

ORIGINAL ARTICLE

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

Zeming Zhang¹ | Qiubo Wang¹ | Baoyuan Chen² | Yancun Wang³  | Yafang Miao¹ | Li Han¹

¹Department of Respiratory Medicine, Shanghai University of medicine & health Sciences Affiliated Zhoupu hospital, Shanghai, China

²Department of Respiratory Medicine, Tianjin Medical University General Hospital, Tianjin, China

³Department of Neurology Medicine, Shanghai University of medicine & health Sciences Affiliated Zhoupu hospital, Shanghai, China

Correspondence

Yancun Wang, Department of Neurology Medicine, Shanghai University of medicine & health Sciences Affiliated Zhoupu hospital, No.1500, Zhouyuan Road, Shanghai 201318, China.
Email: wang_yancun@sina.com

Funding information

National Natural Science Foundation of China, Grant/Award Number: 81170071

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

Zeming Zhang and Qiubo Wang contribute equally to this manuscript.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2019 The Authors. *Molecular Genetics & Genomic Medicine* published by Wiley Periodicals, Inc.

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 ratios 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 (<i>n</i> = 750)	Controls (<i>n</i> = 800)	<i>p</i> 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

TABLE 2 Associations of candidate SNPs with susceptibility of OSA

Genotype	Cases	Controls	Adjusted OR (95% CI) ^a	<i>p</i> Value
<i>VWF</i>				
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
<i>IL-6</i> 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
<i>TNF</i>				
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
<i>CRP</i>				
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

^aAdjusted for age, gender, and BMI.

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.

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	<i>p</i> Value
<i>VWF</i> 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
<i>IL-6</i> 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
<i>TNFTNF</i> 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
<i>CRP</i> 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

^aAdjusted 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.

ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (81170071) and Key Discipline Fund of Health System in Shanghai Pudong district of China

(PWZxk2017-22). We would also like to thank all the teachers from General Hospital of Tianjin Medical University for their help in this project.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ORCID

