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Authors: Chen H, Cade BE, Gleason KJ, Bjonnes AC, Stilp AM, Sofer T, Conomos MP, Ancoli-Israel S, Arens R, Azarbarzin A, Bell GI, Below JE, Chun S, Evans DS, Ewert R, Frazier-Wood AC, Gharib SA, Haba-Rubio J, Hagen EW, Heinzer R, Hillman DR, Johnson WC, Kutalik Z, Lane JM, Larkin EK, Lee SK, Liang J, Loredo JS, Mukherjee S, Palmer LJ, Papanicolaou GJ, Penzel T, Peppard PE, Post WS, Ramos AR, Rice K, Rotter JI, Sands SA, Shah NA, Shin C, Stone KL, Stubbe B, Sul JH, Tafti M, Taylor KD, Teumer A, Thornton TA, Tranah GJ, Wang C, Wang H, Warby SC, Wellman DA, Zee PC, Hanis CL, Laurie CC et al.

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Multi-Ethnic Meta-Analysis Identifies *RAI1* as a Possible Obstructive Sleep Apnea Related Quantitative Trait Locus in Men

Han Chen[1,2,3*], Brian E. Cade[4,5,*], Kevin J. Gleason[4,6], Andrew C. Bjonnes[7,8], Adrienne M. Stilp[9], Tamar Sofer[4,5,9], Matthew P. Conomos[9], Sonia Ancoli-Israel[10], Raanan Arens[11], Ali Azarbarzin[4,5], Graeme I. Bell[12], Jennifer E. Below[2,13], Sung Chun[7,14], Daniel S. Evans[15], Ralf Ewert[16], Alexis C. Frazier-Wood[17], Sina A. Gharib[18], José Haba-Rubio[19], Erika W. Hagen[20], Raphael Heinzer[19], David R. Hillman[21], W. Craig Johnson[9], Zoltan Kutalik[22,23], Jacqueline M. Lane[4,5,8,24], Emma K. Larkin[25], Seung Ku Lee[26], Jingjing Liang[27], Jose S. Loredo[28], Sutapa Mukherjee[29], Lyle J. Palmer[30], George J. Papanicolaou[31], Thomas Penzel[32], Paul E. Peppard[20], Wendy S. Post[33], Alberto R. Ramos[34], Ken Rice[9], Jerome I. Rotter[35], Scott A. Sands[4,5], Neomi A. Shah[36], Chol Shin[37], Katie L. Stone[15], Beate Stubbe[16], Jae -Hoon Sul[7,14,38], Mehdi Tafti[19,39], Kent D. Taylor[35], Alexander Teumer[40], Timothy A. Thornton[9], Gregory J. Tranah[15], Chaolong Wang[1,41], Heming Wang[4,5,27], Simon C. Warby[42], D. Andrew Wellman[4,5], Phyllis C. Zee[43], Craig L. Hanis[2], Cathy C. Laurie[9], Daniel J. Gottlieb[4,5,44], Sanjay R. Patel[45], Xiaofeng Zhu[27], Shamil R. Sunyaev[7,14,24,46], Richa Saxena[4,5,8,24], Xihong Lin[1], Susan Redline[4,5,47]

Affiliations:

[1] Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA

[2] Human Genetics Center, Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, The University of Texas Health Science Center at Houston, Houston, TX 77030, USA

[3] Center for Precision Health, School of Public Health & School of Biomedical Informatics, The University of Texas Health Science Center at Houston, Houston, TX 77030, USA

[4] Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Boston, MA 02115, USA

[5] Division of Sleep Medicine, Harvard Medical School, Boston, MA 02115, USA

[6] Department of Public Health Sciences, University of Chicago, Chicago, IL 60637, USA

[7] Division of Genetics, Brigham and Women's Hospital, Boston, MA 02115, MA

[8] Center for Genomic Medicine and Department of Anesthesia, Pain, and Critical Care Medicine, Massachusetts General Hospital, Boston, MA 02114, USA

[9] Department of Biostatistics, University of Washington, Seattle, WA 98195, USA

[10] Departments of Medicine and Psychiatry, University of California, San Diego, CA 92093, USA

[11] The Children's Hospital at Montefiore, Division of Respiratory and Sleep Medicine, Albert Einstein College of Medicine, Bronx, NY 10467, USA

[12] Section of Adult and Pediatric Endocrinology, Diabetes, and Metabolism, The University of Chicago, Chicago, IL 60637, USA

[13] Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN 37232, USA

[14] Division of Medical Sciences, Harvard Medical School, Boston, MA 02115, USA

[15] California Pacific Medical Center Research Institute, San Francisco, CA 94107, USA

[16] Internal Medicine B, University Medicine Greifswald, Greifswald, Germany

[17] Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX 77030, USA

[18] Computational Medicine Core, Center for Lung Biology, UW Medicine Sleep Center, Division of Pulmonary, Critical Care, and Sleep Medicine, University of Washington, Seattle, WA 98195, USA

[19] Center of Investigation and Research on Sleep, Lausanne University Hospital, BH 06, 1011 Lausanne, Switzerland

[20] Department of Population Health Sciences, University of Wisconsin, Madison, WI 53726, USA

[21] Department of Pulmonary Physiology and Sleep Medicine, Sir Charles Gairdner Hospital, Perth, Western Australia 6009, Australia

[22] Institute of Social and Preventive Medicine, University Hospital of Lausanne, Lausanne 1010, Switzerland

[23] Swiss Institute of Bioinformatics, Lausanne, Switzerland

[24] Program in Medical and Population Genetics, Broad Institute, Cambridge, MA 02142, USA

[25] Department of Medicine, Division of Allergy, Pulmonary and Critical Care, Vanderbilt University Medical Center, Nashville, TN 37232, USA

[26] Institute of Human Genomic Study, College of Medicine, Korea University Ansan Hospital, 123, Jeokgum-ro, Danwon-gu, Ansan-si, Gyeonggi-Do, 15355, Republic of Korea

[27] Department of Epidemiology and Biostatistics, School of Medicine, Case Western Reserve University, Cleveland, OH 44106, USA

[28] Division of Pulmonary Critical Care and Sleep Medicine, Department of Medicine, UC San Diego School of Medicine, La Jolla, CA 92093, USA

[29] Adelaide Institute for Sleep Health, Flinders Centre of Research Excellence, Flinders University, Adelaide, South Australia 5041, Australia

[30] School of Public Health, University of Adelaide, Adelaide, South Australia 5000, Australia

