Genetic variants of rs1275988 and rs2586886 in TWIK-related acid-sensitive K^+ channel-1 gene may be potential risk factors for obese patients with obstructive sleep apnea

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Abstract

Background: The pathogenesis of obstructive sleep apnea (OSA) remains not fully understood. This study aimed to explore the mechanism of OSA by assessing the association between the human tandem of P domains in a weak inwardly rectifying K^+ channel (TWIK)-related acid-sensitive K^+ channel-1 (*TASK-1*) gene and OSA.

Methods: A total of 164 patients with severe OSA and 171 patients without OSA were recruited from the Center for Hypertension of People's Hospital of Xinjiang Uygur Autonomous Region (China) from April to December in 2016. Two single nucleotide polymorphisms (rs1275988 and rs2586886) in the *TASK-1* gene were selected and genotyped using a kompetitive allele specific polymerase chain reaction genotyping system. Clinical-pathological characteristics and genotype data were compared between the severe and non-OSA groups to explore the association between *TASK-1* gene polymorphism and severe OSA.

Results: There were no significant differences in genotype distribution, allele frequency, and the recessive and dominant model of the two selected single nucleotide polymorphisms (rs1275988 and rs2586886) between the severe and non-OSA groups in the total population ($P > 0.05$). However, for patients with a body mass index (BMI) ≥28 kg/m^2, the distribution of genotypes and alleles, and the recessive model (GG + GA *vs.* AA) exhibited significant differences between the severe and non-OSA group (for genotypes: $P = 0.014$ and $P = 0.026$; for alleles: $P = 0.006$ and $P = 0.011$; for the recessive model: $P = 0.005$ and $P = 0.009$, respectively). The simple logistic regression analysis revealed that the GG genotype was a risk factor for OSA. The odds ratio (OR) and 95% confidence intervals (CI) were 4.902 (1.582–15.186, $P = 0.006$) for rs1275988 and 4.420 (1.422–13.734, $P = 0.010$) for rs2586886, respectively. In multivariate logistic regression analysis, the combination of GG genotypes of rs1275988 with BMI ≥28 kg/m^2 increased the risk of severe OSA (OR = 8.916, 95% CI 4.506–17.645, $P < 0.001$).

Conclusion: Both the GG genotype of rs1275988 and GG genotype of rs2586886 in the *TASK-1* gene may play as potential risk factors in obese patients with OSA.

Keywords: Potassium channels; Obstructive sleep apnea; Single nucleotide polymorphism; Body mass index

Introduction

Obstructive sleep apnea (OSA) is one of the most prevalent sleep disorders, and the major clinical manifestations are sleep apnea and frequent snoring, daytime sleepiness and trance.[1] OSA is significantly and independently associated with increased cardiovascular and cerebrovascular morbidity and mortality.[2] Twin studies, familial studies, chromosomal mapping, and racial studies have provided evidence for the possible link between OSA and genetic factors.[3] However, the pathogenesis of OSA is not fully understood, and is affected by genetic and environmental factors.

Recent attention has been directly attached to tandem of P domains in a weak inwardly rectifying K^+ channel (TWIK)-related acid-sensitive K^+ channel-1 (*TASK-1*, also called *KCNK3*), which is one of the members of the two-pore-domain potassium channel family widely expressed in the body.[4]*TASK-1* is highly expressed in respiratory-related brainstem neurons.[5,6] It has been evidenced that the *TASK-1* channel is sensitive to hypoxia and changes in extra-cellular pH, even in the physiological range,[7,8] which are also the hallmarks of OSA.[9] Furthermore, a large genome-wide association meta-analysis revealed that the *KCNK3* gene has been linked to obesity,[10] which is an independent risk factor for OSA.[11] In addition, *TASK-1* is

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involved in the regulation of lipid metabolism, and this can be used to assess the number of thermogenic adipocytes within human adipose tissues.[12]

Based on the above evidence, it would be reasonable to consider that the *TASK-1* gene is relevant to metabolic risk factors (obesity and lipid metabolism) and some of the characteristics (intermittent hypoxia, hypercapnia, and acidity) of OSA. At present, the evidence of the association of the *TASK-1* gene with OSA has mainly been derived from animal experiments. In the present study, two candidate single nucleotide polymorphisms (SNPs) in the *TASK-1* gene were selected, and the genotype distributions were determined among 171 individuals without OSA and 164 patients with severe OSA. The mechanism of OSA was explored by assessing the association between the human *TASK-1* gene and OSA.