Yancun Wang  <https://orcid.org/0000-0002-6532-6402>

REFERENCES

- Akinyemi, R., Arnett, D. K., Tiwari, H. K., Ovbiagele, B., Sarfo, F., Srinivasasainagendra, V., ... Owolabi, M. (2017). Interleukin-6 (IL-6) rs1800796 and cyclin dependent kinase inhibitor (CDKN2A/CDKN2B) rs2383207 are associated with ischemic stroke in indigenous West African Men. *Journal of the Neurological Sciences*, 379, 229–235. <https://doi.org/10.1016/j.jns.2017.05.046>
- Amr, K., El-Awady, R., & Raslan, H. (2016). Assessment of the -174G/C (rs1800795) and -572G/C (rs1800796) interleukin 6 gene polymorphisms in Egyptian patients with rheumatoid arthritis. *Open Access Macedonian Journal of Medical Sciences*, 4(4), 574–577. <https://doi.org/10.3889/oamjms.2016.110>
- Barartabar, Z., Nikzamir, A., Sirati-Sabet, M., Aghamohammadi, E., Chaleshi, V., Rostami Nejad, M., ... Reza Zali, M. (2018). The relationship between 174 G/C and -572 G/C of IL-6 gene polymorphisms and susceptibility of celiac disease in the Iranian population. *Gastroenterology Review*, 13(4), 293–298. <https://doi.org/10.5114/pg.2018.79808>
- Canto Gde, L., Pacheco-Pereira, C., Aydinov, S., Major, P. W., Flores-Mir, C., & Gozal, D. (2015). Biomarkers associated with obstructive sleep apnea: A scoping review. *Sleep Medicine Reviews*, 23, 28–45. <https://doi.org/10.1016/j.smrv.2014.11.004>
- Chu, L., & Li, Q. (2013). The evaluation of adenotonsillectomy on TNF-alpha and IL-6 levels in obese children with obstructive sleep apnea. *International Journal of Pediatric Otorhinolaryngology*, 77(5), 690–694. <https://doi.org/10.1016/j.ijporl.2013.01.019>
- Du, Y., Gao, L., Zhang, K., & Wang, J. (2015). Association of the IL6 polymorphism rs1800796 with cancer risk: A meta-analysis. *Genetics and Molecular Research*, 14(4), 13236–13246. <https://doi.org/10.4238/2015.October.26.20>
- Eftekhari, H., Hosseini, S. R., Pourreza Baboli, H., Mafi Golchin, M., Heidari, L., Abedian, Z., ... Akhavan-Niaki, H. (2018). Association of interleukin-6 (rs1800796) but not transforming growth factor beta 1 (rs1800469) with serum calcium levels in osteoporotic patients. *Gene*, <https://doi.org/10.1016/j.gene.2018.05.118>
- Fernandes, M. T., Fernandes, K. B., Marquez, A. S., Colus, I. M., Souza, M. F., Santos, J. P., & Poli-Frederico, R. C. (2015). Association of interleukin-6 gene polymorphism (rs1800796) with severity and functional status of osteoarthritis in elderly individuals. *Cytokine*, 75(2), 316–320. <https://doi.org/10.1016/j.cyto.2015.07.020>
- Fernandez-Cadenas, I., Del Rio-Espinola, A., Giralt, D., Domingues-Montanari, S., Quiroga, A., Mendioroz, M., ... Montaner, J. (2012). IL1B and VWF variants are associated with fibrinolytic early recanalization in patients with ischemic stroke. *Stroke*, 43(10), 2659–2665. <https://doi.org/10.1161/STROKEAHA.112.657007>
- Fragoso, J. M., Delgadillo, H., Juarez-Cedillo, T., Rodriguez-Perez, J. M., Vallejo, M., Perez-Mendez, O., ... Vargas-Alarcon, G. (2010). The interleukin 6–572 G>C (rs1800796) polymorphism is associated with the risk of developing acute coronary syndrome. *Genetic Testing and Molecular Biomarkers*, 14(6), 759–763. <https://doi.org/10.1089/gtmb.2010.0001>
