); $P = .001$). The LSAO₂ was also significantly lower in rs4686803 CT/TT genotype than rs4686803 CC individuals (83.52 ± 8.63 vs. 85.35 ± 7.51, respectively; $P = .039$). We also measured ASaO₂ levels in these individuals but found no significant differences among groups ($P = .656$).

The AHI was also significantly increased in individuals with ADIPOQ rs3774262 GA/AA genotypes than in those with the GG genotype (23.30 (10.50–36.70) vs. 17.00 (3.60–30.20); $P = .001$), and the LSAO₂ was significantly decreased in rs3774262 GA/AA compared with rs3774262 GG individuals (83.52 ± 8.63 vs. 85.35 ± 7.51, respectively; $P = .039$). Similarly,

a significantly increased AHI was observed in individuals with ADIPOQ rs1063537 CT/TT genotypes compared with those with the CC genotype (23.20 (10.43–36.10) vs. 17.15 (3.70–30.85); $P = .004$). The AHI was significantly decreased in individuals with ADIPOQ rs2082940 CC genotypes than in those with the CT and TT genotype (17.00 (3.70–29.70) vs. 23.40 (10.45–35.15) vs. 22.30 (9.35–39.63); $P = .007$)

3.5. ADIPOQ genotype associated with OSA in overweight patients.

As obesity is common in OSA patients and is also a risk factor for OSA, so we conduct subgroup analysis to further explore genotype frequency differences in OSA patients with and without overweight. As shown in Table 5. Our results demonstrated that in overweight patients, the genotype distributions of rs3774262 ($P = .011$), rs4686803 ($P = .011$), rs1063537 ($P = .016$), and rs2082940 ($P = .017$) were significantly difference in OSA group and Non-OSA group. As shown in Table 6, after adjusting for age, gender, BMI, drinking, TG, TC, LDL, HDL-C, SBP, DBP,

Table 3
Multivariate logistic regression analyses of thirteen SNPs in ADIPOQ gene with the risk of OSA.

	Additive			OR (95%) p2	Dominant			OR (95%) p2	Recessive			OR p2 (95%)
	p0	p1	p2		p0	p1	p2		p0	p1	p2	
rs3774262	0.016	0.053	0.016	1.936 (1.131-3.313)	0.010	0.034	0.010	2.295 (1.223-4.306)	0.395	0.616	0.440	1.722 (0.434-6.840)
rs4686803	0.016	0.053	0.016	1.936 (1.131-3.313)	0.010	0.034	0.010	2.295 (1.223-4.306)	0.395	0.616	0.440	1.722 (0.434-6.840)
rs1063537	0.024	0.080	0.025	1.842 (1.082-3.138)	0.017	0.058	0.017	2.155 (1.149-4.041)	0.395	0.616	0.440	1.722 (0.434-0.840)
rs6414520	0.157	0.154	0.082	0.661 (0.412-1.504)	0.119	0.147	0.099	0.597 (0.324-1.101)	0.642	0.495	0.286	0.570 (0.203-1.601)
rs6773957	0.316	0.620	0.707	0.922 (0.605-1.407)	0.553	0.706	0.760	0.902 (0.468-1.741)	0.278	0.660	0.755	0.890 (0.428-1.852)
rs17846872	0.612	0.711	0.951	1.038 (0.315-3.422)	0.612	0.711	0.951	1.038 (0.315-3.422)				
rs2082940	0.024	0.092	0.027	0.555 (0.330-0.935)	0.464	0.859	0.563	0.692 (0.199-2.409)	0.013	0.046	0.014	0.455 (0.243-0.850)
rs10635388	0.252	0.565	0.635	0.903 (0.592-1.377)	0.463	0.656	0.693	0.876 (0.455-1.687)	0.240	0.615	0.700	0.865 (0.414-1.807)
rs35469083	0.778	0.877	0.450	2.022 (0.325-12.576)	0.778	0.877	0.450	2.022 (0.325-12.576)				
rs4686804	0.501	0.755	0.586	0.890 (0.584-1.355)	0.797	0.815	0.589	0.837 (0.439-1.597)	0.358	0.776	0.733	0.787 (0.372-1.665)
rs1063539	0.123	0.169	0.036	1.777 (1.039-3.038)	0.148	0.185	0.055	1.840 (0.988-3.426)	0.338	0.447	0.188	2.864 (0.598-13.719)
rs17846865	0.990	0.932	0.624	0.829 (0.393-1.752)	0.870	0.857	0.744	0.874 (0.388-1.969)	0.490	0.183	0.415	0.277 (0.013-6.082)
rs2241766	0.152	0.304	0.231	1.346 (0.827-2.191)	0.194	0.324	0.263	1.393 (0.780-2.487)	0.341	0.582	0.467	1.580 (0.406-6.158)