Methods

Ethics approval

The present study was conducted in accordance with the *Declaration of Helsinki*, and was approved by the Local Ethics Committee of People's Hospital of Xinjiang (No. 2016016). An informed written consent was obtained from each patient before enrollment into the study.

Patient selection

Similar to a previous study conducted in our center,[13] the inclusion criteria were as follows: consecutive patients, who were ≥18 years old, clinically suspicious of OSA, and were referred for sleep monitoring for the first time when characterized with one of the following: (1) snoring at night, (2) witnessed apnea and arousal during sleep and daytime sleepiness, (3) morning headache, (4) resistant hypertension, and (5) unexplainable cyanosis. These patients were recruited from the Center for Hypertension of People's Hospital of Xinjiang Uygur Autonomous Region, China from April to December 2016. All subjects underwent polysomnography (PSG) monitoring. The clinical data and venous blood samples of all subjects were collected.

The exclusion criteria for the present study were as follows: (1) central sleep apnea; (2) asthma, acute, and chronic obstructive pulmonary disease, interstitial lung disease, pulmonary tuberculosis, and other respiratory diseases; (3) malignant tumors, acute infections, and autoimmune diseases; (4) acute cardiovascular and cerebrovascular diseases; (5) regular intake of steroid, bronchodilator, antihistamines, and anti-inflammatory drugs; (6) thyroid dysfunction; (7) long-term exposure to industrial dust and toxic gas, and a history of thoracic surgery; (8) severe heart and renal dysfunction; (9) secondary hypertension, such as renal and renovascular hypertension, pheochromocytoma, aldosterone adenoma, Cushing syndrome, and other common secondary hypertensions; (10) psychosis and severe sleep disorders; (11) failure in the nocturnal attended PSG. Subjects who fulfilled the above criteria were excluded, based on their medical history, physical examination, chest X-ray, and PSG monitoring. Finally, a total of 335 subjects (164 severe OSA subjects and 171 non-OSA subjects) were enrolled in the study.

PSG monitoring

All participants underwent overnight attended PSG (Compumedics E series, Australia), according to a previous study.[13]

Diagnostic criteria

The OSA diagnosis was made according to the "Guidelines for the diagnosis and treatment of OSA hypopnea syndrome" in 2009.[14] OSA severity was evaluated based on the apnea-hypopnea index (AHI), and the severity of OSA for the present study was considered, as follows: non-OSA (AHI <5 events/h); and severe OSA (AHI ≥30 events/h).

General data and anthropological indicators

The general information included the following: age, gender, nationality, and occupation; previous and present history (hypertension family history, systolic blood pressure, diastolic blood pressure, and vascular risk stratification); personal history, including whether the subject snores, smoking status (smokers were defined as those who smoked one or more cigarettes a day for longer than one year), and alcohol intake; anthropological indicators, which mainly included height, weight (body mass index [BMI] = weight/height^2, kg/m^2), neck circumference, and abdominal circumference.

Laboratory assessment

Two equal samples of fasting peripheral venous blood (empty stomach for at least 10 h or more, cubital vein blood sample) were collected in the morning after the PSG. The serum was collected from one sample after centrifuging for 60 min (3000 r/min, lasted for 10 min, at 4°C) and stored at –20°C for later use. The biochemical evaluation (blood routine test, urine routine test, erythrocyte sedimentation rate, lipids, glycosylated hemoglobin, fasting blood glucose, renal function, electrolyte, etc) was measured at the central laboratories of the hospital using standard techniques.

Genetic DNA extraction

Three milliliters of venous blood from another sample was collected in ethylene diamine tetraacetic acid (EDTA)-containing tubes for all subjects. The genomic DNA was extracted from whole blood by using a commercially available DNA isolation kit (Beijing, China), according to manufacturer's instructions. Then, the purity of the DNA was measured using a spectrophotometer (NanoDrop, California, USA), and the absorbance ratios that ranged from 1.8 to 2.0 at a length of A260/A280 were determined from the samples. Afterward, the extracted DNA was preserved at −80°C (Plymouth, Minnesota, USA).