- Franklin, K. A., & Lindberg, E. (2015). Obstructive sleep apnea is a common disorder in the population—a review on the epidemiology of sleep apnea. *Journal of Thoracic Disease*, 7(8), 1311–1322. <https://doi.org/10.3978/j.issn.2072-1439.2015.06.11>
- Hirsch, D., Evans, C. A., Wong, M., Machaalani, R., & Waters, K. A. (2018). Biochemical markers of cardiac dysfunction in children with obstructive sleep apnoea (OSA). *Sleep and Breathing*, 23(1), 95–101. <https://doi.org/10.1007/s11325-018-1666-y>
- Jehan, S., Myers, A. K., Zizi, F., Pandi-Perumal, S. R., Jean-Louis, G., & McFarlane, S. I. (2018). Obesity, obstructive sleep apnea and type 2 diabetes mellitus: Epidemiology and pathophysiological insights. *Sleep Medicine and Disorders*, 2(3), 52–58.
- Kaditis, A. G., Gozal, D., Khalyfa, A., Kheirandish-Gozal, L., Capdevila, O. S., Gourgoulianis, K., ... Zintzaras, E. (2014). Variants in C-reactive protein and IL-6 genes and susceptibility to obstructive sleep apnea in children: A candidate-gene association study in European American and Southeast European populations. *Sleep Medicine*, 15(2), 228–235. <https://doi.org/10.1016/j.sleep.2013.08.795>
- Konwar, C., Del Gobbo, G. F., Terry, J., & Robinson, W. P. (2019). Association of a placental Interleukin-6 genetic variant (rs1800796) with DNA methylation, gene expression and risk of acute chorioamnionitis. *BMC Medical Genetics*, 20(1), 36. <https://doi.org/10.1186/s12881-019-0768-0>
- Kotlega, D., Bialecka, M., Kurzawski, M., Drozdziak, M., Cieciewicz, S., Golab-Janowska, M., & Nowacki, P. (2014). Risk factors of stroke and -717A>G (rs2794521) CRP gene polymorphism among stroke patients in West Pomerania province of Poland. *Neurologia I Neurochirurgia Polska*, 48(1), 30–34. <https://doi.org/10.1016/j.pjnns.2013.12.001>
- Kurt, O. K., Tosun, M., & Talay, F. (2013). Serum cardiotrophin-1 and IL-6 levels in patients with obstructive sleep apnea syndrome. *Inflammation*, 36(6), 1344–1347. <https://doi.org/10.1007/s10753-013-9673-4>
- Lacquemant, C., Gaucher, C., Delorme, C., Chatellier, G., Gallois, Y., Rodier, M., ... DESIR Study Group. (2000). Association between high von willebrand factor levels and the Thr789Ala vWF gene polymorphism but not with nephropathy in type I diabetes. The GENEDIAB Study Group and the DESIR Study Group. *Kidney International*, 57(4), 1437–1443. <https://doi.org/10.1046/j.1523-1755.2000.00988.x>
- Li, K., Wei, P., Qin, Y., & Wei, Y. (2017). Is C-reactive protein a marker of obstructive sleep apnea?: A meta-analysis. *Medicine (Baltimore)*, 96(19), e6850. <https://doi.org/10.1097/MD.0000000000006850>
- Li, Q., & Zheng, X. (2017). Tumor necrosis factor alpha is a promising circulating biomarker for the development of obstructive sleep apnea syndrome: A meta-analysis. *Oncotarget*, 8(16), 27616–27626. <https://doi.org/10.18632/oncotarget.15203>
- Li, Y., Tang, H., Qi, H., Shen, C., Sun, L., Li, J., ... Shen, A. (2018). rs1800796 of the IL6 gene is associated with increased risk for anti-tuberculosis drug-induced hepatotoxicity in Chinese Han children. *Tuberculosis (Edinb)*, 111, 71–77. <https://doi.org/10.1016/j.tube.2018.05.011>

