Obstructive Sleep Apnea and Genes

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Obstructive sleep apnea (OSA) is a disorder in which complete or partial obstruction of the airway during sleep causes loud snoring, oxyhemoglobin desaturation, and frequent arousals. As a result, affected persons have unrestful sleep and excessive daytime sleepiness. Potential genetic interaction between obesity and OSA phenotypes is one in which a particular polymorphism leads to both obesity and OSA through independent mechanisms. Reductions in serotoninergic activity, by increasing appetite, could promote obesity and by lowering muscle tone in the upper airway, promote OSA. Presence of the arginine 64 allele of the β3-adrenergic receptor gene does not increase the risk of OSA syndrome, but is associated with the development of obesity in those patients who suffer OSA syndrome. Both shared and unshared genetic factors underlying susceptibility to OSA and obesity, and the genetic determinants of obesity in this population may be modulated by apnea severity. Other genetic loci reviewed likely interact with obesity to influence development of OSA in a gene-by-environment type of effect. Conversely, environmental stressors, such as intermittent hypoxia and sleep fragmentation produced by OSA, may interact with obesity susceptibility genes to modulate the importance that these loci have on defining obesity-related traits. (Sleep and Hypnosis 2010;12(1-2):23-34)

Key words: Obstructive sleep apnea, excessive daytime sleepiness, phenotypes, genetic loci.

INTRODUCTION

Obstructive sleep apnea (OSA) is defined specifically as the occurrence of repetitive episodes of complete or partial obstruction of the upper airway during sleep, usually in association with loud snoring and daytime sleepiness. Such episodes are often associated with arousals, sleep fragmentation, intermittent hypoxaemia and hypercapnia, and nocturnal hypertension (1,2). Associated nocturnal symptoms include restlessness, excessive salivation and sweating, nocturia, and gastro-esophageal reflux. The patient frequently wakes in the morning with a headache and dry mouth or throat. OSA is now recognized to occur commonly, affecting 2 to 3% of children, (3) 2% to 4% of middle-aged adults, (4) and 10% of the elderly population. Among people over 55 years of age, 30 to 60% meet the polysomnographic diagnostic criterion of an apnea-hypopnea index (AHI) of ≥5 (3). The association of OSA with several chronic health conditions, particularly obesity, hypertension, diabetes, and cardiovascular diseases, (5,6,7) has underscored the broad public health importance of this condition.
Millions of adults and children live unaware of OSA, which can have a profound affect on their health and quality of life (4). Common symptoms include loud snoring, restless sleep and sleepiness during the daytime, dry mouth or sore throat upon awakening, headaches in the morning, intellectual impairment, such as trouble concentrating, forgetfulness, or irritability, night sweats, sexual dysfunction, and sudden awakenings with a sensation of gasping or choking.

Obesity, gender, genetic, and hormonal factors mediate risk for OSA and interact in a multifaceted manner in the pathogenesis of this disease. Obesity is the most established and primary risk factor given that body mass index, visceral fat, and neck circumference are major predictors in the clinical expression of OSA. Relative to those with a stable weight, a 10% increase in weight over 4 years is associated with a sixfold increase in the risk of developing moderate to severe OSA (8). Obesity increases susceptibility to OSA due to excess fat deposition in the pharynx, which reduces upper airway caliber and causes hypoventilation from reduced chest wall compliance (5,9,10). Weight loss trials have found significant reductions in apnea severity with moderate weight loss (11,12).

However, the mechanisms by which obesity causes OSA are not completely defined, with many potential pathways hypothesized (13). Perhaps the most obvious is that fat deposition in the neck and airway lumen may lead to increased collapsibility of the upper airway. In addition, adiposity in the chest and abdomen may result in reductions in lung volumes. Recent studies suggest reduced lung volume may independently predispose to upper airway collapse (14). More recently, accumulating evidence indicates OSA promotes weight gain, obesity, and type II diabetes in a variety of ways, such that obesity and OSA form multiple interleaved vicious cycles. Thus, creative strategies to increase physical activity, improve diet, and otherwise facilitate weight management become particularly vital in light of the epidemics of obesity and OSA in the United States (4).

