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Genetic Influences on Snoring: A Narrative Review

Sun A Han, MD[1], Jeong-Whun Kim, MD, PhD[2]

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Korea
[2]Department of Otorhinolaryngology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea

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Corresponding Author
Jeong-Whun Kim, MD, PhD
Department of Otorhinolaryngology,
Seoul National University
Bundang Hospital,
Seoul National University
College of Medicine,
82 Gumi-ro 173beon-gil,
Bundang-gu, Seongnam 13620, Korea
Tel +82-31-787-7405
Fax +82-31-787-4057
E-mail kimemails7@gmail.com

ORCID iDs
Sun A Han
https://orcid.org/0000-0001-7646-8038
Jeong-Whun Kim
https://orcid.org/0000-0003-4858-3316

Snoring is a sound that results from vibrations of soft tissues in the narrowed upper airway during sleep. Obstructive sleep apnea (OSA) is a disease entity that must be properly treated. Snoring, which is also considered a symptom of the spectrum of sleep-related breathing disorders, is often overlooked. Although many studies have been conducted on genetic risk factors related to OSA, studies focusing on snoring are limited. Here, we reviewed the literature regarding the influence of genetics on snoring. Initial studies on the influence of genetics on snoring were based on twin and familial studies. Twin studies demonstrated that the phenotypic correlation of snoring between monozygotic twins was greater than that in dizygotic twins, while family history of snoring increases the risk of snoring. Genome-wide association studies showed that traits such as minimum SpO_2, umbilical hernia or anthropometric measures such as leg fat mass were genetically correlated to snoring. Traits were mapped and genes such as *DLEU7* and *MSRB3* have been identified. Snoring is not a disease that should be overlooked. Those with genetic factors increasing the risk of snoring should put more effort into controlling the modifiable risk factor related to snoring.
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Keywords Snoring; Genetics; Genetic predisposition; Genetic susceptibility.

INTRODUCTION

Snoring is a noise that results from the vibration of the soft tissue as air passes through the narrowed upper airway. According to the International Classification of Sleep Disorders–Third Edition (ICSD-3), snoring is categorized into "isolated symptoms and normal variants" of "sleep-related breathing disorders" [1]. Sleep-related breathing disorders include difficulty breathing during sleep, which encompasses upper airway dysfunction, including snoring and obstructive sleep apnea (OSA). The airway of patients with OSA collapses during sleep, and patients experience symptoms, such as daytime sleepiness, fatigue, and insomnia. According to the ICSD-3, OSA is diagnosed when the patient has sleep apnea symptoms or comorbidities, such as hypertension, diabetes mellitus, and coronary artery disease, and there are five or more obstructive respiratory events per hour on polysomnography or out-of-center sleep testing, or 15 or more events regardless of symptoms or comorbidities. Thus, simple snoring is distinguished from OSA by measuring the apnea–hypopnea index (AHI) and past medical history. Approximately 35%–45% of men and 15%–28% of women are habitual snorers, and 20%–40% also experience OSA [2]. As the most frequent symptom of OSA, up to 95% of patients with OSA snore [3]. Although habitual snoring can be a sign of OSA, it is also recognized as a precursor that progresses into OSA [4]. Some studies have suggested that snoring increases the risk of cardiovascular disease [5,6], whereas others have reported conflicting results [7,8]. As the first stage of sleep-disordered breathing [9] and a possible risk factor for cardiovascular disease, snoring is a symptom that should not be over-

looked. It is important to understand the possible genetic factors that may increase the risk of snoring. Although there are several studies on the genetics of OSA, studies on snoring are limited. We have reviewed the literature between 1990 and June 2023, and summarized the evidence on the genetic influence on snoring. The present narrative review aims to provide an overview while introducing recent findings on genes and traits genetically related to snoring.

GENETIC INFLUENCE AS ONE OF THE RISK FACTORS OF SNORING

Factors that are difficult to modify, such as sex, age, family history, ethnicity, and craniofacial morphology, some of which may be genetically influenced, have an effect on whether one snores. Modifiable factors, such as obesity, alcohol consumption, smoking, and nasal symptoms, are also risk factors for snoring. In previous studies, current smokers had a higher risk (odds ratio [OR], 2.29) of snoring compared to nonsmokers [10], and snoring was more prevalent in smokers and ex-smokers compared to never-smokers [11]. The risk of snoring increased in patients with nasal symptoms (OR, 1.38) even after adjusting for age, sex, and body mass index (BMI) [12] and when having allergic rhinitis (OR, 2.34) [13]. According to a previous meta-analysis, alcohol consumption, which worsens respiratory depression, had been shown to worsen snoring and OSA [14]. In a prior large cohort study, baseline BMI (OR, 1.4 per 3.4 kg/m^2) and change in BMI over time (OR, 1.55 per 2.3 kg/m^2) were associated with developing snoring [15].

