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ORIGINAL ARTICLE

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Association study of genetic variations of inflammatory biomarkers with susceptibility and severity of obstructive sleep apnea

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Abstract

Background: Obstructive sleep apnea (OSA) increases health risks of cardiovascular disease and stroke. Both genetic factors and environmental exposures contribute to the occurrence of OSA. The purpose of this study was to determine the role of four functional inflammatory single nucleotide polymorphisms (SNPs) (*VWF* rs1063856, *IL-6* rs1800796, *TNF* rs1800629, and *CRP* rs2794521) in the susceptibility and severity of OSA.

Methods: A case–control study of OSA among Chinese population was conducted. Genotyping was performed using ABI TaqMan SNP genotyping technique.

Results: We found *VWF* rs1063856 (OR = 1.50, 95% CIs = 1.10–2.04; $p = 0.010$), *IL-6* rs1800796 (OR = 1.32, 95% CIs = 1.11–1.56; $p = 0.002$), *TNF* rs1800629 (OR = 1.44, 95% CIs = 1.13–1.83; $p = 0.003$), and *CRP* rs2794521 (OR = 1.27, 95% CIs = 1.04–1.55; $p = 0.021$) were all significantly associated with increased susceptibility of OSA, while *VWF* rs1063856 (OR = 1.75, 95% CIs = 1.18–2.62; $p = 0.006$), *IL-6* rs1800796 (OR = 1.39, 95% CIs = 1.10–1.76; $p = 0.006$) were associated with the severity of OSA.

Conclusions: Our study indicated that functional variants of inflammatory biomarkers could cause the occurrence of OSA and influence the severity of OSA. These findings further support that inflammatory cytokines were closely related to the occurrence and development of OSA.

KEYWORDS
genetic, *IL-6*, inflammatory biomarkers, obstructive sleep apnea, *VWF*

1 | INTRODUCTION

Obstructive sleep apnea (OSA), characterized by repetitive episodes of shallow or paused breathing during sleep despite the effort to breathe, is a highly prevalent sleep disorder which increases health risks such as cardiovascular disease, stroke, aortic disease, metabolic syndrome, diabetes, and depression (Jehan et al., 2018; Mohammad et al., 2019; Peres et al., 2019; Smith & Amin, 2019; Takagi & Umemoto, 2016; Wanderer & Rathmell, 2019; Wang et al., 2019). It

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was estimated that 13 million people in China suffered from OSA (Young, 2004). OSA with excessive daytime sleepiness (EDS) occurred in 6% (range, 3%–18%) of men and in 4% (range, 1%–17%) of women (Franklin & Lindberg, 2015). EDS can have a serious impact on an individual's health, safety, and quality of life (Young, 2004).

OSA is a complex disease that is affected by multiple factors, including genetic factors and environmental exposures (Sun, Hu, Tu, Zhong, & Xu, 2015). Previous studies have identified higher levels of inflammatory biomarkers contributed to poor sleep, although some results were inconsistent (Canto Gde et al., 2015; Hirsch, Evans, Wong, Machaalani, & Waters, 2018; Nowakowski, Matthews, von Kanel, Hall, & Thurston, 2018; Sun et al., 2015). Among them, *interleukin-6* (*IL-6*, OMIM: 147620), *tumor necrosis factor* (*TNF*, OMIM: 191160), *C Reactive Protein* (*CRP*, OMIM: 123260), and *von Willebrand factor* (*VWF*, OMIM: 613160) antigen were the most frequently assessed inflammatory biomarkers (Canto Gde et al., 2015; Hirsch et al., 2018; Nowakowski et al., 2018; Sun et al., 2015). These findings underscore the important role of inflammatory profile for sleep problems and overall health. Meanwhile, epidemiological studies to date have identified strong associations between genetic variants of some candidate genes and susceptibility of OSA, although further research is needed (Sun et al., 2015).

In current study, we hypothesized that *VWF* Thr789Ala (rs1063856), *IL-6* −572G/C (rs1800796), *TNF* −308G/A (rs1800629), and *CRP* −717A > G (rs2794521) would be associated with elevated serum levels of corresponding inflammatory biomarkers, then caused the occurrence of OSA and influenced the severity of OSA. We hope these stable genetic biomarkers could explain the variability in the relationship between susceptibility of OSA and levels of these inflammatory biomarkers.