p0: no adjust.

p1: adjusted for age, sex, BMI,.

p2: adjusted for Model 1 + TG, TC, LDL-C, HDL-C, FBG, SBP, DBP and Drinker.

OR: adjusted for Model 1 + TG, TC, LDL-C, HDL-C, FBG, SBP, DBP and Drinker.

BMI=body mass index, DBP=diastolic blood pressure, FBG=fasting plasma glucose, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, OSA=obstructive sleep apnea, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides.

and FBG *ADIPOQ* rs4686803 CT/TT genotype was associated with more prevalence of OSA in overweight individuals compared with rs4686803 CC genotype (dominant model: adjusted odds ratio (OR)=2.935, 95% CI=1.271-6.776, *P*=.012; additive model: adjusted OR=2.064, 95% CI=1.051-4.052, *P*=.035). The rs3774262 GA/AA genotypes was associated with more prevalence of OSA in overweight individuals compared with rs3774262 GG genotype (dominant model: adjusted odds ratio (OR)=2.935, 95% CI=1.271-6.776, *P*=.012; additive model: adjusted OR=2.064, 95% CI=1.051-4.052, *P*=.035), as were those with the CT/TT genotypes of rs1063537 compared with the CC genotype (dominant model: adjusted odds ratio (OR)=2.786, 95% CI=1.212-6.406, *P*=.016; additive model: adjusted OR=1.982, 95% CI=1.017-3.861, *P*=.044). The subjects with the *ADIPOQ* rs2082940 CC genotype associated with low prevalence of OSA in overweight patients (recessive model: adjusted OR=0.373, 95% CI=0.164-0.848, *P*=.019) compared with those with the CT and TT genotype. The results suggest that the

variants associated with the prevalence of OSA in overweight participants.

4. Discussion

In this study, the relationship between *ADIPOQ* and OSA was investigated, and *ADPIOQ* rs4686803 CT/TT, rs3774262 GA/AA, and rs1063537 CT/TT genotypes were associated with more prevalence of OSA than that of rs4686803CC, rs3774262GG, and rs1063537CC carriers, respectively. The rs2082940 CC genotype was associated with less prevalence of OSA than that of rs2082940 CT and TT genotype. Individuals with rs4686803 CT/TT, rs3774262 GA/AA, and rs1063537 CT/TT genotypes also had a significantly increased AHI compared with those with rs4686803 CC, rs3774262 GG, and rs1063537 CC genotypes, respectively. Individuals with rs2082940 CC genotype had a significantly decreased AHI compared with those with rs2082940 CT and TT genotype. Additionally, the stratified analysis found that the genotypes of rs4686803 CT/TT,

Table 4
Association of ADIPOQ single nucleotide polymorphisms with clinical data.

