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ORIGINAL RESEARCH

Multiple Allergic Rhinitis Single Nucleotide Polymorphism Variants are Associated with Sleep-Breathing Parameters in Men with Obstructive Sleep Apnea: A Large-Scale Study

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Background: Sleep-disordered breathing is more prevalent in individuals with allergic rhinitis (AR) than in those without AR. In addition to increased risk for sleep-disordered breathing, AR is associated with greater severity of obstructive sleep apnea (OSA) symptoms. The aim of this research study was to evaluate the association of multiple single nucleotide polymorphism (SNP) variations in AR with sleep- and breathing-related parameters in men with OSA.

Methods: Men who had complained of snoring were consecutively enrolled in the Shanghai Sleep Health Study of Shanghai Sixth People's Hospital from 2007 to 2018. After rigorous screening, 5322 men were included in the analysis. Anthropometric, fasting biochemical, and polysomnographic parameters, along with 27 AR-associated SNPs were analyzed. The associations between AR-related genetic polymorphisms and OSA were determined via linear, binary, and multinomial logistic regression analyses.

Results: Rs12509403 had significantly positive associations with most sleep-breathing parameters. While the risk for OSA was increased by rs12509403, it was decreased by rs7717955 [odds ratio (OR) = 1.341, 95% confidence interval [CI] = 1.039–1.732, P = 0.024; OR = 0.829, 95% CI = 0.715–0.961, P = 0.013, respectively]. A graded increase in the risk of being in the highest quartile (Q4) vs the reference category (Q1) for sleep breathing indicators, especially REM-AHI and NREM-AHI, was identified by rs12509403 (OR = 1.496, 95% CI = 1.175–1.904, P = 0.001; OR = 1.471, 95% CI = 1.151–1.879, P < 0.001, respectively).

Conclusion: The association of multiple AR SNPs with OSA-related hypoxia and sleep indices provides a genetic explanation for the higher AR susceptibility of OSA patients. Understanding the AR-related genetic underpinnings of OSA may lead to more personalized treatment approaches.

Keywords: allergic rhinitis, obstructive sleep apnea, single nucleotide polymorphism, polysomnography

Introduction

Obstructive sleep apnea (OSA) is the most common type of sleep-related breathing disorder worldwide, impacting around 936 million adults between the ages of 30 and 69.[1,2] It is characterized by upper airway obstruction during sleep, resulting in pauses in breathing, intermittent hypoxia, and fragmented sleep.[3] Male sex, obesity, nasal obstruction, and allergic rhinitis (AR) are among the risk factors for OSA.[3–5]

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AR is an inflammation response in the nasal mucosa caused by exposure to airborne allergens. Mediated by immunoglobulin E, it affects a significant portion (10–40%) of the global population.[6] The substantial increase in the prevalence of AR in recent decades constitutes a significant public health concern worldwide.[7] A variety of symptoms are associated with AR, including nasal congestion, clear rhinorrhea, sneezing, and less commonly, nasal itching.[8]

AR is a separate risk factor for the development and progression of OSA and may exacerbate OSA.[9,10] It is reported that a prevalence of 11% perennial AR in patients with OSA and more patients with OSA were sensitized to perennial allergens.[11] Compared to the general Thai population, Thai patients with AR are twice as likely to develop OSA.[12] OSA patients undergo heightened oxidative stress, resulting in a decrease in oxygen saturation, which has the potential to worsen preexisting allergic diseases.[13,14] Accordingly, there appears to be a close relationship between AR and OSA. Indeed, a notable and meaningful association was observed between the management of AR symptoms (measured using the Nasal Symptom Severity [NSS] scale) and the management of OSA (measured using the Epworth Sleepiness Scale [ESS]).[15] Steroids and anti-allergy medications have been effectively used in the management of OSA.[10] And these studies explored the correlations between sleep quality and AR using subjective questionnaires instead of objective empirical data.[9,15] Polysomnography (PSG) can be used to measure hypoxia and sleep-related factors, among other parameters, thus facilitating the diagnosis of OSA and evaluations of OSA severity.[16] Given the many possible links between AR and OSA, investigating the genetic susceptibility to AR could provide clues regarding its pathogenesis. Genome-wide association studies (GWASs) have indicated that variants in or near human leukocyte antigen (HLA) (rs7775228), dynein axonemal heavy chain 5 (DNAH5) (rs6554809), WD repeat-containing protein 36-calmodulin-dependent protein kinase 4 (WDR36-CAMK4) (rs1438673), lipoma preferred partner (LPP) (rs9865818), and C-type lectin domain family 16 member A (CLEC16A) (rs7203459) are significantly associated with AR in Han Chinese.[17] In a recent study that examined the entire genome in 59,762 AR patients and 152,358 controls from Europe, 41 genomic variants were strongly linked to the risk for AR.[18] Both OSA and AR are influenced by a combination of genetic and environmental factors. As OSA is closely related to AR, the genetic factors associated with AR may also be associated with OSA. At present, there are insufficient data on the influence of genetic variants related to AR on sleep and OSA-related parameters. To address this issue, we investigated single nucleotide polymorphisms (SNPs) associated with AR in individuals with OSA. Many studies have extensively examined sex differences in relation to OSA and AR. The overall prevalence of OSA, of any severity, ranged from 9% to 38% in the general adult population, from 13% to 33% in men, and from 6% to 19% in women.[19] A recent study in China showed a higher weighted prevalence of AR in men than in women (9.0% vs 7.1%, $p < 0.001$).[20] Women are also less likely than men to be diagnosed with OSA, and they have been under-represented in clinical studies of OSA.[21] Thus, in the present study, only males were recruited.