- Lopez-Pascual, A., Lasa, A., Portillo, M. P., Aros, F., Mansego, M. L., Gonzalez-Muniesa, P., & Martinez, J. A. (2017). Low oxygen consumption is related to a hypomethylation and an increased secretion of IL-6 in obese subjects with sleep apnea-hypopnea syndrome. *Annals of Nutrition & Metabolism*, *71*(1–2), 16–25. <https://doi.org/10.1159/000478276>
- Mohammad, Y., Almutlaq, A., Al-Ruwaita, A., Aldrees, A., Alsubaie, A., & Al-Hussain, F. (2019). Stroke during sleep and obstructive sleep apnea: There is a link. *Neurol Sci*, <https://doi.org/10.1007/s10072-019-03753-2>
- Mufti, A. H., Ogiwara, K., Swystun, L. L., Eikenboom, J. C. J., Budde, U., & Hopman, W. M., ... Clinical Biology of von Willebrand disease Study, G. (2018). The common VWF single nucleotide variants c.2365A>G and c.2385T>C modify VWF biosynthesis and clearance. *Blood Advances*, *2*(13), 1585–1594. <https://doi.org/10.1182/bloodadvances.2017011643>
- Nadeem, R., Molnar, J., Madbouly, E. M., Nida, M., Aggarwal, S., Sajid, H., ... Loomba, R. (2013). Serum inflammatory markers in obstructive sleep apnea: A meta-analysis. *Journal of Clinical Sleep Medicine*, *9*(10), 1003–1012. <https://doi.org/10.5664/jcsm.3070>
- Nowakowski, S., Matthews, K. A., von Kanel, R., Hall, M. H., & Thurston, R. C. (2018). Sleep characteristics and inflammatory biomarkers among midlife women. *Sleep*, *41*(5), <https://doi.org/10.1093/sleep/zsy049>
- Peres, B. U., Hirsch Allen, A. J., Fox, N., Laher, I., Hanly, P., Skomro, R., ... Ayas, N. T. (2019). Circulating biomarkers to identify cardiometabolic complications in patients with Obstructive Sleep Apnea: A systematic review. *Sleep Medicine Reviews*, *44*, 48–57. <https://doi.org/10.1016/j.smrv.2018.12.004>
- Ponce de León-Suárez, V., Valdés-Flores, M., Miranda-Duarte, A., Ramírez-Pérez, E., Pérez-Ríos, A., Barredo-Prieto, B., ... Casas-Avila, L. (2018). Association of the IL6 rs1800796, but not of the IL6 rs1800795, IL6R rs4845617 and rs2228145 polymorphisms with hip fracture in elderly Mexican women. *Aging Clinical and Experimental Research*, *30*(4), 407–410. <https://doi.org/10.1007/s40520-017-0779-7>
- Popko, K., Gorska, E., Potapinska, O., Wasik, M., Stoklosa, A., Plywaczewski, R., ... Demkow, U. (2008). Frequency of distribution of inflammatory cytokines IL-1, IL-6 and TNF-alpha gene polymorphism in patients with obstructive sleep apnea. *Journal of Physiology and Pharmacology*, *59*(Suppl 6), 607–614.
- Shalitin, S., Deutsch, V., & Tauman, R. (2018). Hcpidin, soluble transferrin receptor and IL-6 levels in obese children and adolescents with and without type 2 diabetes mellitus/impaired glucose tolerance and their association with obstructive sleep apnea. *Journal of Endocrinological Investigation*, *41*(8), 969–975. <https://doi.org/10.1007/s40618-017-0823-7>
- Smith, D. F., & Amin, R. S. (2019). Obstructive sleep apnea and cardiovascular risk in pediatrics. *Chest*. <https://doi.org/10.1016/j.chest.2019.02.011>
- Smith, N. L., Chen, M.-H., Dehghan, A., Strachan, D. P., Basu, S., Soranzo, N., ... O'Donnell, C. J. (2010). Novel associations of multiple genetic loci with plasma levels of factor VII, factor VIII, and von Willebrand factor: The CHARGE (Cohorts for Heart and Aging Research in Genome Epidemiology) Consortium. *Circulation*, *121*(12), 1382–1392. <https://doi.org/10.1161/CIRCULATIONAHA.109.869156>
- Sun, J., Hu, J., Tu, C., Zhong, A., & Xu, H. (2015). Obstructive sleep apnea susceptibility genes in Chinese population: A field synopsis and meta-analysis of genetic association studies. *PLoS ONE*, *10*(8), e0135942. <https://doi.org/10.1371/journal.pone.0135942>
- Takagi, H., & Umemoto, T. (2016). Aortic diseases and obstructive sleep apnea. *International Angiology*, *35*(5), 433–439.