[31] Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Bethesda, MD 20892, USA

[32] University Hospital Charité Berlin, Sleep Center, Berlin, Germany

[33] Division of Cardiology, Johns Hopkins University, Baltimore, MD 21287, USA

[34] Department of Neurology, University of Miami Miller School of Medicine, Miami, FL 33136, USA

[35] Institute for Translational Genomics and Population Sciences, Los Angeles BioMedical Research Institute and Department of Pediatrics at Harbor-UCLA Medical Center, Torrance, CA 90502, USA

[36] Division of Pulmonary, Critical Care and Sleep, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

[37] Department of Pulmonary, Sleep and Critical Care Medicine, College of Medicine, Korea University Ansan Hospital, 123, Jeokgum-ro, Danwon-gu, Ansan-si, Gyeonggi-do, 15355, Republic of Korea

[38] Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, CA 90095, USA

[39] Department of Physiology, Faculty of Biology and Medicine, University of Lausanne, 1005 Lausanne, Switzerland

[40] Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany

[41] Computational and Systems Biology, Genome Institute of Singapore, 138672, Singapore

[42] Department of Psychiatry, University of Montréal, Montréal, QC H3T 1J4, Canada

[43] Department of Neurology and Sleep Medicine Center, Northwestern University, Chicago, IL 60611, USA

[44] VA Boston Healthcare System, Boston, MA 02132, USA

[45] Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA 15213, USA

[46] Department of Biomedical Informatics, Harvard Medical School, Boston, MA 02115, USA

[47] Division of Pulmonary, Critical Care, and Sleep Medicine, Beth Israel Deaconess Medical Center, Boston, MA 02215, USA

[*] Equal contribution

Correspondence:

Han Chen, PhD

Human Genetics Center

Department of Epidemiology, Human Genetics and Environmental Sciences

Center for Precision Health

School of Public Health

School of Biomedical Informatics

The University of Texas Health Science Center at Houston

1200 Pressler St, RAS E-517, Houston, TX 77030, USA

Email: Han.Chen.2@uth.tmc.edu

Author Contributions:

H.C., B.E.C., K.J.G., A.C.B., A.M.S., T.S., M.P.C., A.A., G.I.B., J.E.B., S.C., D.S.E., R.E., A.C.F-W., S.A.G., J.H-R., E.W.H., R.H., D.R.H., W.C.J., Z.K., J.M.L., E.K.L., S.K.L., J.L., S.M., L.J.P., G.J.P., W.S.P., A.R.R., K.R., J.I.R., S.A.S., N.A.S., B.S., J.H.S., K.D.T., A.T., T.A.T., C.W., H.W., S.C.W., D.J.G. and S.R. participated in data acquisition, analysis of data; S.A-I., R.A., J.S.L., L.J.P., T.P., P.E.P., C.S., K.L.S., M.T., G.J.T., D.A.W., P.C.Z., C.L.H., C.C.L., D.J.G., S.R.P., X.Z., S.R.S., R.S., X.L. and S.R. participated in study conception and design; all authors participated in interpretation of analysis results, manuscript drafting, and manuscript editing for intellectual content.

Abstract

Obstructive sleep apnea (OSA) is a common heritable disorder displaying marked sexual dimorphism in disease prevalence and progression. Previous genetic association studies have identified a few genetic loci associated with OSA and related quantitative traits, but they have only focused on single ethnic groups and a large proportion of the heritability remains unexplained. The apnea hypopnea index (AHI) is a commonly used quantitative measure characterizing OSA severity. Since OSA differs by sex, and the pathophysiology of obstructive events differ in rapid eye movement (REM) and non-REM (NREM) sleep, we hypothesized that additional genetic association signals would be identified by analyzing the NREM/REM-specific AHI and by conducting sex-specific analyses in multi-ethnic samples. We performed genome-wide association tests for up to 19,733 participants of African-, Asian-, European-, and Hispanic/Latino-American ancestry in seven studies. We identified rs12936587 on chromosome 17 as a possible quantitative trait locus for NREM AHI in men (N = 6,737; $P = 1.7 \times 10^{-8}$), but not in women ($P = 0.77$). The association with NREM AHI was replicated in a physiological research study (N = 67; $P = 0.047$). This locus overlapping the *RAI1* gene and encompassing genes *PEMT1, SREBF1* and *RASD1*, was previously reported to be associated with coronary artery disease, lipid metabolism, and implicated in Potocki-Lupski Syndrome and Smith-Magenis Syndrome, which are characterized by abnormal sleep phenotypes. We also identified gene-by-sex interactions in suggestive association regions, suggesting that genetic variants for AHI appear to vary by sex, consistent with the clinical observations of strong sexual dimorphism.

Keywords: obstructive sleep apnea, genetics, genome-wide association studies, multi-ethnic, sexual dimorphism.

Introduction

Obstructive Sleep Apnea (OSA) is a complex chronic condition that affects more than 10% of the population, and is associated with cardio-metabolic and behavioral morbidity (1-3). The prevalence of OSA is particularly high in minority racial/ethnic groups such as those with African-, Asian- and Hispanic ancestry (4-7). Moreover, OSA is approximately 3-fold more prevalent in men as compared to women (8). In women, OSA severity is less likely to worsen in the supine compared to other sleeping positions (9) and more likely to worsen in rapid eye movement (REM) sleep, when neuromuscular tone and chemoreflexes are reduced (9, 10). These differences have been attributable to sex differences in airway-collapsibility, related to both differences in anatomy and respiratory chemosensitivity (11). An increase in OSA severity in women after menopause also suggests a role for sex hormones in influencing this disorder (12).

The severity of OSA is most often characterized by the apnea hypopnea index (AHI), defined as the number of apnea and hypopnea events per hour of sleep. AHI levels are highly heritable in African-Americans and European-Americans, with 30 to 40% of the variance explained by genetic factors (13, 14). Previous genetic studies have identified several genetic variants associated with AHI, although these findings were based on modest sample sizes or single ethnic groups, and largely have not been replicated across populations (15-18).

Large-scale genome-wide association studies (GWAS) have identified sexual dimorphism in genetic loci for traits associated with OSA, such as body fat distribution, particularly waist circumference and waist-to-hip ratio, each adjusted for body mass index (BMI) (19, 20). Furthermore, measures of adiposity such as waist phenotypes have been shown to be regulated

by sexually dimorphic genes (19, 21). Animal models suggest that both gonadal hormones and X chromosome dose influence lipid levels (22). Despite strong clinical and epidemiological evidence for sex differences in OSA, prior genetic association studies were not sufficiently powered to study consistent sex differences in OSA in multi-ethnic samples (15-17).