Methods

Participants

The present investigation was based on the Shanghai Sleep Health Study (SSHS), a study that has been ongoing since 2007 to explore relationships between OSA, metabolic disorders, and genetic predispositions. Of SSHS, Anthropometric and biochemical indicators, and PSG data were collected, with an extra genomic examination based on PSG results performed in patients with mild to severe OSA and those without OSA.[22–24] Initially, 6433 participants were enrolled. The inclusion criteria were males above the age of 18 years with no record of a return visit or prior therapy. The exclusion criteria were as follows: missing > 15% SNP data, other sleep disorders such as narcolepsy or restless leg syndrome, and missing data for cumulative time points of the oxygen desaturation index (ODI), cumulative time percentage with SpO2 < 90% (CT90), the number of AHI per hour of rapid eye movement sleep (REM-AHI) and per non-REM sleep (NREM-AHI), micro-arousal index (MAI), and minimum oxygen saturation (SaO2). Ultimately, complete data were collected and analyzed from 5322 individuals. This study was approved by the Ethics Committee of Shanghai Sixth People's Hospital [ethical approval number: 2019-KY-050(K)] and each participant provided informed consent before participating.

Anthropometric Measurements

Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Participants were considered smokers if they had smoked one or more cigarettes per day over the past year on average.[25] Alcohol use was defined as consuming alcohol at least once per week on average.[26]

Polysomnographic Evaluation

Overnight standard PSG (Alice 4 or 5; Respironics Inc., Pittsburgh, PA, USA) was used to acquire objective sleep parameters. Various measurements were conducted during sleep, including an electroencephalogram, bilateral electro-oculogram, chin electromyogram, electrocardiogram, nasal and oral airflow test, finger pulse oximetry, chest and abdominal movement assessments, and body posture evaluation. Skilled technicians manually evaluated the sleep stages and respiratory events according to the American Academy of Sleep Medicine (AASM) criteria, established in 2012 (data collected before 2012 were rescored).[27] Apnea was operationally defined as an interruption of airflow reaching a minimum of 90% of the initial level for a period of 10s or more. By contrast, hypopnea was defined as either a 30% reduction in airflow for 10s or a 30% reduction accompanied by either a 3% reduction in oxyhemoglobin saturation or a change in arousal level.[27] The average number of apnea and hypopnea events per hour during sleep was used to determine the AHI. Based on the AHI values, OSA was classified into four categories: No OSA ($AHI < 5$), mild OSA ($5 \leq AHI < 15$), moderate OSA ($15 \leq AHI < 30$) and severe OSA ($AHI \geq 30$). Furthermore, REM-AHI and NREM-AHI were computed by counting the apnea and hypopnea events within each hour of REM and NREM sleep. ODI was operationally defined in terms of the total number of desaturation events, as identified by a decrease in oxygen saturation of no less than 3% per hour. The MAI was defined as the mean number of arousals per hour of sleep, and CT90 as the cumulative proportion of time during which oxygen saturation fell below a threshold of 90%.

SNP Selection

The Affymetrix genome-wide human SNP array 6.0 (SNP6.0) and Affymetrix Axiom™ genome-wide CHB array plates (CHB) were used for genotyping. Genotypes were then generated by Axiom genotyping algorithm v1 (Axiom GT1) and constituted the genetic database. The genotyping processes, quality assurance protocols, and genotype imputation of Chinese data are detailed in our GWAS paper.[24]

All 41 AR SNPs identified as significant in a previous study were included in the present analysis(rs34004019, rs95088, rs5743618, rs1438673, rs7936323, rs2428494, rs11644510, rs12939457, rs148505069, rs13395467, rs9775039, rs2164068, rs2030519, rs11256017, rs17294280, rs7824993, rs9282864, rs9687749, rs61977073, rs6470578, rs3787184, rs7717955, rs63406760, rs1504215, rs28361986, rs2070902, rs111371454, rs12509403, rs9648346, rs35350651, rs2519093, rs62257549, rs11677002, rs35597970, rs2815765, rs11671925, rs2461475, rs6738964, rs10519067, rs138050288 and rs7328203).[18] Of these, 15 were excluded because the call rates were < 90%, the rate of missing data exceeded 10%, or minor allele frequencies were < 1%, such that the quality control criteria were not met. Ultimately, 27 AR-associated SNPs satisfied both the Hardy–Weinberg equilibrium and had a linkage disequilibrium (LD) value < 0.2.

Statistical Analysis

Statistical analyses were conducted using SPSS software (version 26.0, IBM Corp, Armonk, NY, USA). PLINK was used to perform the Hardy-Weinberg equilibrium test for each variant prior to conducting the association analysis (https://zzz.bwh.harvard.edu/plink/data.shtml).

For all statistical comparisons, the normal distribution of the data was tested using the Shapiro–Wilk test. Normally distributed data are expressed in terms of the mean and standard deviation. Skewed data are represented by the median (IQR), and categorical data are represented numerically as a percentage. A chi-squared test and one-way ANOVA were used to examine the disparities among the four sets of descriptive variables. Correlations between AR SNPs and OSA-related parameters were assessed using linear, binary, and multinomial logistic regression analyses. A two-tailed p value < 0.05 was considered statistically significant. To account for multiple testing, two-sided p values were adjusted according to the Benjamini/Hochberg (B/H) method to control the false discovery rate (FDR).[28] An association was considered to be statistically significant if the corresponding B/H-adjusted P value was < 0.05, corresponding to a FDR of 5%.