SNP selection and genotyping

SNPs were selected based on their functional relevance and bioinformatics. The selection criteria were as follows: (1) SNPs in the *TASK-1* gene were selected using the

HaploView software, an open-source project hosted by SourceForge (https://www.broadinstitute.org/haploview/downloads), in which 11 SNPs were collected. Tag SNPs were identified in accordance with the following criteria: a linkage disequilibrium threshold of $r^2 > 0.8$ and a minor allele frequency of ≥0.05. (2) SNP mutations led to amino acid changes according to the single nucleotide polymorphism database (dbSNP) (https://www.ncbi.nlm.nih.gov/snp/). (3) The National Center for Biotechnology Information keyword search was used for research terms *TASK-1* or *KCNK3*, in combination with the following: gene or polymorphism or variants or alleles. Finally, two common SNPs of the *TASK-1* gene were included (rs1275988 and rs2586886). The genotyping was determined using the kompetitive allele specific polymerase chain reaction genotyping system (LGC Science, Shanghai, China). Then, 10% of the samples were randomly selected for type validation and quality control for the accuracy of typing.

Statistical analysis

The statistical analysis was performed using the SPSS 22.0 statistical software (SPSS Inc., Chicago, IL, USA). Quantitative variables are expressed as mean ± standard deviation (for normally distributed data) or median (Q1, Q3) (for non-normally distributed data). The associations between quantitative variables were examined using *t*-test when the data distribution was normal, using Mann-Whitney *U* test for data that are not normally distributed. Deviations from the Hardy-Weinberg equilibrium of the genetic polymorphisms were evaluated using the chi-square test. The comparison of genotypic distribution and allele frequencies between groups was assessed using the R × C contingency table chi-square test. SNPAlyze V8.1.1 (Japan) program was used to compare the frequency distribution of haplotypes between the case and control groups. The odds ratio (OR) of the different genotypes and 95% confidence intervals (CIs) were calculated to represent the relative risk by logistic regression analysis. $P < 0.05$ was considered statistically significant.

Results

The anthropometrical and clinical characteristics of subjects without OSA and severe OSA patients are presented in Table 1. Severe OSA was more prevalent in male subjects (86.0% *vs.* 52.6%, $P < 0.001$). Furthermore, severe OSA subjects comprised of more smokers (53.7% *vs.* 26.9%, $P < 0.001$) and drinkers (51.2% *vs.* 31.6%, $P < 0.001$), when compared to non-OSA subjects. Moreover, severe OSA subjects had a significantly higher BMI (29.40 *vs.* 26.16 kg/m^2, $P < 0.001$), and larger abdominal (110.00 *vs.* 100.00 cm, $P < 0.001$) and neck (44.00 *vs.* 40.00 cm, $P < 0.001$) circumference. Triglyceride (1.96 *vs.* 1.45 mmol/L, $P < 0.001$) and total cholesterol (4.62 *vs.* 4.27 mmol/L, $P = 0.011$) were significantly higher in the severe OSA group, when compared to the non-OSA group, while high density lipoprotein (0.90 *vs.* 1.00 mmol/L, $P < 0.001$) exhibited an opposite trend. There were no significant differences in terms of age, serum potassium, 24-h urine potassium, urine pH value, and systolic and diastolic blood pressure. Apnea index, hypopnea index, AHI, and lowest oxygen saturation were significantly higher in subjects with severe OSA, when compared to non-OSA subjects.

Table 1: Comparison of clinical characteristics of non-OSA and severe OSA groups.