- Tang, S., Liu, Z., Zhang, Y., He, Y., Pan, D., Liu, Y., ... Yuan, Y. (2013). Rather than Rs1800796 polymorphism, expression of interleukin-6 is associated with disease progression of chronic HBV infection in a Chinese Han population. *Disease Markers*, *35*(6), 799–805. <https://doi.org/10.1155/2013/508023>
- von Kanel, R., Lored, J. S., Ancoli-Israel, S., Mills, P. J., Natarajan, L., & Dimsdale, J. E. (2007). Association between polysomnographic measures of disrupted sleep and prothrombotic factors. *Chest*, *131*(3), 733–739. <https://doi.org/10.1378/chest.06-2006>
- Wanderer, J. P., & Rathmell, J. P. (2019). Obstructive sleep apnea and opioid-induced respiratory depression: What do we know? *Anesthesiology*, *130*(2), A19. <https://doi.org/10.1097/ALN.0000000000002621>
- Wang, F., Xiong, X., Xu, H., Huang, H., Shi, Y., Li, X., ... Yin, S. (2019). The association between obstructive sleep apnea syndrome and metabolic syndrome: A confirmatory factor analysis. *Sleep Breath*, <https://doi.org/10.1007/s11325-019-01804-8>
- Wang, L., Lu, X., Li, Y., Li, H., Chen, S., & Gu, D. (2009). Functional analysis of the C-reactive protein (CRP) gene -717A>G polymorphism associated with coronary heart disease. *BMC Medical Genetics*, *10*, 73. <https://doi.org/10.1186/1471-2350-10-73>
- Wang, W., Chen, J., Zhao, F., Zhang, B., & Yu, H. (2014). Lack of association between a functional polymorphism (rs1800796) in the interleukin-6 gene promoter and lung cancer. *Diagnostic Pathology*, *9*, 134. <https://doi.org/10.1186/1746-1596-9-134>
- Wang, Z., Wu, S., Liao, J., Zhong, L., Xing, T., Fan, J., & Peng, Z. (2016). Interleukin-6 and rs1800796 locus single nucleotide polymorphisms in response to hypoxia/reoxygenation in hepatocytes. *International Journal of Molecular Medicine*, *38*(1), 192–200. <https://doi.org/10.3892/ijmm.2016.2595>
- Wu, W., Li, Z., Tang, T., Wu, J., Liu, F., & Gu, L. (2016). 5-HTR2A and IL-6 polymorphisms and obstructive sleep apnea-hypopnea syndrome. *Biomedical Reports*, *4*(2), 203–208. <https://doi.org/10.3892/br.2015.558>
- Wu, Z., Huang, Y., Huang, J., & Fan, L. (2017). Impact of CRP gene and additional gene-smoking interaction on ischemic stroke in a Chinese Han population. *Neurological Research*, *39*(5), 442–447. <https://doi.org/10.1080/01616412.2017.1297905>
- Young, T. B. (2004). Epidemiology of daytime sleepiness: Definitions, symptomatology, and prevalence. *Journal of Clinical Psychiatry*, *65*(Suppl 16), 12–16.
- Zhang, D., Xie, M., Yang, X., Zhang, Y., Su, Y., Wang, Y., ... Wei, J. (2017). Determination of IL-1B (rs16944) and IL-6 (rs1800796) genetic polymorphisms in IgA nephropathy in a northwest Chinese Han population. *Oncotarget*, *8*(42), 71750–71758. <https://doi.org/10.18632/oncotarget.17603>
- Zhang, X., Liu, R. Y., Lei, Z., Zhu, Y., Huang, J. A., Jiang, X., ... Zhang, H. T. (2009). Genetic variants in interleukin-6 modified risk of obstructive sleep apnea syndrome. *International Journal of Molecular Medicine*, *23*(4), 485–493. https://doi.org/10.3892/ijmm_00000155
- Zhang, Y. M., Mao, Y. M., & Sun, Y. X. (2015). Genetic polymorphisms of IL-6 and IL-10 genes correlate with lung cancer in never-smoking Han population in China. *International Journal of Clinical and Experimental Medicine*, *8*(1), 1051–1058.

- Zhao, B., Li, X., & Li, R. (2019). Genetic relationship between IL-6 rs1800796 polymorphism and susceptibility to periodontitis. *Immunological Investigations*, 48(3), 268–282. <https://doi.org/10.1080/08820139.2018.1517365>
- Zhong, A., Xiong, X., Shi, M., & Xu, H. (2016). Roles of interleukin (IL)-6 gene polymorphisms, serum IL-6 levels, and treatment in obstructive sleep apnea: A meta-analysis. *Sleep and Breathing*, 20(2), 719–731. <https://doi.org/10.1007/s11325-015-1288-6>

How to cite this article: Zhang Z, Wang Q, Chen B, Wang Y, Miao Y, Han L. Association study of genetic variations of inflammatory biomarkers with susceptibility and severity of obstructive sleep apnea. *Mol Genet Genomic Med*. 2019;7:e801. <https://doi.org/10.1002/mgg3.801>