Results

Baseline Characteristics

The study included a total of 5322 eligible individuals, with 764 non-OSA patients, 324 mild OSA patients, 985 moderate OSA patients, and 3249 severe OSA patients. The participant characteristics are listed in Table 1. Participants with OSA were more likely to be obese, hypoxic, and to drink alcohol compared to those without it (P for linear trend < 0.001). Furthermore, significant variation in OSA-related parameters was observed among the different groups.

The 27 selected AR SNPs are shown in Table 2. The minor allele distribution was not statistically different between the non-OSA and OSA groups. The P value for Hardy–Weinberg equilibrium was >0.05.

Correlations Between AR SNPs and OSA-Related Parameters

Associations between AR SNPs and OSA-related parameters were examined via linear regression. As shown in Table 3, in all patients, the correlations between rs12509403 and AHI, ODI, CT90, REM-AHI, NREM-AHI, and MAI were significantly positive (β = 0.036, P = 0.004, $P_{BH} = 0.005$; β = 0.036, P = 0.004, $P_{BH} = 0.005$; β = 0.045, P = 0.001, $P_{BH} = 0.003$; β = 0.048, P < 0.001, $P_{BH} < 0.001$; β = 0.042, P = 0.001, $P_{BH} = 0.003$; β = 0.033, P = 0.019, $P_{BH} = 0.022$, respectively). The correlation of rs12509403 with the minimum SaO2 was significantly negative (β = –0.041, P = 0.004, $P_{BH} = 0.005$).

The associations between the AR SNPs and OSA-related parameters in the mild OSA, moderate OSA, and severe OSA groups are shown in Tables S1–S3, respectively. In the mild OSA group (n = 324), the correlation between rs2815765 and the ODI was significantly positive (β = 0.261, P<0.001, $P_{BH} < 0.001$), as was the correlation between rs111371454 and NREM-AHI (β = 0.163, P = 0.005, $P_{BH} = 0.040$). In the moderate OSA group (n = 985), the correlation between rs7936323 and the AHI was significantly negative (β = –0.091, P = 0.005, $P_{BH} = 0.040$), and that between rs2164068 and the CT90 was significantly positive (β = 0.095, P = 0.003, $P_{BH} = 0.024$). In patients diagnosed with severe OSA (n = 3249), the correlation between rs12509403 and the AHI, CT90, REM-AHI, and NREM-AHI was significantly positive (β = 0.043, P = 0.011, $P_{BH} = 0.022$; β = 0.044, P = 0.011, $P_{BH} = 0.022$; β = 0.061, P < 0.001, $P_{BH} < 0.001$; β = 0.045, P = 0.010, $P_{BH} = 0.022$ respectively). The correlation between

Table 1 Basic Characteristics of the Study Population by the Severity of Obstructive Sleep Apnea (OSA)

Variable	Non-OSA (n = 764)	Mild OSA (n = 324)	Moderate OSA (n = 985)	Severe OSA (n = 3249)	P value
Demographics					
Age (years)	38	32	44	43	<0.001
BMI (kg/m2)	24.5 (24.30–24.75)	25.39 (25.0525.72)	26.52 (26.30–26.74)	28.14 (28.01–28.28)	<0.001
Smoker, N (%)	178 (23.3%)	106 (32.7%)	242 (24.6%)	840 (25.9%)	0.010
Drinker, N (%)	374 (49.0%)	104 (32.1%)	448 (45.5%)	1547 (47.6%)	<0.001
Sleep apnea					
AHI total	2.17 (2.06–2.16)	10.83 (10.57–11.10)	22.22 (21.95–22.49)	58.07 (57.49–58.65)	<0.001
Minimum SaO2	91.19 (90.79–91.60)	85.82 (85.01–86.54)	81.16 (80.63–81.70)	69.40 (68.97–69.82)	<0.001
ODI	4.98 (3.94–6.01)	11.44 (10.75–12.14)	23.42 (22.77–24.07)	58.21 (57.51–58.92)	<0.001
Obstructive AHI	0.71 (0.64–0.78)	4.74 (4.25–5.24)	10.90 (10.38–11.41)	34.31 (33.65–34.96)	<0.001
CT90	0.70 (0.29–1.10)	1.41 (0.73–2.10)	3.87 (3.43—4.32)	20.46 (19.81–21.10)	<0.001
REM-AHI	4.53 (3.81–5.25)	20.70 (18.78–22.63)	30.04 (28.80–31.28)	53.60 (52.87–54.33)	<0.001
NREM-AHI	3.60 (2.91–4.30)	11.71 (10.50–12.92)	22.19 (21.60–22.78)	56.68 (56.00–57.37)	<0.001
MAI	18.73 (17.68–19.77)	22.10 (20.41–23.79)	25.80 (24.67–26.93)	39.60 (24.67–26.93)	<0.0001

Notes: The data are presented as the mean and standard deviation; skewed data are presented as the median (IQR), and categorical data as the number (percentage).
Abbreviations: BMI, body mass index; AHI, apnea-hypopnea index (events/h); SaO2, oxygen saturation, %; ODI, oxygen desaturation index (events/h); CT90, cumulative time percentage with SpO2 < 90%, %; REM-AHI, number of AHI per hour of REM sleep (events/h); NREM-AHI, number of AHI per hour of non-REM (NREM) sleep (events/h); MAI, micro-arousal index (events/h).

