REVIEW ARTICLE

Obstructive Sleep Apnea and Genes

Surya Kant, M.D., Harshita Gupta, M.Sc., S.M.Natu, Ph.D,
Pooran Chand, M.D.S, and Saumendra Vikram Singh, M.D.S

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 ß3-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 $\geqslant 5$ (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.

From Department of Pulmonary Medicine (Drs. Kant and Gupta), Department of Pathology (Dr. Natu), and Department of Prosthodontics (Drs. Singh and Chand), C. S. M. Medical University (Erstwhile King George Medical College), U. P., Lucknow, India

Address reprint requests to: Surya Kant, M.D. (Gold Medalist), FCCP (USA), FIMSA, FNCCP, FCAI, FICS, FIAB, Department of Pulmonary Medicine, C. S. M. Medical University (Erstwhile King George Medical College), U. P., Lucknow
Tel: + 91–522–2255167
Fax No: – 0522–2255167
Email: – dr.kantskt@rediffmail.com

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

Rsearchers 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 biologicallyplausible 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)
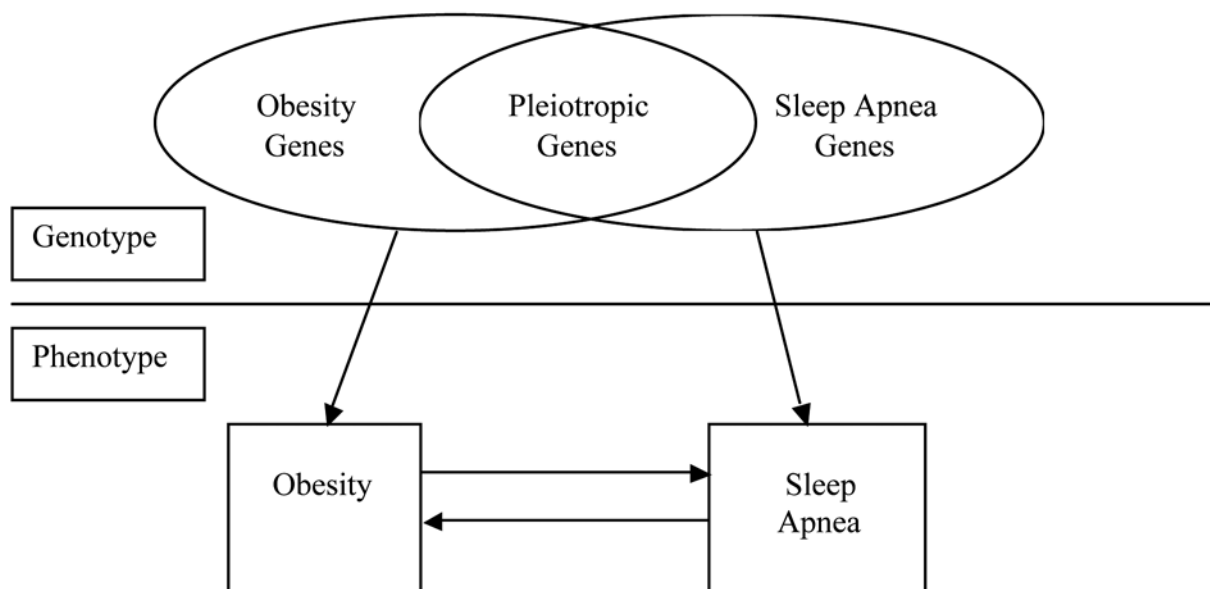