2 | PATIENTS AND METHODS

2.1 | Ethical compliance

This study was approved by the Institutional Review Board for Zhoupu hospital, and written informed consent was obtained from all participants.

2.2 | Study population

Consecutive patients with suspected OSA who were undergoing polysomnography (PSG) test in Affiliated Zhoupu Hospital of Shanghai University of medicine and health science were invited to participate in this study. All the subjects underwent an overnight laboratory-based PSG, and measured the apnea–hypopnea index (AHI). OSA was defined as an AHI > 5 events/hr, and daytime symptoms specific for an OSA syndrome. For the severity of OSAs, patients were grouped according to the following classification by American Academy of Sleep Medicine (AASM 2007): mild group (AHI: 5–15 events/hr), moderate group (AHI: 15–30 events/hr), and severe group (AHI > 30 events/hr). AHI < 5 events/hr was diagnosed as healthy subjects. A total of 750 patients with OSA and 800 healthy controls matched for age, gender, and ethnicity were included in this study. Within 20 min of awakening, 5 ml of peripheral blood was drawn from each patient in EDTA-containing tubes and stored at −80°C.

2.3 | DNA extraction and genotyping

Genomic DNA was extracted from the whole blood by DNA isolation kit (Tiangen, Beijing, China), according to the manufacturer's protocol. The purity and concentration of DNA were measured by a nanodrop spectrophotometer (Thermo Scientific, Waltham, MA, USA), with absorbance rations from 1.8 to 2.0 at the length of A260/A280. Genotyping of *VWF* rs1063856, *IL-6* rs1800796, *TNF* rs1800629, and *CRP* rs2794521 were determined using TaqMan single nucleotide polymorphism (SNP) genotyping technique on an ABI PRISM® 7900HT Fast Real–Time PCR System (Applied Biosystems). Ten percent of the DNA samples were selected randomly for further validation, with a consistency of 100%.

2.4 | Statistical analysis

All data analyses were performed with SPSS (version 22.0) statistical software (Chicago, IL). Statistical significance was accepted at a level of $p < 0.05$. Deviation from the Hardy–Weinberg equilibrium was assessed using a chi-squared test with one degree of freedom. Statistical significance for categorical variables was assessed by the chi-squared or Fisher's exact test. The OSA risk and severity associated with the candidate SNPs were estimated by computing the odds ratios (ORs) and their 95% confidence intervals (CIs) by logistic regression analysis, adjusting for age, gender, and BMI. The analyses were done first per allele (allelic model) and then per genotype (additive model).

3 | RESULTS

3.1 | Demographic, clinical, and anthropometric profiles

As shown in Table 1, the main demographic and clinical characteristics of the 750 OSA cases and 800 healthy controls were presented. There were no significant differences

TABLE 1 Distributions of selected variables in OSA cases and healthy controls

	Cases ($n = 750$)	Controls ($n = 800$)	p value
Age			
<50	361 (48.1%)	384 (48.0%)	0.958
≥50	389 (51.9%)	416 (52.0%)	
Gender			
Male	629 (83.9%)	655 (81.9%)	0.299
Female	121 (16.1%)	145 (18.1%)	
BMI (kg/m^2)			
<25	89 (11.9%)	367 (45.9%)	<0.001
≥25	661 (88.1%)	433 (54.1%)	
Severity of OSA			
Mild	194 (25.9%)		
Moderate	200 (26.6%)		
Severe	356 (47.5%)		

between the OSA cases and control groups in age and gender ($p > 0.05$), which indicated the successful matching. The OSA cases had significantly larger percentages of high BMI than controls ($p < 0.001$), which means high BMI was a risk factor for development of OSA. Patients with OSA were divided into 194 (25.9%) mild patients, 200 (26.6%) moderate patients, and 356 (47.5%) severe patients according to their AHI value.