Pathogenesis of obstructive sleep apnea

Researchers have investigated the pathogenesis of obstructive sleep apnea (OSA) for over 25 years, during which a number of factors that contribute to upper airway (UA) collapse during sleep have been identified. Structural or anatomic factors that constrict space for the soft tissues surrounding the pharynx and its lumen are crucial to the development of OSA in many patients. Enlargement of soft tissues enveloping the pharynx, including hypertrophied tonsils, adenoids, and tongue, is also an important factor predisposing to UA collapse, inasmuch as this can impinge on the pharyngeal lumen and narrow it during sleep. Other factors, including impairment of UA mechanoreceptor sensitivity and reflexes that maintain pharyngeal potency and respiratory control system instability, have also been identified as possible mechanisms facilitating UA instability. This suggests that OSA may be a heterogeneous disorder, rather than a single disease entity. Therefore, the extent to which various pathogenic factors contribute to the phenomenon of repetitive collapse of the UA during sleep probably varies from patient to patient. Further elucidation of specific pathogenic mechanisms in individuals with OSA may facilitate the development of new therapies that can be tailored to individual patient needs according to the underlying mechanism(s) of their disease (15).

Familial Aggregation of Obesity and Sleep Apnea

The fact that obesity is in large part genetically determined has been known for almost three decades (16). A large twin study estimated the heritability of weight to be 78% (17). That is, 78% of the variability in weight across a population is explained by shared intrafamilial factors. Both nontwin family and twin studies have secured evidence for an important genetic component to snoring, sleeping patterns, and OSA (18,19,20,6,21). The molecular genetics of OSA has received little attention to date, and
previous investigations have been limited to candidate-gene association studies (22,14). Subsequent studies demonstrated that adopted children have a body size more closely resembling their biological parents than their adopted parents (17). Studies of pedigrees and twins have suggested that BMI has a heritability of 50%–80% (17,23,24). Studies in Finland and the United Kingdom have estimated the heritability of body mass index (BMI) to be 60–80% (25,26). Linkage to obesity-related phenotypes has been investigated in some 50 genomewide scans to date, with dozens of candidate loci and genes identified (27,28).

Family aggregation is found even after controlling for body mass index (BMI) as a covariate (19), and also when the probands selected for study are relatively nonobese patients with OSA (i.e., BMI < 30 kg/m²) (29). Although familial aggregation has been shown, little is currently known about the genes conferring risk. APOE4 is particularly associated with OSA in younger subjects (30). The increased risk in individuals with this allele who are younger than 65 years of having an AHI of more than 15 episodes/hour is 3.1, whereas there is no increase in risk in subjects 65 years and older (30).

Family–based studies suggest that the risk of OSA is approximately twice as great among relatives of apneic persons (31,19). In addition, a dose–response relationship exists such that the risk of OSA increases with increasing number of apneic relatives (19). Quantitative apnea–related phenotypes also demonstrate substantial heritability. A study of elderly twins found the heritability of both the respiratory disturbance index and the oxygen desaturation index to be nearly 40% (32).

**Obesity and Leptin**

Leptin, a hormone produced by adipose tissue, has important effects on weight regulation, and by stimulating hypothalamic satiety centers, (19,9,32) may have such pleiotropic effects (33). Human obesity is typically associated with elevated leptin levels, suggesting a state of leptin resistance (18). Besides regulating weight, leptin may have important effects on ventilatory drive. Leptin–deficient mice hypoventilate and exhibit a blunted response to hypercapnia (34). Administration of leptin corrects these abnormalities independent of changes in weight (34). Through these effects on ventilatory control, elevated leptin levels (or the underlying leptin resistant state) may play a pathogenic role in the development of OSA. A study concluded that patients with severe OSA have higher level of plasma leptin than patients with mild OSA, and there is a positive correlation, independent of age and BMI, between the plasma leptin levels and the severity of disease in OSA. These results imply that hyperlepidemia may be a prognostic marker of OSA (74).