Characteristics	Non-OSA ($n = 171$)	Severe OSA ($n = 164$)	Statistics	*P*
Male, *n* (%)	90 (52.6)	141 (86.0)	43.479*	<0.001
Age (years)	46 (40, 52)	47 (42, 54)	–1.616†	0.106
Smoker, *n* (%)	46 (26.9)	88 (53.7)	24.974*	<0.001
Drinker, *n* (%)	54 (31.6)	84 (51.2)	13.331*	<0.001
Body mass index (kg/m^2)	26.16 (23.98, 27.77)	29.40 (27.14, 31.69)	–9.109†	<0.001
Waist circumference (cm)	100.00 (96.00, 106.00)	110.00 (105.00, 114.75)	–9.659†	<0.001
Neck circumference (cm)	40.00 (37.00, 42.00)	44.00 (42.00, 46.00)	–10.135†	<0.001
Office systolic blood pressure (mmHg)	148.50 (138.75, 160.00)	148.00 (136.25, 160.00)	–1.307†	0.677
Office diastolic blood pressure (mmHg)	90.00 (81.00, 99.00)	90.00 (81.25, 97.75)	–2.049†	0.521
Triglyceride (mmol/L)	1.45 (1.03, 2.01)	1.96 (1.38, 2.83)	–5.280†	<0.001
Total cholesterol (mmol/L)	4.27 (3.73, 4.95)	4.62 (3.98, 5.20)	–2.535†	0.011
High density lipoprotein cholesterol (mmol/L)	1.00 (0.86, 1.17)	0.90 (0.78, 1.01)	–4.367†	<0.001
Low density lipoprotein cholesterol (mmol/L)	2.67 (2.15, 3.18)	2.74 (2.18, 3.29)	–1.109†	0.267
Serum potassium (mmol/L)	3.97 (3.74, 4.27)	3.95 (3.67, 4.21)	–0.908†	0.364
Urine pH value	5.50 (5.50, 6.50)	5.50 (5.50, 6.50)	–0.244†	0.807
24-h urine potassium (mmol/L)	33.92 (27.40, 41.76)	35.82 (27.06, 46.52)	–1.420†	0.156
Apnea hypopnea index (events/h)	1.80 (0.80, 3.20)	51.65 (39.38, 63.40)	–15.825†	<0.001
Apnea index (events/h)	0.20 (0.00, 0.50)	31.75 (20.93, 50.35)	–15.809†	<0.001
Hypopnea index (events/h)	1.40 (0.50, 2.70)	16.65 (10.30, 24.00)	–14.044†	<0.001
Lowest oxyhemoglobin saturation (%)	88.00 (86.00, 89.00)	72.00 (65.00, 76.00)	–15.810†	<0.001
Total sleep time (min)	406.50 (365.00, 449.00)	419.50 (380.00, 455.50)	–1.520†	0.128
Sleep efficiency (%)	67.60 (60.00, 74.90)	70.50 (60.73, 77.25)	–1.634†	0.102

Data are shown as *n* (%) or median (Q1, Q3). *χ^2 values, †*Z* values, OSA: Obstructive sleep apnea.

Table 2: Genotype and allele distributions in patients with severe OSA and non-OSA individuals.

Genotypes and alleles	Non-OSA ($n = 171$)	Severe OSA ($n = 164$)	χ^2	P	FDR q-value
rs1275988					
Genotype					
GG	95 (55.6)	99 (60.7)	2.767	0.251	0.251
GA	57 (33.3)	54 (33.1)			
AA	19 (11.1)	10 (6.1)			
Allele					
G	247 (72.2)	252 (77.3)	2.278	0.131	0.234
A	95 (27.8)	74 (22.7)			
Recessive model					
GG + GA	152 (88.9)	153 (93.9)	2.606	0.106	0.106
AA	19 (11.1)	10 (6.1)			
Dominant model					
AA + GA	76 (44.4)	64 (39.3)	0.920	0.337	0.625
GG	95 (55.6)	99 (60.7)			
rs2586886					
Genotype					
GG	90 (54.9)	87 (57.6)	3.091	0.213	0.251
GA	55 (33.5)	55 (36.4)			
AA	19 (11.6)	9 (6.0)			
Allele					
G	235 (71.6)	229 (75.8)	1.417	0.234	0.234
A	93 (28.4)	73 (24.2)			
Recessive model					
GG + GA	145 (88.4)	142 (94.0)	3.072	0.080	0.106
AA	19 (11.6)	9 (6.0)			
Dominant model					
AA + GA	74 (45.1)	64 (42.4)	0.239	0.625	0.625
GG	90 (54.9)	87 (57.6)			

Data are shown as n (%). SNPs: Single nucleotide polymorphisms; OSA: Obstructive sleep apnea; FDR: False discovery rate.

