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Review

Genetic factors in sleep-disordered breathing

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ABSTRACT

Sleep-disordered breathing (SDB) is characterized by repetitive episodes of decreased or arrested respiratory airflow during sleep. SDB is common and affects approximately 20% of the Japanese general population. Most traits of normal sleep and SDB show familial aggregation, suggesting significant effects of genetic factors. Obstructive sleep apnea (OSA) is the most common type of SDB and has a high heritability. Regardless of high heritability, no risk locus for OSA has reached a genome-wide level of significance ($P < 5 \times 10^{-8}$) in linkage or candidate gene analysis. However, a recent genome-wide association study identified some genetic risks for OSA with $P < 5 \times 10^{-8}$ for the first time. The identified genes are associated with inflammation, hypoxia signaling, and sleep pathways. The effects of genetic factors on the consequences of OSA has not been determined, although a correlation between OSA and cardiovascular disease may differ across races. Congenital central hypoventilation syndrome (CCHS) is a genetically inherited disorder caused by mutations in the paired-like homeobox 2B (*PHOX2B*) gene of polyalanine repeat mutations in the 20-alanine repeat or non-polyalanine repeat mutations. *PHOX2B* genotypes are also associated with clinical phenotypes of CCHS, including severity of hypoventilation. SDB, including obesity hypoventilation syndrome, is often seen in genetic obesity-associated disorders such as Prader-Willi syndrome. Although advances in genetics have resulted in

Abbreviations: ANS, autonomic nervous system; ANSD, autonomic nervous system dysfunction; APOE, apolipoprotein E; ATS, American Thoracic Society; BMI, body mass index; CARe, Candidate Gene Association Resource; CCHS, congenital central hypoventilation syndrome; CFS, Cleveland Family Study; CI, confidence interval; CRP, C-reactive protein; CSA, central sleep apnea; *DβH*, dopamine β-hydroxylase; FTO, fat mass and obesity-associated protein; GDNF, glial cell-line derived neurotrophic factor; GH, growth hormone; GWAS, genome-wide association study; HTRA2A, serotonin receptor 2a; LEPR, leptin receptor; LO-CCHS, later-onset congenital central hypoventilation syndrome; LPAR1, lysophosphatidic acid receptor 1; NHLBI, National Heart, Lung, and Blood Institute; NPARM, non-polyalanine repeat mutation; NREM, non-rapid eye movement; NRG1, neuregulin 1; NTS, nucleus tractus solitarius; OHS, obesity hypoventilation syndrome; OR, odds ratio; OSA, obstructive sleep apnea; PARM, polyalanine repeat mutation; PHOX2B, paired-like homeobox 2B; PLEK, pleckstrin; PPARGC1B, peroxisome proliferator-activated receptor gamma coactivator 1-beta; PTGER3, prostaglandin E2 receptor EP3 subtype; PWS, Prader-Willi syndrome; RAI1, retinoic acid-induced 1; ROHHAD, rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; RTN, retrotrapezoid nucleus; SDB, sleep-disordered breathing; SLC6A4, solute carrier family 6 member 4; TNF, tumor necrosis factor; TRABD2B, TraB domain containing 2B

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identification of some genetic causes of SDB, further studies are required to elucidate the cellular and molecular mechanisms between genetic risks and clinical manifestations.

Contents

1. Introduction

Sleep-disordered breathing (SDB) is characterized by repetitive episodes of decreased or arrested respiratory airflow during sleep [1]. The prevalence of SDB in the Japanese general population was reported at 18.4% with a 7.1% occurrence among males and 11.1% among females [1]. Untreated SDB is associated with an increased risk of adverse health outcomes, such as cardiovascular events, hypertension, diabetes, metabolic syndrome, stroke, heart failure, motor vehicle accidents, depression, and even mortality [2–4].

Normal sleep traits and SDB are known to be affected by genetic factors, in addition to comorbidities and environmental factors [5,6]. Several studies have revealed that several sleep parameters and SDB are heritable, including electroencephalogram patterns, sleep duration, chronotype, obstructive sleep apnea (OSA), congenital central hypoventilation syndrome (CCHS), and neurobehavioral responses to sleep deprivation [6]. Based on the heritability established in twin and family studies, the genetic risks for individual SDB abnormalities have been explored through linkage analysis, candidate gene analysis, and hypothesis-free genome-wide association studies (GWASs) [5,6].

This mini-review will provide clinicians and researchers with a current overview of SDB genetics by addressing the association of OSA, CCHS, and obesity hypoventilation syndrome (OHS) with genetic disorders.

2. Obstructive sleep apnea

OSA is the most common type of SDB and has a prevalence of approximately 15% in men and 5% in women [7,8]. OSA is characterized by repeated episodes of pharyngeal collapse leading to partial or complete obstruction of the upper airways during sleep. Repeated episodes of nocturnal apnea or hypopnea can cause intermittent hypoxia, sympathetic activation, and sleep fragmentation that result in various adverse outcomes [9,10]. Since OSA is a complex disorder with multiple predisposing factors, such as obesity, older age, male gender, and craniofacial abnormalities, it is unlikely that a single genetic predisposition can account for all of these traits [5]. On the other hand, some predisposing factors, including anatomic abnormalities and obesity, can be determined genetically.

Genetic studies of OSA began with studying familial forms of sleep apnea. The prevalence in first-degree relatives of patients with OSA was reported between 21% and 84%, and the estimated odds ratio ranged from 2 to 46 [5,6]. OSA-related symptoms and anatomical risk factors were also shown to be heritable [6]. As a whole, inherited factors were likely to account for approximately 40% of OSA risk [11]. Furthermore, obesity is a significant risk factor for OSA and shows a high frequency of familial aggregation. Twin and family studies revealed that the estimated heritability of body mass index (BMI) was 50–90% and 20–80%, respectively [11]. The Cleveland Family Study (CFS) demonstrated that African-American ethnicity and first-degree relatives to patients with OSA patients are independent risk factors for pediatric and adolescent OSA [12]. Another family study of participants with BMI < 30 (without obesity) showed that maxillofacial anatomy traits can significantly contribute to familial aggregation of OSA [13]. In the CFS, heritability of the apnea-hypopnea index (AHI)—an index for the severity of OSA—in whites and African-Americans was 36.3% and 32.3% and decreased to 32.3% and 23.7% after adjusting for BMI, respectively [14,15]. The estimates for heritability of BMI were 52.8% for whites and 53.7% for African-Americans, and those for upper airway dimensions were 34% for whites and 39% for African-Americans [16]. A recent population-based study in Brazil reported that heritability of AHI was 23–25% in a rural population with low levels of obesity [17].

Despite high heritability, no linkage analysis or candidate gene analysis identified risk loci with a genome-wide level of statistical significance ($P < 5 \times 10^{-8}$) [6,11]. Nevertheless, several candidate loci or genetic variants have been reported in individual studies, apolipoprotein E (*APOE*), C-reactive

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