GENETIC BASIS OF SNORING

The genetic basis of snoring is supported by the results that snoring is influenced by family history, sex, ethnicity, and craniofacial morphology, which are influenced by genetics. In a previous meta-analysis, the OR of snoring in men compared to women was 1.89 [16]. The prevalence of snoring has been reported to be different across various study populations [17]. In a study involving the National Health and Nutrition Examination Survey in the USA, snoring was more prevalent among other Hispanic/Latino respondents compared to other respondents [18]. Similarly, in a study investigating snoring and sleep-disordered breathing in young children, the ORs of snoring were greater for Black (OR, 2.5) and Hispanic children (OR, 2.3) than for White children [19]. Advancements in methods for genetic analysis, such as genome-wide association studies (GWAS) and next-generation sequencing, have deepened the understanding of the genetic influences on many aspects, including traits that may be related to snoring, such as obesity, craniofacial structures, and sleep-related traits. Although obesity is considered a modifiable risk factor, it is also largely influenced by genetics, such as its association with polymorphisms in the *FTO* gene [20]. GWAS have revealed the association between facial features, such as nose size and shape or midface height, and genome-wide significant loci [21,22]. In a recent multivariate GWAS meta-analysis, normal-range facial variations were associated with 203 genome-wide significant signals [23].

TWIN AND FAMILIAL STUDIES ON SNORING

Early studies that investigated the genetic factors of snoring and OSA explored the traits of twins and families. One of the first studies was a familial study conducted by Redline et al. [24] that compared 272 constituents from 29 families with OSA to 21 control families. In this study, the families completed surveys on their health behaviors. The unadjusted OR of snoring or apnea symptoms when a single relative had the same symptom was 1.40−1.53 ($p < 0.05$). Even after adjusting for BMI, age, and sex, the OR was 1.33−1.42. The OR increased with an increase in the number of relatives with the same symptoms. These results suggest familial aggregation of snoring and OSA.

Another familial study examined the family history of snoring in 487 children between the ages of 4 and 12 years [25]. A questionnaire regarding sleep habits and personal medical history was administered. In logistic regression analysis, snoring by a family member was a significant independent factor associated with habitual snoring ($\chi^2 = 5.1$, $p = 0.02$).

The first twin study published on snoring was in 1995 by Ferini-Strambi et al. [26] that compared snoring, past medical history, and lifestyle of 492 monozygotic twins (246 pairs) to 284 dizygotic (142 pairs) male twins aged between 30 and 60 years. Twins were defined as habitual snorers when they reported that they "always" or "almost always" snored. Although statistical significance was not reached, the probandwise concordance rate for habitual snoring was higher in monozygotic twins than in dizygotic twins (67% vs. 50%, $p = 0.12$). Furthermore, factors such as smoking and respiratory disease were associated with dizygotic twins only, suggesting less significance of lifestyle and a genetic predisposition to the development of habitual snoring.

Another study on snoring in twins, published in 2001, investigated the genetic factors of snoring and excessive daytime sleepiness [27]. A total of 1560 pairs of twins (818 monozygotic and 742 dizygotic twins) from the World War II Twin Registry were analyzed. The twins completed a questionnaire on their overall health and lifestyle between 1998 and 1999. The authors evaluated the genetic factors associated with snoring and excessive daytime sleepiness using methods such as maximum-likelihood model fitting and multivariate genetic analysis. The questions used to determine snoring were as follows: 1) How often do you snore in any way?, 2) How often do you snore

loudly and disruptively?, and 3) How often do you hold your breath during sleep? The Epworth Sleepiness Scale was completed to assess daytime sleepiness, and obesity was defined as BMI ≥ 28 kg/m^2. A bivariate genetic model was used to assess the environmental and genetic factors affecting snoring, and pairwise correlations were analyzed. The correlation between traits, including snoring, was higher in monozygotic twins than in dizygotic twins. Bivariate analysis results indicated that only genetic, and not environmental, associations were significant between snoring and obesity (r_G = 0.38) and between snoring and sleepiness (r_G = 0.44). Although daytime sleepiness and obesity showed significant genetic correlations with snoring, only 30% of the genetic variance in snoring was explained by genes common to obesity or sleepiness. Univariate genetic analysis revealed that the heritability of snoring was 25%. The results of this study suggest that genetic factors substantially influence snoring.