Studies after leptin replacement in mutant obese mice (Lepob) suggest that leptin deficiency causes depressed ventilatory responses to hypercapnia in both wakefulness and sleep (34). Although leptin–deficient mouse models have not been studied for OSA per se, these studies provide important supporting data implicating the pleiotropic effects that a single protein has on several aspects of the OSA phenotype (e.g., obesity, abnormal ventilatory control, and disturbed sleep architecture) (34). Of great interest in this context, the same marker that provides maximal evidence of linkage to BMI in the 2p region (35) has also shown evidence of significant linkage to leptin levels in multiple studies (maximum LOD score 2.8–7.5) (36,37,27) as have nearby markers (20,38). This region on chromosome 2 encompasses the gene encoding proopiomelanocortin (POMC), which may be important in the regulation of appetite, obesity, and variation in leptin levels (37,39,35). Linkage to both AHI and BMI on chromosome 2p, POMC is a biologically plausible candidate that could explain the observed results and would be consistent with a genetically regulated metabolic component to OSA pathogenesis.
Metabolic syndrome X describes a condition marked by obesity, insulin resistance and/or type 2 diabetes, hyperlipidemia and hypertension. OSA is often correlated with the presence of syndrome X, and with the addition of OSA, researchers have identified a new syndrome called syndrome Z, to acknowledge the fact that the presence of OSA exacerbates syndrome X outcomes (40).

Researchers have conjectured that serum leptin levels may be strongly influenced by genes related to metabolic pathways (40). Such central metabolic components include: (a) signaling glycogen synthase kinase 3 beta (linkage peak on chromosome 3 near this gene); (b) insulin receptor substrate–1, a diabetes candidate gene (linkage peak on chromosome 2 near this gene); (c) resting heart rate, which is related to sympathetic nervous system activity (linkage peak on chromosome 4 near this gene); and (d) low-density lipoproteins, total cholesterol, and triglycerides (linkage peak on chromosome 21 near these sites). These components and others, such as inflammatory immunoregulatory substances, corticosteroids and insulin, may influence tissue sensitivity to leptin and/or leptin concentrations and predispose one to OSA (40).

Susceptibility Genes for OSA

Given the strong genetic components of both obesity and apnea phenotypes, as well as the tight association with multiple interweaving links between these two diseases, it would not be surprising for there to exist common susceptibility genes for both obesity and OSA. In fact, it has been suggested that the familial aggregation of OSA may simply be a reflection of that found in obesity. However, this is clearly not the case: Even after controlling for BMI, significant familial aggregation for OSA is still evident (1,19). Furthermore, a study of nonobese apneic patients also demonstrated strong heritability of OSA (29). This finding is not surprising given that other pathophysiological pathways to apnea development, such as craniofacial structure and ventilatory control, also have a heritable component (41,1,29,42,43). Thus the susceptibility genes for OSA are not exclusively the same genes that modulate obesity. That does not mean, however, that no overlap exists.

Potential genetic interaction between obesity and OSA is one in which a particular polymorphism leads to both obesity and OSA through independent mechanisms (Fig. 1).
Some susceptibility genes act directly on one phenotype, and through the causal relationships between obesity and sleep apnea have indirect effects on the other phenotype. Other loci have pleiotropic effects, impacting susceptibility to both obesity and sleep apnea via independent mechanisms. For example, by impacting leptin function, a genetic polymorphism may reduce satiety and also increase ventilatory instability, referred to as genetic pleiotropy. Pleiotropic genetic effects have clearly been described in other situations. A well known example is at the AOE locus, which codes for apolipoprotein E. The 4 allele of APOE is an important risk factor for both atherosclerotic heart disease as well as Alzheimer’s dementia.

Gene Environment Interaction

Another potential genetic interaction between obesity and OSA is a gene–by–environment effect in which the adverse effects of obesity or OSA constitute environmental stressors (Fig. 2). Sleep apnea and susceptibility genes may interact with obesity through numerous mechanisms to influence sleep apnea predisposition. Genetic polymorphisms may modulate the degree to which obesity alters ventilatory drive, reduces lung volume, or narrows the upper airway. Other polymorphisms may affect the degree to which these stresses result in the development of sleep apnea. An increase in fat deposition around the upper

Figure 2. Obstructive Sleep apnea and Susceptible Genes
Obstructive sleep apnea and genes

airway will be more likely to produce apnea in individuals with a compromised ability to respond to stressor due to reduce upper airway dilator muscle tone. Conversely, obesogenic effects of OSA may be influenced by the underlying genetic milieu. Genetic polymorphisms may modulate the effect that exposure to sleep fragmentation from OSA has on leptin and ghrelin dynamics. Other polymorphisms might influence the effect that these hormonal perturbations have on producing further weight gain (44).