Table 2 Information on Each Selected SNP

Loci	SNP	Chromosome	Position	MAF	Minor/Major Allele	Risk Allele	β	$P_{H\text{-}E}$
LRRIQ3	rs2815765	1	72752230	0.08314	T/C	T	−0.051	0.153
FCER1G	rs2070902	1	161187665	0.4537	T/C	T	0.058	1.000
ID2	rs13395467	2	8451498	0.2484	G/A	G	−0.062	0.698
FOSL2	rs11677002	2	28614401	0.2223	C/T	C	−0.041	0.875
IL1RL1	rs950881	2	102932512	0.09417	T/G	T	−0.128	0.916
PLCL1	rs2164068	2	198943852	0.2501	A/T	A	−0.062	0.629
DAW1	rs6738964	2	228739135	0.4547	G/T	G	−0.041	0.380
VPRBP	rs62257549	3	51522676	0.2402	A/G	A	−0.051	0.960
LPP	rs2030519	3	188119901	0.3711	G/A	G	0.058	0.074
NFKB1	rs12509403	4	103525350	0.3838	T/C	T	−0.051	0.420
IL21	rs148505069	4	123417564	0.4865	A/G	G	0.068	0.771
IL7R	rs7717955	5	35862841	0.1803	T/C	T	−0.051	0.198
WDR36	rs1438673	5	110467499	0.4369	C/T	C	0.077	0.796
JAZF1	rs9648346	7	28160113	0.2639	C/G	G	0.049	0.283
ZBTB10	rs7824993	8	81262896	0.4042	G/A	A	0.049	0.429
MYC	rs6470578	8	128809557	0.3324	T/A	T	0.049	0.967
ABO	rs2519093	9	136141870	0.2231	T/C	T	0.058	0.958
GATA3	rs11256017	10	9043919	0.2442	T/C	T	0.068	1.000
LRRC32	rs7936323	11	76293758	0.4883	G/A	A	0.077	0.292
CXCR5	rs28361986	11	118693161	0.132	A/T	A	−0.073	0.812
ACADS	rs2461475	12	121290174	0.4498	T/C	C	0.039	0.107
TNFSF11	rs7328203	13	42988546	0.2165	T/G	G	0.049	0.915
TTC6	rs61977073	14	38151255	0.1151	G/A	G	0.058	0.213
RTF1	rs111371454	15	41760617	0.1796	G/A	G	0.058	0.538
RORA	rs10519067	15	61068347	0.1182	A/G	A	−0.073	0.139
GSDMB	rs12939457	17	38032188	0.2677	C/T	C	−0.062	0.781
CEBPA	rs11671925	19	33718053	0.2195	A/G	A	−0.062	0.672

Abbreviations: SNP, single nucleotide polymorphism; MAF, minor allele frequency; β, effect size of the SNP; $P_{H\text{-}E}$, P value for the Hardy–Weinberg equilibrium.

Table 3 Linear Associations Between SNPs and OSA-Related Parameters in the General Population

SNP		AHI	Minimum SaO2	ODI	Obstructive AHI	CT90	REM-AHI	NREM-AHI	MAI
rs2815765	β	0.622	0.002	0.002	0.001	−0.004	−0.009	−0.004	−0.020
	P	0.618	0.862	0.886	0.950	0.751	0.494	0.741	0.147
	P_{BH}	0.950	0.950	0.950	0.950	0.950	0.950	0.950	0.950
rs2070902	β	−0.007	0.016	−0.004	−0.006	−0.005	0.010	−0.004	0.019
	P	0.586	0.260	0.772	0.658	0.390	0.457	0.765	0.210
	P_{BH}	0.772	0.772	0.772	0.772	0.772	0.772	0.772	0.772
rs13395467	β	0.001	0.006	−0.005	−0.007	−0.007	0.001	0.008	−0.001
	P	0.931	0.638	0.638	0.577	0.575	0.927	0.559	0.948
	P_{BH}	0.948	0.948	0.948	0.948	0.948	0.948	0.948	0.948
rs11677002	β	−0.006	−0.006	−0.006	−0.017	−0.022	−0.011	−0.010	−0.015
	P	0.602	0.654	0.637	0.202	0.101	0.387	0.435	0.279
	P_{BH}	0.654	0.654	0.654	0.654	0.654	0.654	0.654	0.654
rs950881	β	−0.007	0.019	−0.006	−0.005	−0.016	−0.011	−0.004	−0.010
	P	0.585	0.138	0.138	0.138	0.217	0.388	0.768	0.489
	P_{BH}	0.669	0.368	0.368	0.368	0.434	0.621	0.768	0.652

(*Continued*)

Table 3 (Continued).