LARGE POPULATION STUDIES ON SNORING

One of the first cohort studies on the genetic factors of snoring included 3308 men aged 54−74 years from a cardiovascular disease cohort [28]. Habitual snorers were defined as those who answered "often or always" to the question "Do you know or have you been told that you snore during the night?" Habitual snoring was significantly associated with family history of snoring in parents, grandparents, siblings, and even in children (OR, 2.4−4.2). When habitual snorers and non-snorers were compared, the factor that differed the most between habitual snorers and non-snorers was family history of habitual snoring. Habitual snorers were further classified as severe habitual snorers according to whether they used a separate bedroom due to snoring. A self-reported family history of snoring was significantly more prevalent among severe habitual snorers than among non-severe habitual snorers (35.2% vs. 29.0%, p < 0.05).

Another observational study analyzed 408317 subjects and their genetic data from the UK Biobank [2]. Those who reported that their partner or housemate complained of snoring were classified as snorers. Subjects were classified as having OSA based on the International Classification of Disease-10th Revision code for OSA or self-report of having been diagnosed with OSA. In total, 37% of the subjects snored. Compared with non-snorers, a larger proportion of snorers were diagnosed with OSA (2.88% of snorers vs. 0.63% of non-snorers). Snoring was significantly associated with age (OR, 1.011) and sex (OR_{males}, 2.264). Snoring was positively correlated with BMI, smoking frequency, and alcohol consumption frequency, whereas socioeconomic status showed a negative correlation.

In the GWAS of snoring conducted in this study, 127 independent genome-wide significant associations were found at 41 genomic risk loci. The overall single nucleotide polymorphism (SNP) heritability was 9.9% on the liability scale. The results of the genomic correlation study showed that self-reported snoring was most highly correlated with self-reported sleep apnea. Snoring also showed a moderate correlation with indices, such as minimum oxygen saturation (SpO_2) and percent sleep with SpO_2 < 90% (Perc90), which are known indicators of sleep-disordered breathing. Some traits that showed the strongest genetic correlation with snoring were BMI, risk of psychiatric disease, lung function, and heart disease. Sensitivity GWAS after adjusting for BMI showed 97 genome-wide significant SNPs across 34 genomic risk loci, with the SNP heritability on the liability scale of 8.67%. After adjusting for BMI, whole-body fat, body fat percentage, hypertension, smoking, and alcohol consumption were no longer significantly correlated genetically, but minimum SpO_2 and Perc90 showed an increase in correlation. Both the BMI-adjusted GWAS and unadjusted GWAS showed strong genetic correlations, which suggests that BMI alone cannot explain a considerable predisposition for snoring.

The functions of genome-wide significant variations were explored through expression quantitative trait loci mapping and genome-wide gene-based association analysis, and 149 protein-coding genes were identified. The genes nearest to the highest signal were *DLEU7* on chromosome 13 and *MSRB3* on chromosome 12. Other genes, including *BCL11B*, *FTO*, *SMG6*, and *BCL2*, which were previously associated with smoking, and *BLC11B*, *FTO*, and *RNA5SP471* were reported to be related to alcohol consumption in previous studies. *FTO*; *SND1*, which was related to coffee consumption; *LMO4*, which was associated with insomnia; *FNA5SP471*, which was associated with narcolepsy; and other genes related to heel bone mineral density were also identified. The genes mapped in association with snoring were those previously associated with other cognitive/neurological, respiratory, and psychiatric traits or diseases.

Through generalized summary-data-based Mendelian randomization, the causal relationships between traits were analyzed. The results suggested that snoring had a causal effect on increasing heart rate, whereas snoring and BMI or snoring and heart attack showed a bidirectional relationship. The results revealed that whole-body fat mass also had a causal effect on snoring, and that snoring had a causal effect on increasing blood pressure.