In addition mutant animals demonstrate an overall increase in caloric intake associated with a phenotype of obesity and metabolic syndrome (75).

Similarly, given the large number of neurological, metabolic, and mechanical linkages between obesity and OSA, it is likely that a polymorphism affecting one biochemical system may affect the risk for both disorders via multiple paths. For example, disruptions of the orexin system could potentially result in a common link between obesity and OSA. Orexinergic neurons in the lateral hypothalamus play an important role in sustaining wakefulness with projections to all of the wake–promoting areas of the brain (45). Loss of these neurons is associated with a narcolepsy phenotype (46). These neurons, as the name orexin implies, also play an important role in stimulating appetite, projecting on to the arcuate nucleus of the hypothalamus (47). Thus mutations affecting orexin, the orexin receptor, or proteins involved in the downstream signaling of orexin binding might simultaneously affect metabolic and sleep–related function. Several other potential candidate genes are listed in Table 1.

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<thead>
<tr>
<th>Candidate Gene</th>
<th>Relationship to Obesity</th>
<th>Relationship to Sleep Apnea</th>
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<tbody>
<tr>
<td>POMC</td>
<td>Mediator of leptin effects on appetite</td>
<td>Mediator of leptin effects on ventilatory drive</td>
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<tr>
<td>COH1</td>
<td>Regulation of fat deposition pattern</td>
<td>Regulation of craniofacial development</td>
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<tr>
<td>SLC6A14</td>
<td>Serotoninergic regulation of weight</td>
<td>Serotoninergic control of upper airway muscle activity</td>
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**Gene Environment Interaction**

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<th>Candidate Gene</th>
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<tbody>
<tr>
<td>PPARG</td>
<td>Regulation of adipocyte differentiation</td>
<td>Down regulated by hypoxia</td>
</tr>
<tr>
<td>UCP1, UCP2</td>
<td>Regulation of thermogenesis</td>
<td>Upregulated by sleep deprivation</td>
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Multiple genomic regions have been linked to obesity related phenotypes in genome–scan linkage studies (36), and 59 loci has been linked to obesity measures in genome wide scans of humans (48). Evidence for linkage of obesity–related phenotypes to the three most promising regions for BMI, chromosomes 2p, 7p, and 12q, has been reported in previous studies. The chromosome 2p region has been linked to BMI, fat mass, and skinfold thickness in previous linkage studies (49,50,36,27,38). The 7p (51,52) and 12q (53,28) regions have also been previously linked to obesity measures. Research that reported linkage scans from the Cleveland Family Study represents the first genomewide linkage study of OSA phenotypes (54). The results provide insight into possible genetic overlaps between obesity and OSA. Linkage to the apnea–hypopnea index (AHI), as a measure of OSA, and BMI as a measure of obesity, was tested across the autosomal chromosomes in both a Caucasian and an African–American cohort. The heritability of AHI in both groups was ~33%, whereas the heritability of BMI was over 50%. After controlling for BMI, significant heritability for AHI remained, supporting the notion that the genetic susceptibility to OSA is not completely defined by weight. In further multivariate modeling of a larger subset of the Cleveland Family Study, obesity measures such as BMI and serum leptin explained 50–55% of the genetic variation.
variance in AHI (76). This suggests that about half of the genetic determinants of AHI are obesity related and half are obesity independent.