The genotype distributions for rs1275988 in the total population did not consist of the predicted Hardy-Weinberg equilibrium values, but this was in agreement for both severe OSA and non-OSA patients. Furthermore, rs2586886 was in agreement with the predicted Hardy-Weinberg equilibrium values (data not shown). As presented in Table 2, the distribution of the two selected SNP (rs1275988 and rs2586886) genotypes, alleles, recessive model, and dominant model had no significant differences between the severe and non-OSA group.

Since the *KCNK3* gene locus is linked to obesity,[15] which is an independent predictor for OSA,[16] subjects were subdivided into obese (BMI ≥28 kg/m^2) and non-obese (BMI <28 kg/m^2) groups [Table 3]. For the obese population, in the rs1275988 loci, the genotype distribution (GG 57.5% *vs.* 41.0%, GA 35.8% *vs.* 35.9%, AA 6.6% *vs.* 23.1%, $P = 0.014$), allele frequency (G 75.5% *vs.* 59.0%, A 24.5% *vs.* 41.0%, $P = 0.006$), and implicit model (GG + GA 93.4% *vs.* 76.9%, AA 6.6% *vs.* 23.1%, $P = 0.005$) exhibited significant differences between the severe OSA and non-OSA group, while the dominant model exhibited no significant differences between the severe and non-OSA groups. Furthermore, the rs2586886 loci genotype distributions (GG 56.1% *vs.* 41.0%, GA 36.7% *vs.* 35.9%, AA 7.1% *vs.* 23.1%, $P = 0.026$), allele frequencies (G 74.5% *vs.* 59.0%, A 25.5% *vs.* 41.0%, $P = 0.011$), and implicit model (GG + GA 92.9% *vs.* 76.9%, AA 7.1% *vs.* 23.1%, $P = 0.009$) were significantly different between the severe and non-OSA group, while the dominant model exhibited no significant differences between the two groups. Moreover, significantly fewer patients with OSA possessed the AA genotype, while significantly more patients possessed the GG genotype, when compared to controls. For non-obese subjects, the SNP (rs1275988 and rs2586886) genotype distributions, allele frequencies, implicit model, and dominant model exhibited no significant differences between the severe and non-OSA group.

In order to further confirm the link between these two selected SNPs (rs1275988 and rs2586886) and OSA in obese patients, simple logistic regression modeling was employed, and the genotype together with the two SNPs were used as the input. As shown in Table 4, it can be identified that the GG genotype is a risk factor for obese OSA in both SNPs (OR = 4.902, 95% CI 1.582–15.186 and OR = 4.420, 95% CI 1.422–13.734, respectively). The G allele in the rs1275988 loci was a risk factor of OSA (GG>GA>AA), as well as for the rs2586886 loci. In multivariate logistic regression analysis, which was used to correct the confounding factors of rs1275988, rs2586886, sex, smoking, drinking, total cholesterol, and BMI in total. The interaction between rs1275988 locus of *TASK-1* gene and BMI entered the equation. In addition, gender and total cholesterol were risk factors for severe OSA, in

Table 3: Genotype and allele distributions in patients with severe OSA and non-OSA individuals.