	rs4686803			rs3774262			rs1063537			rs2082940			
	CC	CT+TT	<i>P</i>	GG	GA+AA	<i>P</i>	CC	CT+TT	<i>P</i>	TT	CT	CC	<i>P</i>
BMI (kg/m ²)	26.18±3.97	26.55±3.83	.384	26.18±3.97	26.55±3.83	.384	26.24±4.05	26.49±3.75	.551	27.33±4.62	26.38±3.62	26.17±4.00	.348
SBP (mmHg)	125.77±20.40	125.44±16.60	.870	125.77±20.40	125.44±16.60	.870	125.70±20.34	125.51±16.60	.924	120.29±13.07	126.47±16.96	125.78±20.51	.272
DBP (mmHg)	77.13±13.27	76.14±11.62	.484	77.13±13.27	76.14±11.62	.484	76.99±13.21	76.22±11.67	.568	75.43±11.06	76.25±11.70	77.12±13.33	.721
FBG (mmol/L)	4.02±1.45	4.46±2.20	.041*	4.02±1.45	4.46±2.20	.041*	4.09±1.61	4.39±2.10	.174	5.30±3.66	4.28±1.66	14.00±1.45	.004
TG (mmol/L)	1.46 (1.03-2.02)	1.47 (1.03-2.13)	.965	1.46 (1.03-2.02)	1.47 (1.03-2.13)	.965	1.47 (1.02-2.02)	1.45 (1.03-2.13)	.893	1.44 (0.98-2.32)	1.47 (1.04-2.14)	1.46 (1.02-1.98)	.982
TC (mmol/L)	4.30±1.07	4.45±1.14	.211	4.30±1.07	4.45±1.14	.211	4.31±1.09	4.44±1.12	.271	4.29±1.60	4.47±1.03	4.31±1.07	.386
LDL-C (mmol/L)	2.55±0.99	2.65±0.91	.345	2.55±0.99	2.65±0.91	.345	2.56±1.01	2.64±0.90	.405	2.33±1.05	2.11±0.87	2.55±1.00	.114
HDL-C (mmol/L)	1.10±0.27	1.08±0.28	.523	1.10±0.27	1.08±0.28	.523	1.10±0.28	1.07±0.27	.283	1.02±0.30	1.08±0.28	1.10±0.27	.382
AHI (times/h)	17.00	23.30	.001*	17.00	23.30	.001*	17.15	23.20	.004*	22.30	23.40	17.00	.007*
	(3.60-30.20)	(10.50-36.70)		(3.60-30.20)	(10.50-36.70)		(3.70-30.85)	(10.43-36.10)		(9.35-39.63)	(10.45-35.15)	(3.70-29.70)	
Lowest SaO ₂ (%)	85.35±7.51	83.52±8.63	.039*	85.35±7.51	83.52±8.63	.039*	85.17±7.69	83.68±8.50	.094	83.25±8.70	83.62±8.60	85.33±7.54	.135
Average SaO ₂ (%)	93.12±8.06	93.46±1.86	.656	93.12±8.06	93.46±1.86	.656	93.13±8.06	93.46±1.86	.780	92.50±2.50	93.63±1.70	93.12±8.06	.711

Results are expressed as mean±standard deviation or median (interquartile range). Differences between groups were analyzed by independent student t-test or Wilcoxon test.

AHI=apnea-hypopnea index, BMI=body mass index, DBP=diastolic blood pressure, FPG=fasting plasma glucose, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, SBP=systolic blood pressure, TG=triglycerides, TC=total cholesterol.

* *P* < .05.

Table 5
Genotypes distribution in patients and controls according to weight.

	Normal weight			Overweight		
	Non-OSA	OSA	P value	Non-OSA	OSA	P value
rs3774262						
GG	26 (55.3%)	22 (52.4%)	.961	32 (69.6%)	93 (45.4%)	.011
GA	19 (40.4%)	18 (42.8%)		11 (23.9%)	94 (45.8%)	
AA	2 (4.3%)	2 (4.8%)		3 (6.5%)	18 (8.8%)	
rs4686803						
CC	26 (55.3%)	22 (52.4%)	.961	32 (69.6%)	93 (45.4%)	.011
CT	19 (40.4%)	18 (42.8%)		11 (23.9%)	94 (45.8%)	
TT	2 (4.3%)	2 (4.8%)		3 (6.5%)	18 (8.8%)	
rs1063537						
CC	26 (55.3%)	23 (54.8%)	.993	32 (69.6%)	95 (46.3%)	.016
CT	19 (40.4%)	17 (40.5%)		11 (23.9%)	92 (44.9%)	
TT	2 (4.3%)	2 (4.7%)		3 (6.5%)	18 (8.8%)	
rs2082940						
TT	2 (4.3%)	2 (4.7%)	.961	4 (8.7%)	20 (9.8%)	.017
TC	19 (40.4%)	18 (42.9%)		11 (23.9%)	93 (45.4%)	
CC	26 (55.3%)	22 (52.4%)		31 (67.4%)	92 (44.8%)	
rs1063539						
GG	26 (55.3%)	24 (57.1%)	.965	30 (65.2%)	103 (50.2%)	.167
GC	18 (38.3%)	15 (35.7%)		14 (30.4%)	84 (41.0%)	
CC	3 (6.4%)	3 (7.2%)		2 (4.4%)	18 (8.8%)	
rs6773957						
AA	13 (27.7%)	15 (35.7%)	.698	14 (30.4%)	65 (31.7%)	.755
AG	23 (48.9%)	19 (45.2%)		22 (47.8%)	105 (51.2%)	
GG	11 (23.4%)	8 (19.1%)		10 (21.8%)	35 (17.1%)	