Linkage findings are described by the logarithmic odds (LOD) score, a measure of the odds ratio of linkage to no linkage. Although none of the linkage findings in either racial group achieved genome wide significance (LOD > 3.3) (16), there were several regions with intermediate LOD scores, indicative of possible linkage in the setting of complex, multifactorial diseases such as obesity and OSA (2). Furthermore, the change in linkage evidence for AHI after adjustment for BMI provides insight into mechanisms of action if a susceptibility locus is present. Among the Caucasians, a LOD score of 1.4 was found for AHI and 1.7 for BMI on chromosome 12p (54). After adjustment for BMI, the maximal LOD for AHI in this region dropped to only 0.4 whereas the LOD for BMI adjusted for AHI fell to 0.2. These data suggest that if a susceptibility gene for AHI exists in this region, it likely mediates its effect on apnea via obesity. On the other hand, a maximal LOD for AHI of 1.4 was found on 19q with no linkage evidence for BMI in this region (54). Adjustment for BMI had no effect on the AHI LOD, suggesting that a susceptibility gene in this region exerts its effect on AHI through obesity-independent mechanisms.

A different pattern of linkage findings was found at the short arm of chromosome 2. Among the Caucasians, the maximal LOD for AHI is 1.6 and for BMI is 3.1 in this region, again suggesting that a susceptibility locus for both phenotypes might exist in this region (56). However, adjustment for BMI only dropped the LOD for AHI to 1.3, suggesting that the obesity effect at this locus does not fully explain the apnea effect. This may represent two independent loci, one influencing AHI and one BMI. Another possibility is that there is only one locus at 2p regulating both AHI and BMI but via independent mechanisms. A strong candidate gene for both phenotypes in this region is proopiomelanocortin (POMC). The POMC locus, found at 2p23.3, encodes for a number of hormones including melanocyte-stimulating hormone (MSH). POMC neurons in the arcuate nucleus of the hypothalamus are important in energy homeostasis via MSH. Leptin’s anorexic activity is mediated via depolarization of these neurons, and use of an MSH agonist decreases both body fat and leptin levels in humans (55,57). Obesity phenotypes have been consistently linked to the POMC locus, (58,59,37,60) haplotypes in this gene have been associated with leptin, (37,39) and severe mutations in this gene produce a severe childhood obesity phenotype (61).

Leptin’s effects on ventilatory drive in mouse models are also mediated via MSH, suggesting that this pathway may independently predispose to apnea as well (47).

Evidence for pleiotropy also exists at chromosome 8q. Among African–Americans in the Cleveland Family Study, the peak LOD scores were 1.3 and 1.6 for AHI and BMI, respectively (54). Again, after controlling for BMI, the AHI LOD only dropped to 1.1, suggesting that the obesity and apnea promoting effects in this region were independent. A potential candidate locus in this region is the COH1 gene at 8q22–23. This gene encodes a transmembrane protein with a presumed role in vesicle-mediated sorting and intracellular protein transport on the basis of its structure (62). Severe mutations in this gene have been associated with Cohen syndrome, an autosomal recessive condition characterized by truncal obesity (63).

**Serotonin Transporter Gene polymorphism**

The serotoninergic system is another common pathway that could link obesity and OSA. Serotonin has important effects on the stimulation of satiety centers in the arcuate nucleus (64). In addition, serotonin potentiates hypoglossal neural output, which increases upper airway dilator muscle activity (65,66). Thus reductions in serotoninergic activity, by increasing appetite, could promote obesity and, by lowering muscle tone in the upper airway, could promote OSA. Both linkage and haplotype
association studies in a Finnish population suggest a serotonin-related gene at Xq24 is associated with obesity (7,2). The SLC6A14 gene encodes for a sodium chloride-dependent transporter of neutral and cationic amino acids, which appears to play an important role in the transport of tryptophan, the precursor of serotonin, into the central nervous system (60). A French study has confirmed the association of this polymorphism with obesity, and an association with hunger and satiety scores was also found (67).