Genotypes and alleles	BMI ≥28 kg/m^2				BMI <28 kg/m^2			
	Non-OSA	Severe OSA	χ^2	*P*	Non-OSA	Severe OSA	χ^2	*P*
rs1275988								
Genotype								
GG	16 (41.0)	61 (57.5)	8.477	0.014	79 (59.8)	38 (66.7)	0.867	0.648
GA	14 (35.9)	38 (35.8)			43 (32.6)	16 (28.1)		
AA	9 (23.1)	7 (6.6)			10 (7.6)	3 (5.3)		
Allele								
G	46 (59.0)	160 (75.5)	7.542	0.006	201 (76.1)	92 (80.7)	0.952	0.329
A	32 (41.0)	52 (24.5)			63 (23.9)	22 (19.3)		
Recessive model								
GG + GA	30 (76.9)	99 (93.4)	7.881	0.005	122 (92.4)	54 (94.7)	0.332	0.564
AA	9 (23.1)	7 (6.6)			10 (7.6)	3 (5.3)		
Dominant model								
AA + GA	23 (59.0)	45 (42.5)	3.125	0.077	53 (40.2)	19 (33.3)	0.785	0.376
GG	16 (41.0)	61 (57.5)			79 (59.8)	38 (66.7)		
rs2586886								
Genotype								
GG	16 (41.0)	55 (56.1)	7.297	0.026	90 (54.9)	87 (57.6)	1.097	0.578
GA	14 (35.9)	36 (36.7)			55 (33.5)	55 (36.4)		
AA	9 (23.1)	7 (7.1)			19 (11.6)	9 (6.0)		
Allele								
G	46 (59.0)	146 (74.5)	6.405	0.011	235 (71.6)	229 (75.8)	1.417	0.234
A	32 (41.0)	50 (25.5)			93 (28.4)	73 (24.2)		
Recessive model								
GG + GA	30 (76.9)	91 (92.9)	6.867	0.009	145 (88.4)	142 (94.0)	3.072	0.080
AA	9 (23.1)	7 (7.1)			19 (11.6)	9 (6.0)		
Dominant model								
GA + AA	23 (59.0)	43 (43.9)	2.547	0.111	74 (45.1)	64 (42.4)	0.239	0.625
GG	16 (41.0)	55 (56.1)			90 (54.9)	87 (57.6)		

Data are shown as *n* (%). BMI: Body mass index; OSA: Obstructive sleep apnea.

Table 4: The logistic regression analysis for the genotypes related risk factors with obstructive sleep apnea.

Genotypes	OR	95% CI	*P*
BMI ≥ 28 kg/m^2			
rs1275988			
AA	1.0	–	0.022
GA	3.490	1.091–11.159	0.035
GG	4.902	1.582–15.186	0.006
rs2586886			
AA	1.0	–	0.036
GA	3.306	1.013–10.597	0.044
GG	4.420	1.422–13.734	0.010
BMI < 28 kg/m^2			
rs1275988			
AA	1.0	–	0.650
GA	1.240	0.302–5.091	0.765
GG	1.603	0.417–6.166	0.492
rs2586886			
AA	1.0	–	0.592
GA	2.317	0.462–11.623	0.307
GG	2.162	0.448–10.432	0.337

BMI: Body mass index; OR: Odds ratio; CI: Confidence interval; –: Blank.

Table 5. The combination of GA and GG genotypes of rs1275988 with BMI ≥28 kg/m^2 increased the risk of severe OSA (OR = 4.180, 95% CI 1.988–8.788, $P < 0.001$; OR = 8.916, 95% CI 4.506–17.645, $P < 0.001$, respectively).

Discussion

There is growing evidence that genetic factors and their interaction with environmental exposures influence the development of OSA. In the present study, it was hypothesized that variability in the gene regulating *TASK-1* channel might be involved in OSA. Hence, two SNPs (rs1275988 and rs2586886) were genotyped in severe and non-OSA subjects, and the association between the polymorphism of the *TASK-1* gene and OSA was assessed.

The importance of the *TASK* background potassium channels in central and peripheral respiratory chemoreception has been widely expressed in a variety of putative respiratory neurons in the brainstem,[6,15,16] and has been demonstrated in previous studies.[17,18] The *TASK-1* channel is sensitive to hypoxia and changes in extracellular pH, even in the physiological range, and plays an

Table 5: The logistic regression analysis for the genotypes related risk factors with obstructive sleep apnea.

Factors	β	SE	Wald χ^2	OR	95% CI	*P*
Sex	1.736	0.322	29.032	5.675	3.018–10.671	<0.001
Total cholesterol	0.679	0.325	4.357	1.972	1.042–3.731	<0.001
BMI ≥28 kg/m^2*rs1275988 AA genotype	–	–	45.674	1.0	–	<0.001
BMI ≥28 kg/m^2*rs1275988 GA genotype	1.430	0.379	14.228	4.180	1.988–8.788	<0.001
BMI ≥28 kg/m^2*rs1275988 GG genotype	2.188	0.348	39.468	8.916	4.506–17.645	<0.001
Constant	−2.197	0.321	46.768	0.111	–	<0.001

*Interaction model. OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; –: Blank.