Normal weight: body mass index (BMI) <24 (kg/m²), overweight: BM ≥ 24 (kg/m²). OSA=obstructive sleep apnea.

rs3774262 GA/AA, and rs1063537 CT/TT were associated with more prevalence of OSA in overweight participants than that of rs4686803CC, rs3774262GG, and rs1063537CC carriers, respectively. The rs2082940 CC genotype was associated with less prevalence of OSA in overweight patients than that of rs2082940 CT and TT genotype.

OSA is associated with hypoadiponectinaemia, so it is relevant to determine whether SNPs of the adiponectin gene correlate with

the occurrence of OSA. Previous studies reported that *ADIPOQ* SNPs were not directly associated with an increased risk of OSA in the Chinese Han population.^[12,13] However, they just research limited SNPs of *ADIPOQ*. In our study, we used targeted sequencing analysis to analyze entire *ADIPOQ* gene. We found some different results, for example, the matched case-control study found that the *ADIPOQ* variant rs6773957 was associated with OSA in overweight individuals; however, we found no

Table 6
Multivariate logistic regression analyses of thirteen SNPs in *ADIPOQ* gene with the risk of OSA in overweight and normal weight patients.

Genotype SNP	Normal-weight		Overweight	
	OR (95CI)%	P-value	OR (95CI)%	P-value
rs4686803				
Dominant				
CC/CT + TT	1.579 (0.420–5.303)	.460	2.935 (1.271–6.776)	.012*
Additive				
Rs4686803				
CC/CT/TT	1.917 (0.620–5.928)	.259	2.064 (1.051–4.052)	.035*
rs3774262				
Dominant				
GG/GA+AA	1.579 (0.420–5.303)	.460	2.935 (1.271–6.776)	.012*
Additive				
rs3774262				
GG/GA/AA	1.917 (0.620–5.928)	.259	2.064 (1.051–4.052)	.035*
rs1063537				
Dominant				
CC/CT+TT	1.207 (0.363–4.012)	.759	2.786 (1.212–6.406)	.016*
Additive				
rs1063537				
CC/CT/TT	1.518 (0.499–4.616)	.462	1.982 (1.017–3.861)	.044*
Recessive				
rs2082940				
TT+TC/CC	0.829 (0.249–2.755)	.759	0.373 (0.164–0.848)	.019*
Additive				
rs2082940				
TT/TC/CC	0.522 (.169–1.614)	.259	0.543 (0.287–1.028)	.061

p: adjusted for Model 1 + TG, TC, LDL-C, HDL-C, FBG, SBP, DBP and Drinker.

BMI=body mass index, DBP=diastolic blood pressure, FBG=fasting plasma glucose, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, OSA=obstructive sleep apnea, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides.