β3-Adrenergic receptor Trp64Arg polymorphism

The presence of the arginine 64 allele of the β3-adrenergic receptor gene does not increase the risk of OSA but is associated with the development of obesity in patients with OSA. A study of Spanish patients provides two findings of interest. First, the genotypic and allelic frequencies of the ADRB3 gene variants observed in Spanish patients with OSA did not differ from those in healthy controls of the same ethnic origin. Secondly, BMI was significantly greater in those patients with OSA who carried the Arg variant of the ADRB3 gene (Trp/Arg and Arg/Arg genotypes) than in those with the Trp/Trp genotype. These two observations suggest that the Trp64Arg polymorphism is not associated with the development of OSA, but may favor the development of obesity in patients who already experience OSA. Consistent with this hypothesis, a previous study has recently shown an independent effect of this polymorphism on BMI in Chinese patients with OSA (68).

ACE Polymorphism and Ethnic Differences

Angiotensin–Converting Enzyme (ACE) plays an important role in blood pressure regulation and electrolyte balance and is encoded in a gene located on chromosome 17. Polymorphisms of this gene involve an insertion (I) or deletion (D) of a repeating sequence within this gene. A 1994 epidemiology study explored ACE gene polymorphisms in white Europeans, black Nigerians, Samoan Polynesians, and Yanomami Indians, and showed that the I allele was more frequent in the latter two populations than the former two (69). In another study, the I allele and I/I genotype were significantly more frequent in OSA Chinese patients than Chinese controls without OSA (13,68). In addition, those patients with the I/I genotype had significantly longer apnea time, lower minimum SaO2 levels, and greater AHI than OSA patients with the I/D genotype (70). No members of the OSA group presented with the D/D genotype.

Craniofacial Profile

Structural narrowing of the upper airway is a major factor contributing to pharyngeal occlusion during sleep in the obstructive sleep apnea–hypopnea syndrome (OSAHS) (71). Craniofacial bone and soft tissue features and their associated ventilatory control effects explain some of the genetic association with OSA. Certain craniofacial features are characteristic of chromosomal disorders such as trisomy 21 or Down syndrome; such craniofacial features often predispose to OSA. The craniofacial abnormalities include microcephaly, facial hypotonia, and laryngomalacia, all of which could predispose to OSA. Thus mutations in this gene that are milder but more common may play a role, via separate pathways, in contributing to nonsyndromic forms of both obesity and OSA. Studies have estimated that nearly 55 percent of children with Down syndrome have sleep apnea, which often persists despite previous tonsillectomy and adenoidectomy (72).

Patients with OSA of differing ethnicity and varying degrees of obesity have a crowded posterior oropharynx and a steep thyromental plane (73). In a recent study that sought to objectively measure craniofacial features, (73) the following measurements were made:

- Thyromental angle (TMA): the angle between the soft tissue plane of the anterior neck and the plane running through the lowest point
of chin soft tissue and the thyroid prominence.

- Thyromental distance (TMD): the horizontal distance from the thyroid prominence to the lowest point of chin soft tissue.
- Mallampati oropharyngeal score (MS): a measure of posterior oropharynx occlusion when breath is held at end-tidal inspiration, tongue maximally protruded, and no phonation or attempted elevation of the soft palate.
- Neck circumference (NC): at the level of the cricothyroid membrane, measured with a tape measure.

The researchers found that participants with OSA had a higher MS score, larger TMA, and higher AHI than participants without OSA. Asians tended to have higher MS and TMD than Caucasian participants, although Asians tended to be less obese than Caucasian participants given the same severity of OSA. Females had smaller neck circumferences and lower AHI. A crowded posterior oropharynx (high MS) and steeper thyromental plane (larger TMA) were the strongest predictors of OSA, even after ethnicity and obesity were corrected for statistically.

In summary, obesity and craniofacial features that reflect structural narrowing of the upper airway can be readily identified and can easily be incorporated into the routine physical examination. Patients with OSA of differing ethnicity and varying degrees of obesity have a crowded posterior oropharynx and a steep thyromental plane (73). Such craniofacial features, often dictated by genetic makeup, help explain hereditary and ethnic predisposition to OSA. Recognition of these abnormalities in the craniofacial profile should alert the physician to the possibility of OSA (73).

**CONCLUSION**

There are likely multiple genetic determinants of OSA and these linkage analyses of quantitative phenotypes have identified several regions of interest on which to focus fine mapping efforts. Investigation of candidate genes in the regions of linkage will be necessary.

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