important role in respiratory regulation. Intermittent hypoxia combined with hypercapnia in animal models of central sleep apnea is positively correlated with the expression of *TASK-1* and *TASK-3* in the brainstem.[19] In addition, respiratory chemoreception in the central nervous system maintains physiologically appropriate pH and PCO_2 *via* the control of breathing, and studies on animal models have revealed that *TASK* channel knock-out mice are profoundly pH-sensitive and capable of driving respiratory output in response to local pH changes *in vivo*.[20] Indeed, it has been evidenced in *TASK-1* knock-out mice models that *TASK-1* channels significantly contribute to the increase in carotid body chemoafferent discharge in response to a decrease in arterial PO_2 or an increase in P $(CO_2)/[H^+]$,[5] and this was also found to be functionally expressed in isolated carotid body cells.[21]

In fact, OSA induces markedly negative intra-thoracic pressure, and also provokes hypoxia, hypercapnia, and acidity,[12] which is similar to the *TASK-1* gene, in terms of physiological characteristics. In the total population, the distribution of genotypes, alleles, recessive model, and dominant model of the two selected SNPs exhibited no significant differences between the severe and non-OSA group. However, it was found that the distribution of GG genotypes and G allele frequencies in the two SNP locus cases was higher, when compared to the control group. In the rs1275988 loci, G allele frequencies in controls and cases were 72.7% and 77.3%, respectively, while the prevalence of the GG homozygote were 55.6% and 60.7%, respectively. In the rs2586886 loci, G allele frequencies in controls and cases were 71.6% and 75.8%, respectively, while the prevalence of the GG homozygote were 54.9% and 57.6%, respectively. In the present study, there was no significant difference between *TASK-1* gene polymorphism and OSA in the severe OSA and non-OSA groups. Considering that the *TASK-1* gene polymorphism is a polygenic disease with OSA, the *TASK-1* gene polymorphism only had a slight effect on OSA, while gender, age, and obesity were independent and powerful risk factors of OSA.

The present study revealed that the GG genotype is highly prevalent in obese OSA patients, and that obesity may be a strong interaction factor. In addition, a further simple logistic regression analysis demonstrated that the GG genotype is an independent risk factor for OSA in both SNPs. The *KCNK3* gene locus has been linked to obesity,[10,22] can serve as molecular markers secondary to *UCP1* for assessing the number of thermogenic adipocytes within human adipose tissues,[12,23] and is involved in lipid metabolism. Therefore, it is reasonable to consider that the results of the present study are consistent with the hypothesis of the investigators, in which the genetic polymorphisms of *TASK-1* are involved in OSA, and are characterized as a risk factor of the rs1275988 and rs2586886 GG genotype. The simple logistic regression analysis was able to further prove that the GG genotype was a risk factor for OSA. Furthermore, the incidence of OSA significantly increased as general and abdominal obesity increased. Thus, obesity is an independent risk factor for OSA.[16,24] In the present baseline data, BMI was significantly higher in the severe OSA group, when compared to the non-OSA group [Table 1]. However, differences were not observed in the results between two groups when obesity was not considered [Table 2]. For the obese population, the distribution of SNP (rs1275988 and rs2586886) genotype distributions, allele frequencies and implicit model had significant differences between the severe and non-OSA groups [Table 3].

The limitations of the present study included the following: First, since the *TASK-1* gene is a minor gene, extreme (severe OSA subjects) cases were chosen to amplify the effect of the genes. Hence, this needs to be further validated in mild and moderate OSA populations. Second, due to the lack of artery blood gas analysis during sleep, the degree of hypoxemia and hypercapnia could not be assessed. The pH of arterial blood is influenced by many factors. Although this may be corrected during the day, this cannot reflect the degree of nocturnal hypoxia and hypercapnia. Third, in the present study, a candidate gene strategy was used to investigate the association between the disease and gene polymorphism, in which other SNPs of the *TASK-1* gene polymorphism associated with severe OSA may have been omitted.

In conclusion, both the GG genotype of rs1275988 and GG genotype of rs2586886 in the *TASK-1* gene may play as potential risk factors in obese patients with OSA. The mechanism responsible for the correlation between rs1275988 and rs2596996 with OSA remains unknown. Thus, the exact mechanism and contribution of the *TASK-1* GG genotype in OSA need further studies.

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Conflicts of interest

None.

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