3.2 | Associations of candidate SNPs with susceptibility of OSA

As shown in Table 2, all four functional inflammatory SNPs (*VWF* rs1063856, *IL-6* rs1800796, *TNF* rs1800629, and *CRP* rs2794521) were genotyped, and the genotypic distribution of the four functional SNPs in the healthy controls met the Hardy–Weinberg equilibrium ($p > 0.05$). We found the minor alleles of *VWF* rs1063856 (OR = 1.50, 95% CIs = 1.10–2.04; $p = 0.010$), *IL-6* rs1800796 (OR = 1.32, 95% CIs = 1.11–1.56; $p = 0.002$), *TNF* rs1800629 (OR = 1.44, 95% CIs = 1.13–1.83; $p = 0.003$), and *CRP* rs2794521 (OR = 1.27, 95% CIs = 1.04–1.55; $p = 0.021$) were all significantly associated with increased susceptibility of OSA, compared with their major alleles. The associations kept robust even after Bonferroni adjustment for *VWF* rs1063856, IL-6 rs1800796, and *TNF* rs1800629.

3.3 | Associations of candidate SNPs with severity of OSA

All four inflammatory SNPs were observed in the different severity of OSA patients groups, and the severe OSA cases were compared with the mild and moderate OSA (Table 3). Among them, minor alleles of *VWF* rs1063856 (OR = 1.75, 95% CIs = 1.18–2.62; $p = 0.006$), IL-6 rs1800796 (OR = 1.39, 95% CIs = 1.10–1.76; $p = 0.006$) were associated with the severity of OSA.

TABLE 2 Associations of candidate SNPs with susceptibility of OSA

Genotype	Cases	Controls	Adjusted OR (95% CI)[a]	p Value
VWF rs1063856				
AA	650	720	1.00 (reference)	
AG	89	76	1.35 (0.95–1.92)	0.098
GG	11	4	3.17 (1.08–9.32)	0.036
G versus A			1.5 (1.1–2.04)	0.010
IL-6 rs1800796				
GG	327	409	1.00 (reference)	
CG	351	334	1.37 (1.09–1.72)	0.007
CC	72	57	1.64 (1.11–2.42)	0.012
C versus G			1.32 (1.11–1.56)	0.002
TNF rs1800629				
GG	576	656	1.00 (reference)	
AG	153	132	1.37 (1.04–1.82)	0.027
AA	21	12	2.07 (1.02–4.22)	0.044
A versus G			1.44 (1.13–1.83)	0.003
CRP rs2794521				
AA	471	541	1.00 (reference)	
AG	237	226	1.25 (0.97–1.61)	0.082
GG	42	33	1.52 (0.93–2.49)	0.097
G versus A			1.27 (1.04–1.55)	0.021

[a]Adjusted for age, gender, and BMI.

4 | DISCUSSION

The current study explored associations between four functional inflammatory SNPs (*VWF* rs1063856, IL-6 rs1800796, *TNF* rs1800629, and *CRP* rs2794521) with the susceptibility, as well as severity of OSA in a large case–control study in Chinese population. We found all four functional SNPs were significantly associated with increased susceptibility of OSA, and minor alleles of *VWF* rs1063856 and *IL-6* rs1800796 were associated with the increased severity of OSA. These findings further confirmed the crucial role of inflammatory biomarkers in the occurrence and development of sleep disorder.

Meta-analyses revealed that inflammatory cytokines were closely related to the occurrence and development of OSA (Li

TABLE 3 Associations of candidate SNPs with severity of OSA

Genotype	Severe	Mild and moderate	Adjusted OR (95% CI)[a]	*p* Value
VWF rs1063856				
AA	298	352	1.00 (reference)	
AG	50	39	1.57 (0.99–2.5)	0.055
GG	8	3	3.28 (0.94–11.44)	0.063
G versus A			1.75 (1.18–2.62)	0.006
IL-6 rs1800796				
GG	138	189	1.00 (reference)	
CG	177	174	1.45 (1.05–2)	0.024
CC	41	31	1.88 (1.12–3.17)	0.017
C versus G			1.39 (1.1–1.76)	0.006
TNFTNF rs1800629				
GG	275	301	1.00 (reference)	
AG	72	81	1.01 (0.87–1.17)	0.874
AA	9	12	0.85 (0.44–1.67)	0.644
A versus G			0.98 (0.88–1.08)	0.680
CRP rs2794521				
AA	220	251	1.00 (reference)	
AG	115	122	1.12 (0.71–1.77)	0.632
GG	21	21	1.19 (0.54–2.59)	0.668
G versus A			1.12 (0.78–1.61)	0.540