We conducted genome-wide association studies in multi-ethnic samples from 7 cohorts to identify genetic variants with sex-specific association for AHI. Given differences in the physiological bases for OSA in REM and non-REM sleep (23), we performed analyses for AHI calculated for each sleep state (REM; non-REM). Although BMI is a significant risk factor for OSA, only 40% of the genetic variance for OSA is shared with BMI (14).Therefore, we adjusted for BMI in order to discover genetic loci acting independently of BMI, which may provide insights into novel etiological mechanisms. We focused on association signals that show concordant direction of effects across African-, Asian-, Hispanic/Latino- and European-Americans through BMI-independent pathways.

Materials and Methods

Study Subjects

We included seven cohorts in the discovery analyses: the Atherosclerosis Risk in Communities Study (ARIC, n=1,463 European-Americans), the Cleveland Family Study (CFS, n=731 African-Americans and 702 European-Americans), the Framingham Heart Study (FHS, n=646 European-Americans), the Hispanic Community Health Study / Study of Latinos (HCHS/SOL, n=11,317 Hispanic/Latino-Americans), the Multi-Ethnic Study of Atherosclerosis (MESA, n=490 African-Americans, 228 Asian-Americans, 707 European-Americans, and 458 Hispanic/Latino-

Americans), the Osteoporotic Fractures in Men Study (MrOS, n=2,209 European-Americans), and the Starr County Health Studies (Starr, n=782 Hispanic/Latino-Americans) (Table 1). An additional six cohort studies and data from one physiological research study were analyzed to examine for generalizability across samples. Details about the study subjects are provided in the online supplement.

Phenotypes and Covariates

OSA was quantified using the AHI, defined as the number of episodes of complete (apnea) or partial (hypopnea) cessations of airflow per hour of sleep (or recording time). In this study, sleep data from all seven discovery studies were scored in our Sleep Reading Center. Details of the sleep testing and scoring procedures for each cohort are provided in the online supplement. The primary phenotype was the AHI calculated across the total sleep (or recording) period (AHI-Total; AHI-T). All studies used a hypopnea definition that required a $\geq$ 3% event-related desaturation. Covariates include age, sex and BMI. AHI measured during REM (AHI-R) and non-REM (AHI-N) sleep periods also were analyzed where available (ARIC, CFS, FHS, MESA and MrOS).

Genotyping and Quality Control

Study participants in ARIC, MESA, and Starr County were genotyped using the Affymetrix 6.0 array; CFS participants were genotyped using the Illumina OmniExpress, Affymetrix 6.0 and the ITMAT-Broad-CARe (IBC) (24) arrays; FHS participants were genotyped using the Affymetrix 500K mapping array and Illumina Omni5 array; HCHS/SOL participants were genotyped using the Illumina Omni 2.5M array with custom content; and MrOS participants were genotyped

using the Illumina Omni 1M array. Data from CFS, FHS, MESA, MrOS and Starr were phased using SHAPEIT (25) and imputed using IMPUTE2 (26) and a 1000 Genomes Project Phase 3 background (version 5, all populations, which contains haplotypes on 2,504 samples for a total of about 81.2 million polymorphic markers); ARIC and HCHS/SOL were imputed using a 1000 Genomes Project Phase 1 background. Single nucleotide polymorphism (SNP) strands were checked in Ensembl and with 1000 Genomes data in SHAPEIT. SNPs with an IMPUTE2 Info score less than 0.88, or a minor allele frequency less than 1% in each study cohort were excluded from analyses.

Statistical Analysis

Rank normalized age and sex-adjusted residuals were analyzed using linear mixed models with a genetic relatedness matrix (GRM) in GEMMA (27) to control for population stratification and relatedness, adjusting for BMI and BMI^2. Multi-ethnic meta-analyses were performed using the inverse variance weighted fixed-effects approach in METAL (28). Details on statistical analysis are provided in the online supplement.

Results

Demographics

Key characteristics of each cohort were presented in Table 1, with additional details in the online supplement. Across the seven distinct cohorts, data were available for 19,733 individuals, including 10,113 women. Participants were on average middle-aged to elderly and are overweight to obese. The proportion with moderate to severe sleep apnea (AHI ≥ 15 events per hour) ranged from 11.7% to 54.8%. In general, the AHI varied with the mean age of the cohort

(higher in the older cohorts). Overall, the sample ancestry was 29.0% European, 6.2% African, 63.6% Hispanic and 1.2% Asian.

Sex-Combined and Sex-Stratified Analyses

The top results of the multi-ethnic meta-analyses were shown in Table 2. In sex-combined results, eight loci showed suggestive association ($P < 1.0 \times 10^{-6}$) with AHI-T, five loci with AHI-N, and two loci with AHI-R. These regions included rs146579140, where variation was associated with AHI-N at an almost significant level ($P = 8.8 \times 10^{-8}$). In sex-stratified results, six loci showed suggestive association with AHI-T, three loci with AHI-N, and three loci with AHI-R in women; eleven loci showed suggestive association with AHI-T, three loci with AHI-N, and two loci with AHI-R in men. In addition, there was one locus significantly associated with AHI-N in men on chromosome 17 (Figure 1), with a lead SNP rs12936587 ($P = 1.7 \times 10^{-8}$). This locus overlapped with the gene *RAI1* (Figure 1C), which codes retinoic acid induced 1 that has been implicated in Smith-Magenis Syndrome (SMS)(29). This lead SNP also showed suggestive association with AHI-N in sex-combined analysis, although the findings reflected associations in men and not women. Figure 2 showed that compared to men with a homozygous genotype of the ancestral allele (A), men with more risk alleles (G) had a higher age- and BMI-adjusted AHI-N on average, but there was no such pattern in women.

Gene-by-Sex Interaction

We performed gene-by-sex interaction analyses for top loci in Table 2 and identified thirteen gene-sex interactions in multi-ethnic meta-analyses, after Bonferroni correction to control for family-wise significance level of 0.05. Of these thirteen gene-sex interactions, twelve had

significant or suggestive association in men but not in women (including rs12936587 with AHI-N; interaction $P = 2.6 \times 10^{-5}$), and one had suggestive association in sex-combined results but neither in men nor in women (although the *P* value in men was still several orders of magnitude lower than in women). These results suggested there might be different genetic mechanisms for obstructive sleep apnea in women and men.