In a study by Garcia-Marin et al. [29], the causal relationships between sleep-related traits and 1527 phenotypes were analyzed by combining summary statistics from two previous publications based on data from the UK Biobank [2] and 23andMe [30]. The summary statistics were readjusted and analyzed using the complex trait genetics virtual lab, and the latent causal variable method was used to estimate the genetic correlation between two traits. A total of 299 traits with significant correlations with snoring were identified, and 10 of these traits had a causal relationship. Some of the traits that showed genetic correlation and increased risk of snoring were umbilical hernia (r_G = 0.25, GCP =

Table 1. Main results of studies on genetic influences of snoring

Study	Type of study	Number of subjects, age*	Assessment of snoring	Main results	Genes associated with snoring†
Redline et al. (1992) [24]	Familial study	272 Subjects from 29 families vs. 21 control families, age N/S	Self-reported snoring and obstructive sleep apnea Habitual or disruptive snoring was considered present if the subject of bed partner reported that the subject snored always or almost always or disturbed others because of snoring.	Odds ratio (adjusted) of having habitual or disruptive snoring was 1.33−1.42 when single relative has same symptom.	N/A
Teculescu et al. (1994) [25]	Familial study	487 Children, age 4 to 12	Self-reported snoring Questionnaire on sleeping habits (specific question not mentioned in the article)	Snoring by family member ($\chi^2 = 5.1$, $p = 0.02$) independently significantly associated with snoring in multiple logistic regression.	N/A
Ferini-Strambi et al. (1995) [26]	Twin study	492 Monozygotic twins and 284 dizygotic male twins, age 30 to 60	Self-reported snoring Habitual snoring, if the twin (and bed partner) reported that the subject snored "always" or "almost always."	Probandwise concordance rate was 67% for monozygotic and 50% for dizygotic twins ($p = 0.12$).	N/A
Carmelli et al. (2001) [27]	Twin study	818 Monozygotic twins and 742 dizygotic male twins, age N/S	Self-reported snoring Responses to three questions: 1) How often do you snore in any way? 2) How often do you snore loudly and disruptively? 3) How often do you hold your breath during sleep? Questions were based on the time frame of the previous 6 months and could be answered with any of the following responses: "never," "just a few times," "sometimes," "fairly often," or "don't know."	Within-pair correlation for snoring was higher in monozygotes than in dizygotes (0.2370 vs. 0.0925). Heritability of snoring 23% (maximum likelihood estimate from best fitting model).	N/A
Jennum et al. (1995) [28]	Cohort study (cardiovascular disease cohort)	3308 Males, age 54 to 74	Self-reported snoring Men who reported that they snored often or always were considered habitual snorers, and those who reported that they seldom or never snored were considered non-snorers.	OR of habitual snoring was 2.4−4.2 when having family history of snoring.	N/A
Campos et al. (2020) [2]	Genome-wide association study (GWAS)	408318 Subjects from UK Biobank, age N/S	Self-reported snoring Snoring "cases" based on their report that a partner or housemate had complained to the participant about their snoring. Snoring was assessed as a single item: "Does your partner or a close relative or friend complain about your snoring?" This question could be answered with "Yes," "No," "Don't know," or "Prefer not to answer."	Genetic correlation with SpO_2 minimum, percent of sleep with SpO_2 under 90%, body mass index, risk for psychiatric disease, lung function, heart disease etc. 127 Independent genome-wide significant associations across 41 genomic risk loci.	Nearest gene of top 5 risk loci: *DLEU7*, *MSRB3*, *AC073551.1*, *POC5*, *BCL11B*, *TRAM1*

Table 1. Main results of studies on genetic influences of snoring (continued)

Study	Type of study	Number of subjects, age*	Assessment of snoring	Main results	Genes associated with snoring†
Garcia-Marin et al. (2021) [29]	GWAS	GWAS summary statistics from 2 GWAS studies (UK Biobank, 23andMe cohorts)	Self-reported snoring UK Biobank: same as above 23andMe: unavailable	Latent causal variable method: Snoring genetically correlated with 299 traits, 10 traits with causal effect including umbilical hernia (r_G = 0.25), angina pectoris (r_G = 0.26), obesity (r_G = 0.27).	N/A
Chen et al. (2022) [31]	GWAS	GWAS summary statistics from 2 GWAS studies (UK Biobank, 23andMe cohorts)	Self-reported snoring UK Biobank: same as above 23andMe: unavailable	Linkage disequilibrium score regression analysis: Snoring genetically correlated with BMI (r_G = 0.404), waist circumference (r_G = 0.389), whole-body fat mass (r_G = 0.355), leg fat mass (r_G = 0.376), arm fat mass (r_G = 0.370) among 11 traits.	Traits mapped on *GDF5* and *FTO* gene

*Indicated as N/S when not specified; †Indicated as N/A when not assessed.
r_G, genetic correlation.