[a]Adjusted for age, gender, and BMI

& Zheng, 2017; Nadeem et al., 2013). Among them, *VWF*, which encodes a glycoprotein involved in hemostasis, could cause lower sleep efficiency ($b/SE = 0.02/0.08$), $p = 0.002$) (Nowakowski et al., 2018). Measures of sleep fragmentation were also related to *VWF* (von Kanel et al., 2007). *VWF* rs1063856 was first associated with higher *VWF* levels and myocardial infarction risk in patients with Type I diabetes (Lacquemant et al., 2000). Then, it was found to influence plasma levels of FVIII and modify *VWF* biosynthesis and clearance (Mufti et al., 2018; Smith et al., 2010). Fernandez-Cadenas et al. (2012) found *VWF* rs1063856 was associated with fibrinolytic early recanalization in patients with ischemic stroke. However, none of the studies have evaluated the association of *VWF* rs1063856 with OSA. In the current study, we first identified *VWF* rs1063856 was not only associated with the susceptibility, but also with the severity of OSA.

IL-6 was the most focused inflammatory biomarker for OSA (Chu & Li, 2013; Kaditis et al., 2014; Kurt, Tosun, & Talay, 2013; Lopez-Pascual et al., 2017; Popko et al., 2008; Shalitin, Deutsch, & Tauman, 2018; Wu et al., 2016; Zhong, Xiong, Shi, & Xu, 2016). *IL-6* rs1800796, a function variant located in the promoter region of *IL-6*, has been evaluated for its association with many kinds of diseases, including cancers, celiac disease, chronic HBV infection, acute coronary syndrome, ischemic stroke, periodontitis, IgA nephropathy, hip fracture, osteoarthritis, acute chorioamnionitis, etc., (Akinyemi et al., 2017; Amr, El-Awady, & Raslan, 2016; Barartabar et al., 2018; Du, Gao, Zhang, & Wang, 2015; Eftekhari et al., 2018; Fernandes et al., 2015; Fragoso et al., 2010; Kaditis et al., 2014; Konwar, Del Gobbo, Terry, & Robinson, 2019; Li et al., 2018; Ponce de Leon-Suarez et al., 2018; Tang et al., 2013; Wang, Chen, Zhao, Zhang, & Yu, 2014; Wang et al., 2016; Zhang et al., 2017; Zhang, Mao, & Sun, 2015; Zhao, Li, & Li, 2019). Although two previous studies evaluated the associations of *IL-6* rs1800796 with the development of OSA, the results were not significant, which may be caused by the relatively small sample size (Kaditis et al., 2014; Zhang et al., 2009). In our study, we have enough power to identified *VWF* rs1063856 was significantly associated with both the susceptibility and severity of OSA.

TNF was significantly higher in OSA patients, and more pronounced with the more severe grades of OSA (Li & Zheng, 2017). A meta-analysis revealed that *TNF* rs1800629 was significantly associated with OSA under an allele frequency model (three studies, odds ratio [OR] = 1.82, 95% confidence interval [CI] 1.26–2.61). This result was consistent with our findings, although we did not find significant association between *TNF* rs1800629 and the severity of OSA. *CRP* was a crucial inflammatory component of OSA pathophysiology, and meta-analysis showed that serum *CRP*/hs-*CRP* levels were discovered to be higher in OSA patients compared with control subjects (Li, Wei, Qin, & Wei, 2017). *CRP* rs2794521 has been found to be associated with stroke, coronary heart disease, and preeclampsia (Kotlega et al., 2014; Wang et al., 2009; Wu, Huang, Huang, & Fan, 2017). However, it was not evaluated for OSA. Our results represent the first report of *CRP* rs2794521 in OSA occurrence.

5 | CONCLUSIONS

In conclusion, we deduced that *VWF* rs1063856, *IL-6* rs1800796, *TNF* rs1800629, and *CRP* rs2794521 contribute to develop OSA in a Chinese population, while *VWF* rs1063856 and *IL-6* rs1800796 were associated with the increased severity of OSA. Our study, together with previous studies, would benefit the construction of early warning model, early prevention, and screening of OSA. Our results also provided a new therapeutic target for treatment of OSA. These findings further support that inflammatory cytokines were closely related to the occurrence and development of OSA.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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