SNP		AHI	Minimum SaO2	ODI	Obstructive AHI	CT90	REM-AHI	NREM-AHI	MAI
rs2164068	β	−0.009	0.001	−0.013	−0.007	0.005	−0.034	−0.011	0.006
	P	0.489	0.940	0.940	0.940	0.940	0.009	0.398	0.659
	P_{BH}	0.940	0.940	0.940	0.940	0.940	0.072	0.940	0.940
rs6738964	β	0.010	−0.008	−0.003	0.003	0.018	−0.006	−0.002	0.006
	P	0.442	0.552	0.795	0.795	0.179	0.636	0.870	0.674
	P_{BH}	0.870	0.870	0.870	0.870	0.870	0.870	0.870	0.870
rs62257549	β	0.018	0.008	0.013	0.017	0.003	0.012	0.019	−0.005
	P	0.157	0.538	0.294	0.197	0.793	0.353	0.155	0.155
	P_{BH}	0.394	0.615	0.470	0.394	0.793	0.471	0.394	0.394
rs2030519	β	−0.009	0.010	0.002	−0.005	0.012	−0.013	−0.002	−0.015
	P	0.477	0.297	0.870	0.870	0.369	0.369	0.855	0.297
	P_{BH}	0.763	0.738	0.870	0.870	0.738	0.738	0.870	0.738
rs12509403	β	**0.036**	**−0.041**	**0.036**	0.026	**0.045**	**0.048**	**0.042**	**0.033**
	P	**0.004**	**0.004**	**0.004**	0.054	**0.001**	**0.000**	**0.001**	**0.019**
	P_{BH}	**0.005**	**0.005**	**0.005**	0.054	**0.003**	**0.000**	**0.003**	**0.022**
rs148505069	β	−0.013	0.010	−0.022	−0.012	−0.003	−0.010	−0.013	−0.025
	P	0.298	0.448	0.081	0.358	0.802	0.433	0.330	0.078
	P_{BH}	0.512	0.512	0.324	0.512	0.802	0.512	0.512	0.324
rs7717955	β	−0.019	0.009	−0.016	−0.026	−0.008	−0.014	−0.012	−0.005
	P	0.122	0.505	0.194	0.052	0.552	0.285	0.333	0.713
	P_{BH}	0.488	0.631	0.517	0.416	0.631	0.533	0.533	0.713
rs1438673	β	0.002	0.001	−0.003	−0.014	−0.010	−0.003	−0.006	0.000
	P	0.846	0.950	0.811	0.811	0.430	0.835	0.653	0.997
	P_{BH}	0.997	0.997	0.997	0.997	0.997	0.997	0.997	0.997
rs9648346	β	−0.021	**0.030**	−0.025	−0.013	−0.022	−0.013	−0.005	−0.012
	P	0.096	**0.020**	0.053	0.321	0.089	0.324	0.705	0.393
	P_{BH}	0.192	0.160	0.192	0.432	0.192	0.432	0.705	0.449
rs7824993	β	0.005	0.005	0.007	−0.001	0.018	0.009	0.007	0.017
	P	0.678	0.717	0.556	0.957	0.173	0.510	0.597	0.242
	P_{BH}	0.819	0.819	0.819	0.957	0.819	0.819	0.819	0.819
rs6470578	β	−0.011	0.008	−0.013	−0.007	−0.003	−0.030	−0.008	−0.007
	P	0.371	0.557	0.305	0.586	0.810	0.022	0.520	0.604
	P_{BH}	0.690	0.690	0.690	0.690	0.810	0.176	0.690	0.690
rs2519093	β	−0.012	−0.004	−0.013	−0.009	0.010	−0.014	−0.004	−0.008
	P	0.358	0.787	0.320	0.488	0.454	0.294	0.741	0.570
	P_{BH}	0.760	0.787	0.760	0.760	0.760	0.760	0.787	0.760
rs11256017	β	0.010	−0.003	−0.001	0.020	0.019	0.008	0.019	0.014
	P	0.434	0.924	0.131	0.152	0.549	0.153	0.324	0.324
	P_{BH}	0.579	0.924	0.408	0.408	0.627	0.408	0.518	0.518
rs7936323	β	−0.009	−0.011	−0.006	−0.004	0.012	−0.011	−0.014	−0.020
	P	0.453	0.377	0.643	0.748	0.340	0.409	0.278	0.146
	P_{BH}	0.604	0.604	0.735	0.748	0.604	0.604	0.604	0.604
rs28361986	β	−0.006	−0.006	−0.004	0.013	−0.002	0.022	0.000	−0.017
	P	0.616	0.622	0.744	0.330	0.894	0.102	0.996	0.230
	P_{BH}	0.992	0.992	0.992	0.880	0.996	0.816	0.996	0.880
rs2461475	β	0.004	0.012	0.016	0.001	0.014	−0.018	0.014	**0.036**
	P	0.740	0.342	0.194	0.917	0.274	0.159	0.280	**0.011**
	P_{BH}	0.846	0.456	0.448	0.917	0.448	0.448	0.448	0.088

(*Continued*)

Table 3 (Continued).