Expression Quantitative Trait Loci Databases

We examined our most significant SNPs in the *RAI1* region (NCBI build 37 locations: chr17:17531709-17644364; $P < 1 \times 10^{-7}$) in expression quantitative trait loci (eQTLs) databases that associate SNPs with gene expression in specific cell lines and tissues (Table E1). Five of the eight genes associated with the *RAI1* locus SNPs had minimum eQTL $P < 1 \times 10^{-6}$: *PEMT* (whole blood $P = 2.1 \times 10^{-20}$), *SREBF1* (whole blood $P = 5.0 \times 10^{-20}$), *RASD1* (monocyte $P = 6.8 \times 10^{-12}$), *RAI1* (lymphoblastoid $P = 3.4 \times 10^{-7}$), and *TOM1L2* (pituitary $P = 9.4 \times 10^{-7}$).

Assessment of Generalizability in Independent Samples

In summary data provided by replication cohort studies (Table E2), we found no evidence for association with AHI-N for *RAI1* in men ($P = 0.34$). However, a consistent direction of association was found in the Cardiovascular Health Study (CHS), the only replication cohort in which sleep studies were scored by the same Sleep Reading Center that scored data in the discovery cohorts.

We replicated the association with rs12936587 in an independent physiological research study of 67 individuals (70% male) (Table E3) studied with in-laboratory polysomnography for the

purposes of elucidating the physiology of OSA. Details about the study subjects are provided in the online supplement. The sample included 55 patients with moderate to severe OSA without other significant co-morbidities and 12 healthy controls. In this well phenotyped sample, after adjusting for age, sex and BMI, the risk G allele of rs12936587 was associated with increasing AHI-N ($P = 0.047$). The association was stronger when we restricted the analysis to AHI-N in the supine position ($P = 0.017$), when airway collapsibility is high.

Discussion

To our knowledge, this is the largest genome-wide analysis of AHI and the only multi-ethnic sex-specific AHI meta-analysis to date. It is also the first human genetic epidemiological study that has examined AHI in REM- and non-REM sleep. Analyses of rigorously collected quantitative sleep data and genome-wide genotype data identified several novel genetic regions with at least suggestive association evidence with each AHI measure. The most significant findings emerged from sex-specific and sleep state-specific analyses. Across all cohorts and race/ethnic groups, the most significant finding was for an association between a locus in *RAI1* in men for AHI measured in Non-REM sleep. Our results identify several biologically-plausible candidates for future functional studies, and highlight genetic variants that may specifically influence OSA propensity in REM vs non-REM sleep, which may have different associations in men and women. The finding of multiple significant gene-by-sex interactions further provides statistical evidence of distinct genetic mechanisms influencing OSA in men and women.

RAI1 is a promising candidate gene for OSA. It encodes a protein that is highly expressed in neuronal tissues and is involved in early neural differentiation and transcriptional regulation of

circadian clock components. Haploinsufficiency of the *RAI1* gene has been implicated in Smith Magenis Syndrome (SMS) (29), a complex neurobehavioral disorder that is characterized by multiple craniofacial abnormalities, sleep disturbances, and obesity (30). The craniofacial features include a brachycephalic head form and mid face hypoplasia, which are anatomic risk factors for OSA (30, 31). A majority of individuals with SMS have significant sleep difficulties and disturbed sleep architecture and circadian rhythms (32) and excessive daytime sleepiness. Speech abnormalities, a hoarse voice, and airway hypotonia are also reported (33), suggesting a role of *RAI1* in influencing upper airway function. Abnormalities in *RAI1* also have been implicated in Potocki-Lupski Syndrome (PTLS) (34-36). PTLS patients often have developmental delay and mild dysmorphic facial features (34, 35), and can exhibit multiple neurological and cardiovascular abnormalities. Eight of the nine patients with PTLS in the initial study displayed central and/or obstructive sleep apnea (36). Both SMS and PTLS appear to involve the *RAI1* gene on the short arm of chromosome 17 (37). A de novo *RAI1* mutation has been reported in a boy with rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation. The individual displayed an AHI of 10 at age 5 and 27 at age 8, hypercholesterolemia, and macrocephaly (38). In mice, *Rai1* haploinsufficiency is associated with hyperphagia and obesity and abnormal expression of multiple genes in the hypothalamus, including *BNDF* (associated with behavioral and psychiatric morbidities) and *WNT9B* (associated with midfacial development) (39). Although the authors suggested the value in further investigating the role of *RAI1* in growth, adiposity and behavior, our results also suggest value in considering sleep apnea as a relevant *RAI1* phenotype.

RAI1 and other genes in the locus may be involved in OSA etiology. Multiple SNPs in the locus overlap epigenetic and/or expression quantitative trait loci (eQTL) evidence that may indicate

regulatory effects. The SNP rs12938840 ($P = 3.97 \times 10^{-7}$) overlaps enhancer regions in 127 Roadmap Epigenomics and ENCODE cell lines and in a further 129 samples of brain regions (40-43). Lead SNPs are associated with expression of five genes (minimum eQTL $P < 1 \times 10^{-6}$; Table E1), including *PEMT*, *SREBF1*, *RAI1*, and *RASD1* (44-47). *SREBF1* (formerly *SREBP1*), an important cholesterol biosynthesis regulator, is activated in mice subjected to intermittent hypoxia, leading to hyperlipidemia (48). Activation of *Srebf1* in mouse type 2 alveolar cells leads to lipotoxicity, chronic pulmonary inflammation, and alveolar remodeling (49). *Pemt*, also involved with lipid metabolism, displays sex-specific effects in regulation of HDL and VLDL in mice (50). A waist-hip ratio GWAS association with rs4646404 at the *PEMT* locus was largely sex-specific (21). *RAI1* and *RASD1* (formerly *DEXRAS1*) regulate circadian rhythm (32, 51, 52). *Rai1* haploinsufficiency in mice leads to sex-specific differences in subcutaneous and abdominal fat distributions (39). The lead SNP rs12936587 (*RAI1*) is also significantly associated with coronary artery disease. A sex-stratified analysis indicated that this result was almost entirely due to an association in men (53), providing an exciting avenue for investigating sex differences in not only OSA but also in the association between OSA with coronary artery disease (reported to be stronger in men compared to women) (2). These results also support the importance of future assessment of pleiotropy, specifically the influence of genetic variants that influence both OSA and cardio-metabolic disease and other co-occurring traits.