-0.42), angina pectoris (r_G = 0.26, GCP = -0.80), self-reported high cholesterol level (r_G = 0.17, GCP = -0.43), obesity (r_G = 0.27, GCP = -0.73), and age at smoking cessation (r_G = 0.27, GCP = -0.70).

In a study by Chen et al. [31], data from the same cohorts as the study mentioned previously was analyzed for genetic correlations between sleep-related phenotypes and body anthropometric measures using linkage disequilibrium score regression. Four sleep-related phenotypes (dozing, napping, snoring, and insomnia) and 11 measures of body composition were genetically correlated. Snoring showed significant genetic correlation with the 11 measures. Snoring correlated with BMI (r_G = 0.404), whole-body fat mass (r_G = 0.355), whole-body fat-free mass (r_G = 0.183), waist circumference (r_G = 0.389), hip circumference (r_G = 0.313), leg fat mass (r_G = 0.376), arm fat mass (r_G = 0.370), trunk fat mass (r_G = 0.329), leg fat-free mass (r_G = 0.213), arm fat-free mass (r_G = 0.206), and trunk fat-free mass (r_G = 0.141). Mendelian randomization analysis revealed that BMI, whole-body fat mass, and waist circumference, among other anthropometric measures, were causal risk factors for snoring. The results of the studies are summarized in Table 1.

DISCUSSION

Early studies on the genetic influence of snoring were based on twin and familial studies. Comparison of monozygotic and dizygotic twins revealed that traits between pairs were more highly correlated, and that environmental factors had less effect on this correlation in monozygotic twins, suggesting a genetically influenced component of snoring. An investigation of family history showed that having a relative who snores increased the odds of snoring. Genetic correlation analysis and GWAS showed that snoring is genetically correlated with BMI, heart disease, and minimum SpO_2, among other traits. Genome-wide significant SNPs were mapped, and protein-coding genes previously associated with traits, such as smoking and alcohol consumption, were identified. Traits such as angina pectoris and obesity exhibited causal relationships, increasing the risk of snoring. Body composition measures were significantly correlated with snoring. These studies have shown that various phenotypes are genetically correlated with snoring, some of which have causal relationships.

A limitation of the included studies is that the definition of snoring was based on self-reports, which is inevitably subjective. Although one study, the Copenhagen Male Study [28], validated the self-reporting of snoring by randomly sampling self-reported snorers to take night recordings, the remaining studies were dependent solely on self-reports of snoring. Furthermore, the difference between simple and habitual snoring is not always clear. Due to the lack of international consensus on the definition of snoring, studies have used different definitions. The sound

intensity thresholds used to define snoring have also been reported differently in various studies. We recently reported that the snoring episode index is highly correlated with AHI and may be utilized as a definition of snoring [32]. Another limitation of this study is that the trait of snoring may not be distinguishable from OSA, especially if diagnosed by self-reports and questionnaires. More studies need to analyze the genetics of snoring using definition of snoring based on objective measures such as polysomnography to differentiate from OSA. By using objective measures to establish a clearer definition of snoring and reaching an international consensus, more refined studies can be conducted on the genetic influences and the prevalence, risk factors, diagnosis, and management of snoring.

Although further investigation is warranted to determine how certain traits or SNPs increase the risk of snoring, there is clear evidence that genetic factors affect snoring. Weight gain increases the risk of snoring and OSA [15,33]. Similarly, GWAS and genetic correlation studies have demonstrated that measures, such as BMI, whole-body fat mass, and waist circumference, are causal risk factors for snoring. The clinical significance of snoring must be recognized, and those at risk may need to monitor signs of snoring more vigilantly and also put more effort into controlling modifiable risk factors.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

Author Contributions

Conceptualization: Jeong-Whun Kim. Data curation: Sun A Han. Formal analysis: Sun A Han. Investigation: Sun A Han. Methodology: Jeong-Whun Kim. Project administration: Jeong-Whun Kim. Resources: Jeong-Whun Kim. Supervision: Jeong-Whun Kim. Validation: Jeong-Whun Kim. Visualization: Sun A Han. Writing—original draft: Sun A Han. Writing—review & editing: Sun A Han, Jeong-Whun Kim.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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