SNP		AHI	Minimum SaO2	ODI	Obstructive AHI	CT90	REM-AHI	NREM-AHI	MAI
rs7328203	β	0.009	0.006	0.008	0.008	0.000	−0.006	−0.001	−0.011
	P	0.493	0.644	0.508	0.528	0.986	0.660	0.963	0.433
	P_{BH}	0.880	0.880	0.880	0.880	0.986	0.880	0.986	0.880
rs61977073	β	0.004	0.001	0.006	0.004	−0.001	−0.011	0.003	−0.002
	P	0.714	0.922	0.615	0.772	0.945	0.422	0.844	0.866
	P_{BH}	0.945	0.945	0.945	0.945	0.945	0.945	0.945	0.945
rs111371454	β	0.005	−0.016	−0.004	0.001	0.009	0.007	0.001	−0.014
	P	0.713	0.221	0.735	0.939	0.482	0.587	0.958	0.310
	P_{BH}	0.958	0.958	0.958	0.958	0.958	0.958	0.958	0.958
rs10519067	β	−0.023	0.003	−0.025	−0.016	0.002	−0.012	−0.019	−0.026
	P	0.074	0.829	0.048	0.231	0.880	0.347	0.147	0.070
	P_{BH}	0.197	0.880	0.197	0.370	0.880	0.463	0.294	0.197
rs12939457	β	0.017	−0.015	0.014	0.017	0.020	0.011	0.020	−0.008
	P	0.160	0.244	0.276	0.194	0.363	0.813	0.215	0.250
	P_{BH}	0.368	0.368	0.368	0.368	0.415	0.813	0.368	0.368
rs11671925	β	−0.021	−0.006	−0.025	−0.014	−0.020	−0.027	−0.027	−0.004
	P	0.110	0.671	0.057	0.326	0.141	0.044	0.043	0.788
	P_{BH}	0.220	0.767	0.152	0.435	0.226	0.152	0.152	0.788

Notes: β and P were adjusted for age, BMI, smoking, and alcohol consumption when multiple linear regression models were adopted. P_{BH} after Benjamini–Hochberg (BH) multiple testing correction. Significant results are shown in bold.

Abbreviations: SNP, single-nucleotide polymorphism; AHI, apnea-hypopnea index; SaO2, oxygen saturation; ODI, oxygen desaturation index; CT90, cumulative time percentage with SpO2 < 90%; REM-AHI, number of AHI per hour of REM sleep; NREM-AHI, number of AHI per hour of non-REM (NREM) sleep; MAI, micro-arousal index.

rs6738964 and the AHI was also significantly positive (β = 0.050, P = 0.003, P_{BH} = 0.024). All P values shown above were adjusted for age, BMI, smoking, and alcohol consumption.

Associations Between AR SNPs and OSA Risk

A binary logistic regression analysis was used to examine the relationships between AR SNPs and OSA risk (Table 4). Rs12509403 increased the risk for OSA (OR = 1.350, 95% CI = 1.066–1.711, P = 0.013), even after adjusting for age, BMI, smoking status, and alcohol consumption (OR = 1.341, 95% CI = 1.039–1.732, P = 0.024). By contrast, rs7717955 decreased the risk of OSA (OR =0.845, 95% CI =0.736–0.969, P = 0.016), even after adjustments (OR =0.829, 95% CI =0.715–0.961, P = 0.013).

Next, the OSA-related parameters were divided into quartiles, denoted as Q1 (reference group), Q2, Q3, and Q4. The multinomial logistic regression analysis indicated that, compared to Q1 and after adjusting for age, BMI, smoking status, and alcohol intake, rs12509403 was related to a graded increase in the risk of being in the highest quartile (Q4) for the AHI, minimum SaO2, ODI, CT90, REM-AHI, NREM-AHI, and MAI (OR = 1.362, 95% CI = 1.045–1.776, P = 0.022; OR = 1.388, 95% CI = 1.095–1.759, P = 0.007; OR = 1.466, 95% CI = 1.121–1.917, P = 0.010; OR = 1.381, 95% CI = 1.087–1.755, P = 0.008; OR = 1.496, 95% CI = 1.175–1.904, P = 0.001; OR = 1.471, 95% CI = 1.151–1.879, P < 0.001; OR = 1.270, 95% CI = 1.010–1.598, P = 0.041, respectively) (Table 5). There were no associations between the other SNPs and OSA-related parameters.

There were no notable correlations between rs12509403 and the quartiles of the OSA-related parameters in the mild OSA (Table S4) or moderate OSA (Table S5) groups. However, in the severe OSA group, this SNP was related to a graded increase in the risk of being in Q4 for the REM-AHI, compared to Q1 and after adjusting for age, BMI, smoking status, and alcohol intake (OR = 1.534, 95% CI = 1.132–2.080, P = 0.006) (Table S6).