There are several possible explanations for stronger associations between the *RAI1* locus and AHI-N in men compared to women. Men are more likely to have a higher AHI in non-REM sleep than women (9), which has been attributed to poorer neuromuscular compensatory mechanisms. Thus, genetic variants that further reduce airway patency or ventilatory stability in

sleep may have stronger effects in men due to underlying anatomic or physiological risk factors. Conversely, factors that protect women in NREM sleep from recurrent apneas, such as sex hormone-mediated modulation of respiratory chemosensitivity in NREM sleep, may attenuate effects of some genetic variants. It is also possible that sex steroids interact with genetic variants in *RAI1* to differentially affect the development of the brain or craniofacial structures, or otherwise interact with genes regulated by sex hormones. *RAI1* is upregulated by retinoic acid, which can interact with sex steroids. In the western mosquitofish, *Gambusia affinis*, retinoic acid controls sex-specific development of motor neurons within the spinal cord (54). Furthermore, it has been reported that male *Rai1*-transgenic mice are more growth retarded than are female transgenic mice (55). *Rai1* haploinsufficiency in mice leads to sex-specific differences in adiposity, with greater abdominal fat in females compared to males (39).

This study has several strengths, including the rigorous phenotyping for all discovery cohorts by a central Sleep Reading Center of the sleep studies to ensure high degrees of quality control. Participants in 5 of the 7 cohorts were studied using almost identical equipment and scoring techniques. Consistency of findings for our most significant finding was observed across the 5 distinct discovery cohorts with available data on NREM AHI as well as across all ethnic/racial groups, even when using data from alternative sleep apnea testing devices. The inclusion of multiple ethnic/race groups allowed leveraging different LD structures across populations to identify genetic variants consistently associated with the phenotypes across multiple ethnic/race groups. Genome-wide genotype data were available for the largest sample with OSA phenotypes to date.

The AHI was defined using standard approaches that are used commonly, are reproducible, and show heritability. Hypopneas minimally required a ≥ 3% oxyhemoglobin desaturation. Although AHI levels are highly correlated regardless of hypopnea definition (56), it is possible that associations may have varied because of use of different measurement approaches. The strongest findings for the NREM AHI may not only reflect the specificity of this phenotype, but also the greater accuracy of AHI measures scored from polysomnograms that include electroencephalography recording. The power for replication was limited due to modest sample size (particularly for stage-specific results), although associations in the CHS European-Americans, which had undergone identical phenotyping as several of the discovery cohorts, provided evidence consistent with the discovery finding in the *RAI1* region. In addition, in an independent in-laboratory physiological research study of carefully phenotyped individuals that explicitly recruited known cases of OSA without other significant co-morbidities, the association with NREM AHI in the *RAI1* region was replicated in sex-combined analysis. This sample, however, was too small to test for sex-specific differences in associations. Although this observation needs to be cautiously interpreted, it is of interest that the strongest finding was for AHI in NREM sleep in the supine position. Men have a significantly higher proportion of apneas in NREM sleep than women, likely due to the occurrence of greater breathing instability in NREM sleep in men compared to women. Men also have more severe sleep apnea in the supine compared to non-supine position, attributed to the effects of positional-dependent airway collapsibility. In contrast, women show a REM-predominant pattern and less positional dependency (57). In other words, the lead SNP associated most strongly with a phenotype subtype most characteristic of "male" sleep apnea. The lack of significant association for this phenotype in our sex-combined discovery sample may reflect differences in the spectrum of

sleep apnea in the physiological study compared to the predominant community-based samples, where sleep apnea in women tends to be mild.

Our study, while identifying novel genetic pathways that may influence OSA, was not designed to identify specific mechanisms. In particular, we were not able to assess to what extent the genetic associations with AHI could be explained by craniofacial features, differences in body fat distribution (particularly, neck circumference) or physiological traits due to lack of information on specific intermediate phenotypes in most of the study samples.

In conclusion, we have identified from multi-ethnic meta-analyses several interesting biological candidates for sex-specific and sleep state-specific associations with AHI, the most widely used clinical measure for OSA. The approach underscores the value of sex-specific analyses in a trait such as OSA, for which there are significant differences in presentation and pathogenesis between men and women. It is widely recognized that the overall AHI likely reflects a heterogeneous set of phenotypes. The analysis of sleep state-specific (REM; Non-REM) findings allowed assessment of more specific OSA phenotypes (i.e., operating in the background of different levels of neuromuscular control) than the overall AHI. Further investigation of the *RAI1* regional association is particularly promising given its role in at least three congenital syndromes associated with sleep abnormalities and its influence on metabolic and physiological traits closely associated with OSA. However, future large-scale studies are warranted for replication and refinement of signals. These studies could lead to important insights into the underlying pathogenesis of the disorder, resulting in targeted treatments, as well as inform screening and risk

stratification. Additional insights into the genetic bases for OSA may be gleaned from further detailed phenotyping, including assessments of neuromuscular control of the airway.

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Figures

Figure 1. Manhattan, quantile-quantile (Q-Q), and regional association plots of multi-ethnic meta-analysis results for AHI-N in men. A) The Manhattan plot shows minus log 10 p-values against genomic coordinates (NCBI build 37), and consecutive chromosomes were colored in black and grey alternately; B) The Q-Q plot shows observed minus log 10 p-values against expected values under no association; C) The regional association plot of multi-ethnic meta-analysis results for AHI-N in men near the *RAI1* gene on chromosome 17.