* P < .05.

connection between rs6773957 and OSA in the present study. Conversely, we found an association with the rs3774262 genotype and an increased OSA risk, which was found not associated with the prevalence of OSA in previously study. The reason for this discrepancy might be that the earlier study did not adjust for BMI, SBP, DBP, LDL, TC, HDL, TG, FBG, or drinking, which was all closely related to OSA and adiponectin. Second, the exclusion criteria differed between the two studies. For instance, the first study did not exclude pregnant patients, or those with cancer, sleep disorders, and those taking medication likely to affect the function of the nervous system.^[24]

Li et al,^[25] Gu et al,^[26] and Davis et al certified that SNPs rs3774262, rs2082940, and rs1063537 were associated significantly with adiponectin levels. However, no previous studies examining the association between rs3774262, rs2082940, and rs1063537 with the risk of OSAS have been published. Our research demonstrated that the genotype frequencies of rs3774262, rs2082940, and rs1063537 in *ADIPOQ* are significant difference in overweight patients with and without OSA. Our results also suggested that the genotype distributions of rs3774262, rs4686803, rs1063537, and rs2082940 were associated with the risk of OSAS in overweight individuals. It is well known that obesity is an independent risk factor for OSA,^[27] with >50% of OSA diagnoses attributable to being overweight. Obesity might contribute to OSAS through imposed mechanical loads on the upper airway, resulting in flow limitation and OSAS. Compared with the lean control subjects, the obese populations commonly have more para-pharyngeal fat deposition, which in turn causes upper airway caliber narrowing and collapsing. Moreover, through reduced lung volume, obesity results in decreased tracheal tug and increased airway resistance.^[28] In addition, it has been demonstrated that adiponectin contributors to fat distribution,^[29] previous studies found adiponectin genotype rs1501299 GG has significantly neck circumference compared with rs1501299 GT+TT genotypes.^[12] So, adiponectin might increase the occurrence of OSA by the increased fat distribution on neck.

OSA is associated with age and sex, and the prevalence of moderate to severe sleep disordered breathing (≥ 15 events per hour) was shown to be 23.4% (95% CI=20.9–26.0) in women and 49.7% (95% CI=46.6–52.8) in men in some advanced age groups.^[30] At the clinically important ≥ 15 AHI level, the prevalence in the overall adult population (aged >18 years) was much higher (36%) in older groups.^[31] Therefore, to avoid confounding effects, we adjusted age, sex, and BMI in our study. As shown in Table 1, dyslipidaemia, SBP, DBP, and FBG differed significantly between OSA and control groups, and another study also found that *ADIPOQ* influenced the TG and LDL-C uptake.^[32] Therefore, we additionally adjusted for these factors as well as drinking, which is linked to TG levels, in the present study.

Care was taken to avoid bias in this study. Genomic DNA extraction and targeted sequencing were performed according to the manufacturer's instructions (Thermo Fisher Scientific, Waltham, MA, USA) by a trained experimenter (Analyses Technology Co. Ltd.), who was unaware of patient clinical data. Moreover, adjustments were made for the confounding effects of risk factors for OSA and *ADIPOQ*. This study had a cross-sectional design, and subjects were consecutively recruited to reduce the effects of outcome selection bias. Lu et.al have demonstrated that the serum/plasma adiponectin levels in OSA patients were significantly lower than that in controls. Subgroup analysis indicated that the heterogeneity would decrease when

subgroup analysis was stratified by race. In addition, meta-regression analysis also suggested that the adiponectin levels were only significantly correlated with race.^[33] So, race might be a strong influence factor of adiponectin. Here, we selected Chinese Han population to avoid the influence of race.

Nevertheless, this study had a number of limitations. First, it had a small sample size, so larger samples are needed to confirm the results. Second, the participants may not be entirely representative of the general Han Chinese population. Additionally, potential false-positive results may still be possible after multiple corrections, so prospective cohort studies are needed to confirm the variants identified in our study. Finally, the exact mechanism of these variants is not fully understood and requires further functional studies.

In conclusion, we identified four *ADIPOQ* variants, rs4686803, rs3774262, rs1063537, and rs2082940, associated with OSA after adjusting for confounding effects. Our findings confirmed that *ADIPOQ* variants are involved in the etiology of OSA. In addition, gene analysis may be helpful for individualized typing of patients with OSA and could contribute to personalized diagnosis and treatment in the future. The specific mechanism of these variants requires further study.

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