Table 4 Associations of the SNPs with OSA Risk

SNP	OR (95% CI)	P	OR (95% CI)*	P*
rs2815765	0.871 (0.718–1.057)	0.162	0.855 (0.693–1.054)	0.141
rs2070902	1.049 (0.934–1.178)	0.416	1.038 (0.914–1.178)	0.567
rs13395467	0.968 (0.855–1.096)	0.607	0.971 (0.848–1.112)	0.672
rs11677002	0.934 (0.822–1.063)	0.303	0.955 (0.830–1.099)	0.519
rs950881	0.958 (0.798–1.150)	0.646	0.952 (0.782–1.160)	0.625
rs2164068	0.945 (0.834–1.072)	0.378	0.935 (0.815–1.073)	0.338
rs6738964	0.951 (0.852–1.060)	0.363	0.919 (0.815–1.035)	0.165
rs62257549	1.062 (0.932–1.210)	0.369	1.108 (0.961–1.276)	0.157
rs2030519	1.030 (0.920–1.154)	0.607	1.007 (0.890–1.139)	0.914
rs12509403	**1.350 (1.066–1.711)**	**0.013**	**1.341 (1.039–1.732)**	**0.024**
rs148505069	0.975 (0.874–1.087)	0.644	1.011 (0.899–1.137)	0.858
rs7717955	**0.845 (0.736–0.969)**	**0.016**	**0.829 (0.715–0.961)**	**0.013**
rs1438673	1.034 (0.927–1.154)	0.549	1.044 (0.927–1.176)	0.477
rs9648346	0.915 (0.807–1.038)	0.169	0.939 (0.819–1.076)	0.363
rs7824993	1.072 (0.959–1.198)	0.221	1.081 (0.957–1.221)	0.208
rs6470578	0.964 (0.860–1.081)	0.534	0.974 (0.861–1.101)	0.672
rs2519093	0.911 (0.802–1.035)	0.152	0.933 (0.813–1.071)	0.323
rs11256017	1.026 (0.903–1.166)	0.693	0.977 (0.851–1.121)	0.739
rs7936323	0.935 (0.839–1.041)	0.22	0.918 (0.817–1.031)	0.15
rs28361986	0.995 (0.844–1.174)	0.955	1.009 (0.845–1.206)	0.918
rs2461475	0.947 (0.848–1.059)	0.341	0.975 (0.865–1.100)	0.685
rs7328203	1.070 (0.941–1.218)	0.301	1.108 (0.963–1.275)	0.151
rs61977073	0.977 (0.826–1.157)	0.791	0.973 (0.810–1.170)	0.773
rs111371454	0.998 (0.978–1.018)	0.848	0.991 (0.970–1.013)	0.428
rs10519067	0.935 (0.791–1.104)	0.427	0.909 (0.759–1.088)	0.299
rs12939457	1.046 (0.923–1.184)	0.482	0.994 (0.870–1.136)	0.931
rs11671925	0.927 (0.811–1.059)	0.264	0.934 (0.809–1.079)	0.356

Notes: P value without adjustments. *Value adjusted for age, BMI, smoking, and alcohol consumption as confounding factors. Significant results are shown in bold.

Abbreviations: SNP, single-nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval.

Table 5 Associations Between rs12509403 and OSA According to the Quartile of the OSA-Related Parameters of All Patients

	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
	AHI		**Minimum SaO2**		**ODI**		**Obstructive AHI**	
Q1	1			–	1	–		–
Q2	1.358 (0.911–2.024)	0.132	1.137 (0.901–1.436)	0.280	1.243 (0.980–1.578)	0.070	0.984 (0.780–1.241)	0.890
Q3	1.302 (0.966–1.754)	0.083	1.144 (0.902–1.451)	0.269	1.146 (0.895–1.467)	0.280	1.111 (0.883–1.399)	0.368
Q4	**1.362 (1.045–1.776)**	**0.022**	**1.388 (1.095–1.759)**	**0.007**	**1.466 (1.121–1.917)**	**0.010**	1.199 (0.950–1.514)	0.127
	CT90		**REM-AHI**		**NREM-AHI**		**MAI**	
Q1	1	–	1	–	1	–	1	–
Q2	1.107 (0.878–1.396)	0.388	1.075 (0.846–1.365)	0.554	1.164 (0.916–1.480)	0.220	1.000 (0.792–1.261)	0.997
Q3	0.977 (0.767–1.246)	0.854	1.278 (1.007–1.622)	0.043	1.128 (0.883–1.443)	0.340	0.923 (0.728–1.169)	0.505
Q4	**1.381 (1.087–1.755)**	**0.008**	**1.496 (1.175–1.904)**	**0.001**	**1.471 (1.151–1.879)**	**<0.001**	**1.270 (1.010–1.598)**	**0.041**

Note: Significant results are shown in bold.

Abbreviations: OR, odds ratio; 95% CI, 95%confidence interval; AHI, apnea-hypopnea index; SaO2, oxygen saturation; ODI, oxygen desaturation index; CT90, cumulative time percentage with SpO2 < 90%; REM-AHI, number of AHI per hour of REM sleep; NREM-AHI, number of AHI per hour of non-REM (NREM) sleep; MAI, micro-arousal index.; Q, quantile.

Discussion

To the best of our knowledge, this study is the first to comprehensively examine the association between AR SNPs and OSA-related parameters in Chinese OSA patients using large-scale sampling and strict data-acquisition protocols. Many AR SNPs were shown to be closely related to OSA-related parameters. In particular, SNP rs12509403 carried an increased risk for OSA, while rs7717955 was associated with a decreased risk for OSA. Rs12509403 was related to a graded increase in the risk of being in the highest quartile for the studied sleep-breathing indicators compared to the reference, particularly for the REM-AHI and NREM-AHI. In individuals with severe OSA, rs12509403 indicated a greater chance of being in a higher-order REM-AHI category.