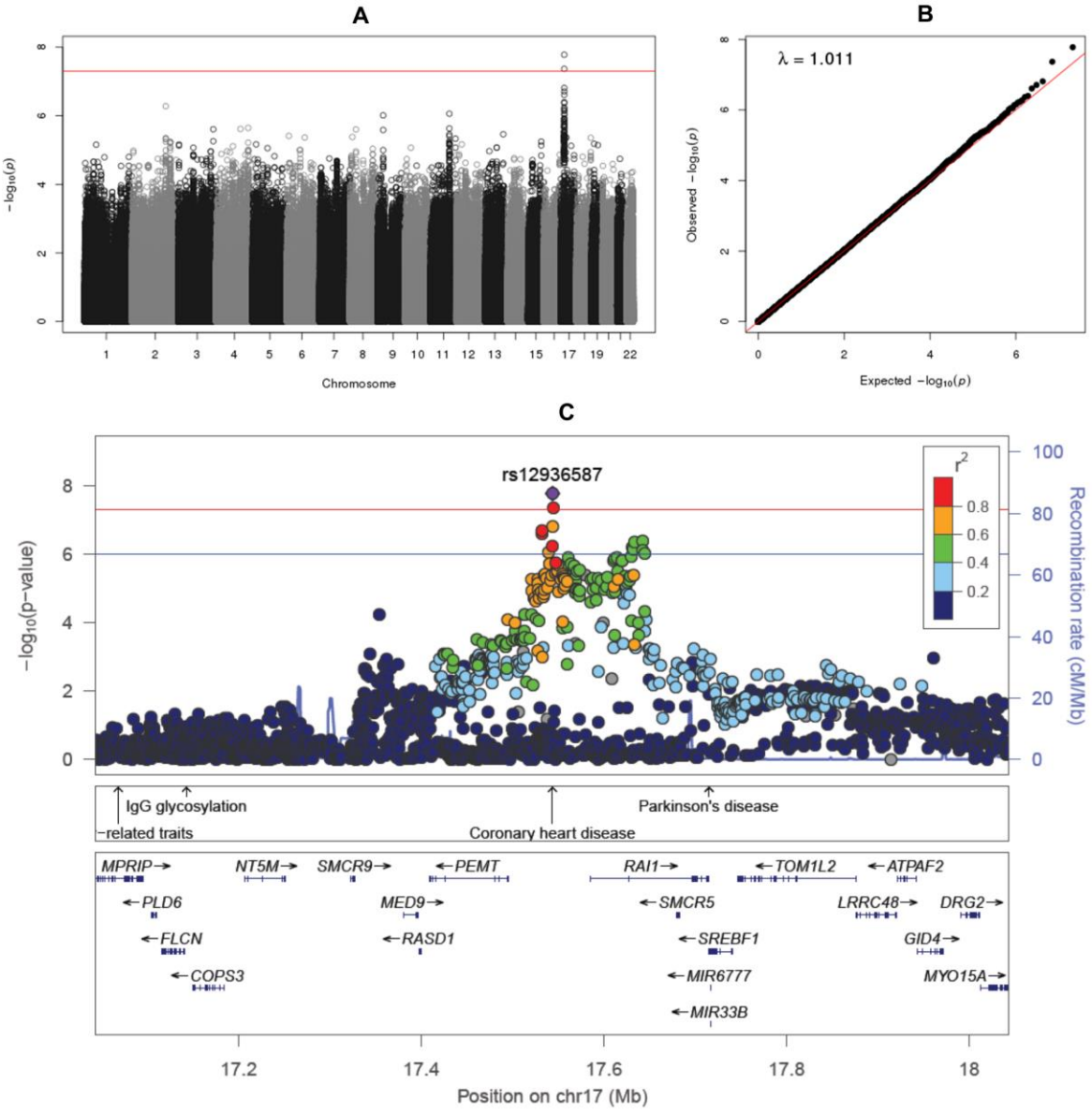
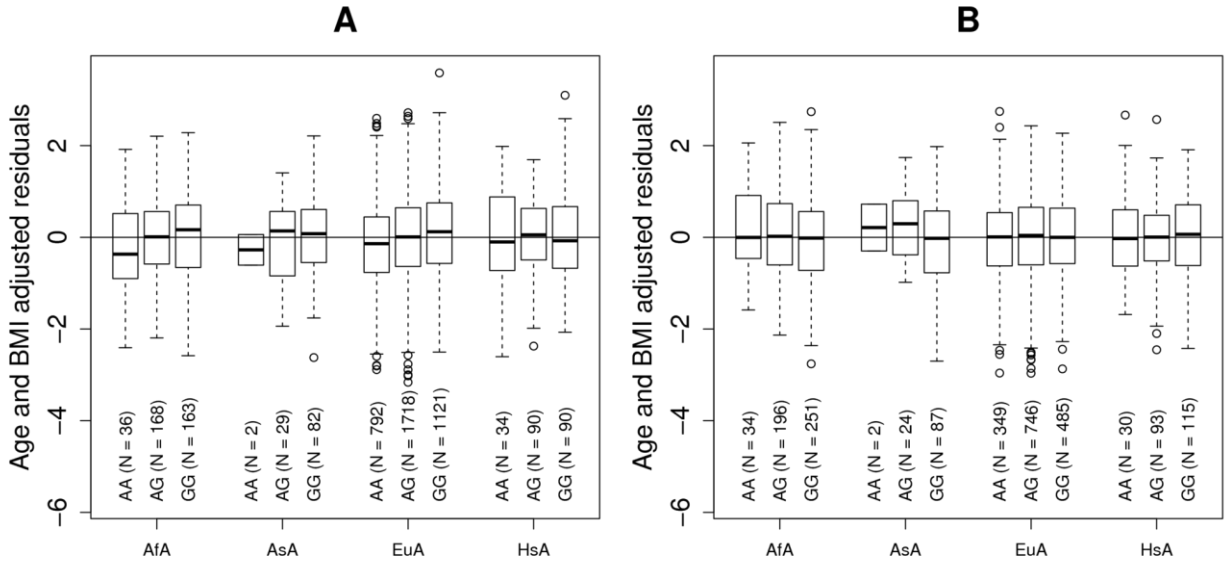


Figure 2. Sex differences in the distribution of BMI and BMI^2 adjusted residuals for study subjects with different genotypes (AA, AG, and GG) of rs12936587. The phenotype is rank normalized sex-stratified residuals of AHI-N adjusting for age, age^2. A) Men; B) Women. AfA: African-Americans; AsA: Asian-Americans; EuA: European-Americans; HsA: Hispanic/Latino-Americans.



Tables

Table 1. Sample description of study subjects in discovery cohorts.

Ethnic Group	Cohort	N	Age (years)	Percent Female	BMI (kg/m^2)	Apnea Hypopnea Index	Percent OSA	AHI-N	AHI-R	AHI-R/ AHI-N
African-Americans	CFS*	731	37.84 (19.44)	56.2	31.63 (9.69)	5.85 (19.70)	31.7	2.47 (12.19)	9.23 (30.87)	2.89 (8.70)
	MESA	490	69.13 (9.10)	54.3	30.42 (5.71)	13.34 (21.16)	46.5	8.64 (20.1)	30.97 (39.83)	2.64 (5.09)
Asian-Americans	MESA	228	68.13 (9.19)	50.4	24.08 (3.19)	13.97 (23.90)	47.4	11.61 (24.31)	21.77 (34.19)	1.68 (2.64)
European-Americans	ARIC	1,463	62.43 (5.69)	51.5	28.83 (5.13)	8.70 (15.50)	32.5	5.75 (13.78)	16.46 (27.68)	2.58 (4.69)
	CFS*	702	41.59 (19.45)	52.7	30.24 (8.66)	5.59 (18.99)	31.1	2.07 (13.14)	7.06 (21.20)	2.28 (7.40)
	FHS*	646	59.38 (8.97)	50.0	28.49 (5.01)	8.18 (14.51)	30.0	5.25 (13.66)	15.25 (23.60)	2.48 (4.98)
	MESA	707	68.52 (9.10)	53.6	27.99 (5.21)	12.62 (20.67)	44.0	9.61 (20.45)	22.31 (30.65)	1.80 (2.97)
	MrOS	2,209	76.68 (5.66)	0.0	27.22 (3.74)	12.73 (18.11)	43.7	10.93 (19.58)	18.30 (24.17)	1.53 (2.42)
Hispanic/Latino-Americans	HCHS/SOL	11,317	46.17 (13.79)	59.1	29.79 (6.00)	1.97 (6.20)	11.7	NA	NA	NA

Ethnic Group	Cohort	N	Age (years)	Percent Female	BMI (kg/m^2)	Apnea Hypopnea Index	Percent OSA	AHI-N	AHI-R	AHI-R/ AHI-N
	MESA	458	68.34 (9.20)	52.8	30.07 (5.52)	16.94 (23.05)	54.8	12.16 (23.12)	30.00 (36.09)	2.13 (3.50)
	Starr	782	52.34 (11.29)	71.9	32.15 (6.78)	10.35 (17.18)	37.1	NA	NA	NA

Seven studies included 19,733 individuals with genotypes and phenotypes (1,221 African-Americans; 228 Asian-Americans; 5,727 European-Americans; 12,557 Hispanic/Latino-Americans). NREM- and REM-specific data are only available in a sample of the CFS data and were not collected in HCHS/SOL and Starr County. Mean (standard deviation) are listed for Age and BMI, and median (interquartile range) are listed for Apnea Hypopnea Index, AHI-N, AHI-R, and AHI-R/AHI-N. OSA: obstructive sleep apnea, defined as Apnea Hypopnea Index ≥ 15. AHI-N: NREM-specific Apnea Hypopnea Index. AHI-R: REM-specific Apnea Hypopnea Index. *: Family cohorts.

Table 2. Significant and suggestive multi-ethnic meta-analysis results for AHI (total), AHI-NREM, and AHI-REM.

					Sex-combined			Women			Men			Sex diff
Trait	SNP	Chr	Locus	Alleles	N	Effect	P	N	Effect	P	N	Effect	P	P
AHI-T	rs76321756	1		C/T	2,381	0.130	9.7×10^{-5}	1,289	-0.017	7.0×10^{-1}	1,092	0.244	2.3×10^{-7}	**2.7×10^{-6}**
AHI-T	rs11897825	2	AC011752.1; AC067959.1	G/A	15,364	0.026	2.2×10^{-2}	7.650	0.080	3.3×10^{-7}	7,714	-0.014	3.6×10^{-1}	2.8×10^{-3}
AHI-T	rs999944	2		G/A	19,733	0.072	9.7×10^{-7}	10,113	0.063	2.0×10^{-3}	9,620	0.077	2.6×10^{-4}	5.5×10^{-3}
AHI-T	rs35520189	2		C/A	19,733	0.052	6.1×10^{-7}	10,113	0.064	5.8×10^{-6}	9,620	0.042	5.3×10^{-3}	5.9×10^{-1}
AHI-T	rs72149316:AATAA	2	*SCN3A*	GATAA/	1,679	0.428	6.0×10^{-7}	919	0.326	3.7×10^{-3}	764	0.606	5.9×10^{-7}	2.3×10^{-3}

					Sex-combined			Women			Men			Sex diff
				AATAA										
AHI-T	rs34526934	2	HOXD-AS2;HOXD3;HOXD4;MIR10B	A/T	19,505	0.060	1.1×10^{-6}	9,998	0.024	1.7×10^{-1}	9,507	0.087	3.6×10^{-7}	1.8×10^{-3}
AHI-T	rs62189527	2	HDAC4	C/T	12,665	0.174	4.6×10^{-5}	7,384	0.067	2.3×10^{-1}	5,281	0.320	7.4×10^{-7}	**9.7×10^{-4}**
AHI-T	rs35001935:CGTGTGT	3	C3orf67;RP11-147N17.1	CGTGT/CGTGTGT	1,679	0.251	7.7×10^{-7}	919	0.091	1.9×10^{-1}	760	0.339	1.3×10^{-6}	**3.3×10^{-4}**
AHI-T	chr3:166153534:D	3		A/AAC	2.461	0.249	3.4×10^{-5}	1,481	0.376	6.1×10^{-7}	980	0.157	9.4×10^{-2}	3.2×10^{-1}
AHI-T	rs34188544	4		G/A	2,135	0.522	3.6×10^{-7}	1,264	0.333	1.4×10^{-2}	871	0.728	2.1×10^{-6}	8.2×10^{-3}
AHI-T	rs73352871	5		C/A	12,996	0.082	2.4×10^{-3}	7,610	-0.025	4.8×10^{-1}	5,386	0.203	5.9×10^{-7}	**2.2×10^{-6}**
AHI-T	rs79987021	7		T/C	12,265	0.256	6.2×10^{-7}	7,199	0.186	5.4×10^{-3}	5,066	0.316	7.7×10^{-5}	1.5×10^{-2}
AHI-T	rs117004340	8	DLC1	T/A	19,504	0.079	2.2×10^{-5}	9,997	-0.001	9.7×10^{-1}	9,507	0.136	1.8×10^{-7}	**9.2×10^{-4}**
AHI-T	rs3736021	8	*ENTPD4*	T/G	19,732	0.065	7.2×10^{-7}	10,112	0.057	1.1×10^{-3}	9,620	0.071	3.4×10^{-4}	1.1×10^{-1}
AHI-T	rs35857674	8	*SNTG1*	A/G	19,732	0.024	2.2×10^{-2}	10,112	0.070	7.9×10^{-7}	9,620	-0.016	2.8×10^{-1}	5.2×10^{-3}
AHI-T	rs117169866	10		G/A	18,512	0.150	5.6×10^{-7}	9,436	0.116	7.0×10^{-3}	9,396	0.158	1.1×10^{-4}	6.7×10^{-2}