Previous studies reported that AR is closely related to OSA.[9,12] Treatments for AR, including immunotherapy, intranasal corticosteroids (ICS), and oral antihistamines, have been shown to effectively improve OSA symptoms.[10] The main mechanisms underlying the association between AR and altered sleep patterns can be summarized as follows.[29] Inflammatory cytokines produced by AR interact directly with the central nervous system, causing sleep disruptions and daytime sleepiness.[30,31] Histamine, a mediator of inflammation, can also affect sleep-wake cycle regulation, potentially disturbing wakefulness.[30] Furthermore, AR has been shown to increase levels of three serum cytokines: interleukin (IL)-1β, IL-4, and IL-10, which are correlated with increased latency to REM sleep, decreased time in REM sleep, and decreased latency to sleep onset.[32] In addition, AR induces heightened nasal resistance and consequently elevates upper airway resistance. At the same time, breathing through the mouth can lead the mandible to be pushed downwards, decreasing the front-back size of the pharynx.[33] These two mechanisms synergistically contribute to an augmented susceptibility to obstructive upper airway events during sleep. There is also evidence of autonomic nervous system dysfunction in people with AR.[34] In addition, the nasal trigeminal reflex is believed to contribute to the development of sleep disorders.[35]

Few studies have explored the genetic link between AR and OSA. However, genetic variants in AR patients have been linked with various medical conditions, such as early-onset schizophrenia, celiac disease, primary biliary cholangitis, pathogenic variants of atopic dermatitis, and eosinophilic esophagitis.[36–40] Our results showed that a rs12509403 variant increased the risk for OSA. rs12509403 is located within the DNA sequence of the NFKB1 gene. Reactive oxygen species induced by hypoxia play a key role in OSA and its comorbidities through the nuclear factor-kappa B (NF-κB) pathway.[41] Indeed, OSA patients have significantly elevated levels of NF-κB in peripheral blood mononuclear cells compared to controls, and this is positively related to disease severity.[42] A randomized controlled trial indicated that mindfulness meditation may serve as a temporary remedy for mild sleep disruptions in elderly individuals, and the observation that NF-κB levels decrease following meditation reinforces this finding.[43]

Our study showed that rs7717955 was associated with a reduced risk for OSA. rs7717955 is located in the interleukin 7 receptor (IL7R) gene region. Cortisol levels significantly increase in the late stages of sleep and can acutely increase the expression of IL7R.[44] The increase in IL-7 levels during late sleep may be due to an increase in IL7R expression, suggesting that late sleep promotes IL-7 signaling.[44,45] Indeed, sleep induces a discrete increase in serum levels of IL-7, whereas sleep disorders are associated with decreased levels of IL-7.[45,46]

The SOMNIAAR study showed that sleep quality is markedly worse in individuals with severe AR than in those with mild AR.[47] The inflammatory mediators associated with AR can inhibit both REM sleep and NREM sleep.[32,48] A previous study found that individuals who were allergic to house dust mites (HDM) and those allergic to non-HDM allergens were more likely to have an REM-AHI within the moderate to severe range.[49] Our results are consistent with these findings, as they showed a relationship between rs12509403 and a graded increase in the risk for a heightened REM-AHI in individuals with severe OSA. Thus, our findings suggest that AR has a more pronounced influence on REM sleep in individuals with severe OSA. Nasal congestion is also worse during REM sleep.[50] Future investigations should examine the environmental and genetic factors associated with this relationship.

NREM sleep includes stages N1, N2, and N3, and constitutes approximately 80% of the complete sleep cycle.[51] A moderate negative correlation has been reported between IL-10 and the durations of sleep stages N1 and N2.[52] Anti-inflammatory cytokines, including IL-4, IL-10, and IL-13, inhibited NREM sleep in animal models.[33] Since AR has been shown to increase levels of IL-4, and IL-10, it is plausible that AR can reduce the duration of NREM sleep by elevating these levels.[32] The mechanism by which AR contributes to OSA by influencing the NREM phase of sleep requires further investigation.

In this study, accurate PSG data were collected in a laboratory setting and the sample size was substantial. In addition, multiple AR SNPs were used to assess the correlation between genetic variants in AR and OSA. However, several limitations of our study should be addressed.[24] First, the study design did not include the collection of clinical diagnostic data for AR within our patient cohort. This limitation might impact the generalizability of our findings, as the severity and specific characteristics of AR may influence the correlations with sleep-breathing parameters. Second, the SNPs were identified in European, not in East Asian populations, due to a lack of GWASs in the latter, particularly in the Chinese population. Third, because our study was cross-sectional, it was not possible to establish a causal relationship between AR SNPs and OSA. Fourth, other types of mutations were not considered, including but not limited to point mutations, mutations affecting splice sites, and chromosomal translocations, insertions, and deletions. In addition, we did not take into account other intricate environmental factors such as socioeconomic status, physical activity, lifestyle, and educational level. However, we did attempt to create a diverse sample population by selecting subjects with similar lifestyles and ethnic backgrounds, and controlling for confounding factors such as age, BMI, smoking status, and alcohol consumption. Despite these constraints, we investigated the possible correlation between genes linked with AR vulnerability and OSA. The mechanisms underlying the relationship between AR and OSA require further investigation.

Conclusion

Several AR SNPs are associated with sleep- and breathing-related parameters in individuals with OSA. This may provide a genetic explanation for the combined susceptibility to AR and OSA and thus guide the development of new therapies or interventions that target the genetic risk factors associated with OSA.

Ethics Approval and Consent to Participate

The Ethics Committee of Shanghai Jiao Tong University Affiliated with the Sixth People's Hospital approved this study according to Helsinki Declaration II. All participants provided informed consent before taking part in the study. The ethical approval number is 2019-KY-050(K).

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Author Contributions

All authors made a significant contribution to the work reported, including to the conception, study design, execution, acquisition of data, analysis and interpretation, or in all of these areas. They also took part in drafting, revising or critically reviewing the article, gave final approval of the version to be published, agreed on the journal to which the article has been submitted, and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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