					Sex-combined			Women			Men			Sex diff
AHI-T	rs1387259	12	RP11-370I10.2; *ZNF641*	A/G	19,733	0.052	2.3×10^{-6}	10,113	0.031	4.1×10^{-2}	9,620	0.078	3.7×10^{-7}	2.3×10^{-2}
AHI-T	rs9600832	13	NBEA	C/T	19,733	0.064	1.2×10^{-5}	10,113	0.012	5.4×10^{-1}	9,620	0.104	5.6×10^{-7}	**7.8×10^{-5}**
AHI-T	rs75900232	13		G/A	16,337	0.159	2.1×10^{-4}	8,942	-0.037	5.2×10^{-1}	8,199	0.307	6.5×10^{-7}	**4.9×10^{-5}**
AHI-T	rs115432071	16	C16orf62	T/A	12,996	0.197	8.5×10^{-6}	7,610	0.055	3.4×10^{-1}	5,386	0.346	3.0×10^{-7}	**1.6×10^{-4}**
AHI-T	rs4787347	16	*HS3ST4*	G/A	19,733	0.029	3.3×10^{-3}	10,113	0.067	7.2×10^{-7}	9,620	0.002	8.8×10^{-1}	1.9×10^{-1}
AHI-T	rs112190082	17	*STX8*	G/T	13,905	0.099	1.0×10^{-3}	8,188	0.200	3.6×10^{-7}	5,717	0.013	7.7×10^{-1}	3.4×10^{-2}
AHI-T	rs113724004	17		T/C	19,505	0.069	5.9×10^{-5}	9,998	0.020	4.0×10^{-1}	9,507	0.123	8.0×10^{-7}	**3.9×10^{-4}**
AHI-T	rs142002225	20		T/C	19,733	0.055	2.8×10^{-4}	10,113	0.108	3.2×10^{-7}	9,620	0.022	3.1×10^{-1}	3.4×10^{-1}
AHI-N	rs146579140	2		C/T	6,737	0.206	8.8×10^{-8}	2,412	0.092	1.6×10^{-1}	4,212	0.237	5.2×10^{-7}	1.3×10^{-2}
AHI-N	rs10474877	5	*ANKRD33B*	T/C	6,737	0.039	1.1×10^{-1}	2,412	0.203	2.1×10^{-7}	4,212	-0.015	6.2×10^{-1}	3.7×10^{-2}
AHI-N	rs73686127	7		A/T	1,300	0.508	2.6×10^{-7}	719	0.509	4.7×10^{-5}	367	0.464	4.6×10^{-3}	2.2×10^{-1}
AHI-N	rs10968431	9	LINGO2	G/A	1,300	0.239	5.3×10^{-4}	719	-0.030	7.5×10^{-1}	581	0.474	9.7×10^{-7}	**1.3×10^{-5}**
AHI-N	rs79697311	11		C/A	6,029	0.215	5.2×10^{-3}	1,295	0.719	6.9×10^{-7}	3,885	0.176	6.9×10^{-2}	4.2×10^{-1}
AHI-N	rs34174435	11	*OR5AN1*	GA/G	5,304	0.101	6.4×10^{-7}	1,673	0.105	4.4×10^{-3}	3,631	0.086	3.3×10^{-4}	1.1×10^{-1}

					Sex-combined			Women			Men			Sex diff
AHI-N	rs75482679	11	CNTN5	T/C	6,737	0.128	1.0×10^{-5}	2,412	-0.019	6.9×10^{-1}	4,325	0.176	8.7×10^{-7}	**1.3×10^{-4}**
AHI-N	rs72986876	11	*PDGFD*	A/T	6,511	0.223	7.8×10^{-7}	2,299	0.194	1.3×10^{-2}	4,212	0.217	7.9×10^{-5}	4.4×10^{-1}
AHI-N	rs116696666	16		A/T	1,300	0.290	1.6×10^{-3}	719	0.608	5.9×10^{-7}	581	0.136	3.1×10^{-1}	2.5×10^{-1}
AHI-N	rs12936587	17	RAI1	G/A	6,737	0.083	6.9×10^{-7}	2,412	-0.008	7.7×10^{-1}	4,325	0.116	**1.7×10^{-8}**	**2.6×10^{-5}**
AHI-R	chr1:74135031	1	RP4-788P17.1	A/T	1,546	0.310	9.8×10^{-7}	858	0.208	1.0×10^{-2}	688	0.403	5.2×10^{-5}	1.2×10^{-1}
AHI-R	rs72956768	4	TMEM154	G/T	1,290	0.254	6.4×10^{-4}	714	0.020	8.3×10^{-1}	576	0.563	5.2×10^{-7}	**1.5×10^{-4}**
AHI-R	rs35077018	7	*HUS1*; *PKD1L1*	G/GCTA GTGCGT GCATGA ACTAGT TGGTCT GCAAGT ACAAGA TGTATA AATATA CAGGG GAAAA AACATC	1,290	0.198	5.5×10^{-4}	714	0.357	8.2×10^{-7}	576	0.049	5.9×10^{-1}	3.4×10^{-2}
AHI-R	rs9297743	8	RP11-89K10.1	G/A	6,700	0.127	5.5×10^{-4}	2,400	-0.037	5.1×10^{-1}	4,300	0.241	9.2×10^{-7}	2.6×10^{-3}
AHI-R	rs79697311	11		C/A	5,998	0.173	1.8×10^{-2}	1,289	0.692	4.4×10^{-7}	3,867	0.068	4.7×10^{-1}	4.6×10^{-2}

					Sex-combined			Women			Men			Sex diff
AHI-R	rs201360344	12	*C12orf55*	G/GA	924	0.478	5.5×10^{-7}	498	0.516	3.2×10^{-5}	426	0.329	3.1×10^{-2}	4.1×10^{-1}
AHI-R	rs41408454	15		G/A	1,290	0.287	1.1×10^{-3}	714	0.523	8.8×10^{-7}	576	0.019	8.9×10^{-1}	1.2×10^{-2}

SNPs with significant ($p < 5.0 \times 10^{-8}$) and suggestive ($p < 1.0 \times 10^{-6}$) p-values. SNPs that were present in only one ethnic group were excluded. AHI-T: AHI (total). AHI-N: AHI during NREM. AHI-R: AHI during REM. Alleles: effect allele / non-effect allele.