Figure 1. Genetic interaction between Obesity and Sleep Apnea

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
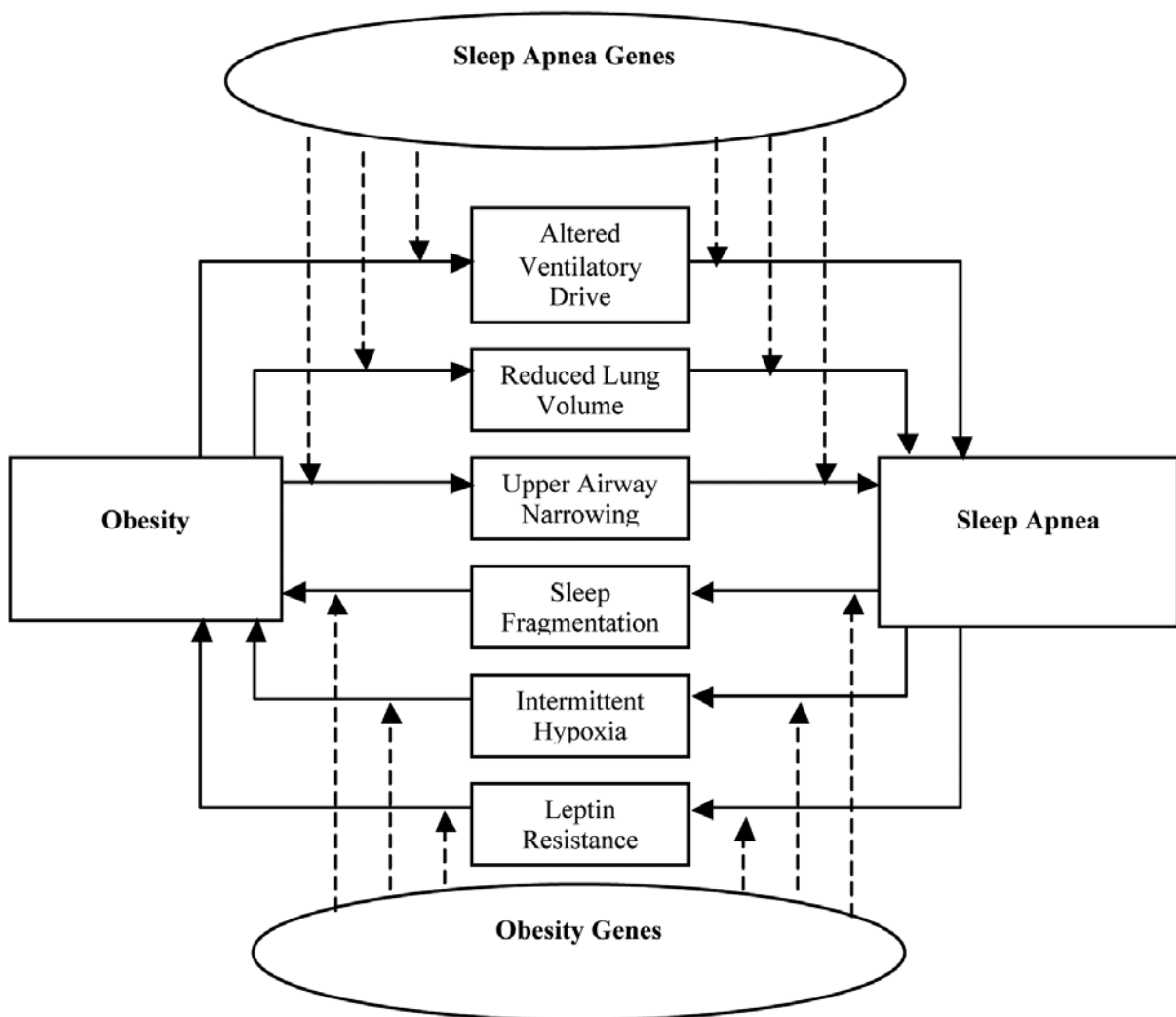

Figure 2. Obstructive Sleep apnea and Susceptible Genes

airway will be more likely to produce apnea in individuals with a compromised ability to respond to stressor due to reduce upper airway

might simultaneously affect metabolic and sleep–related function. Several other potential candidate genes are listed in Table 1.

Table 1. Candidate genes showing relationship to Obesity and Obstructive Sleep Apnea

Candidate Gene	Relationship to Obesity	Relationship to Sleep Apnea
Pleiotropy		
POMC	Mediator of leptin effects on appetite	Mediator of leptin effects on ventilatory drive
COH1	Regulation of fat deposition pattern	Regulation of craniofacial development
SLC6A14	Serotoninergic regulation of weight	Serotoninergic control of upper airway muscle activity
Gene Environment Interaction		
PPARG	Regulation of adipocyte differentiation	Down regulated by hypoxia
UCP1, UCP2	Regulation of thermogenesis	Upregulated by sleep deprivation

POMC; proopiomelanocortin; PPARG, peroxisome proliferator-activated receptor-γ; UCP1 and UCP2, uncoupling protein-1 and -2, respectively.

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

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

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).

ß₃-Adrenergic receptor Trp64Arg polymorphism

The presence of the arginine 64 allele of the ß₃–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 SaO_2 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 Causcaian 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 crani ofacial 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.

REFERENCES

Book

1. *Guilleminault C. Clinical features and evaluation of obstructive sleep apnea. In: Kryeger M, Roth T, Dement WC (eds). Principles and practice of sleep medicine. 2nd ed. Philadelphia: WB Saunders,1994.*

Articles

2. *Weeks DE, Conley YP, Mah TS, et al. A full genome scan for age-related maculopathy. Hum Mol Genet 2000;9: 1329–1349.*

3. *Rosen CL, Larkin EK, Kirchner HL, et al. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. J Pediatr. 2003;142:383-9.*

4. *Rotimi CN, Comuzzie AG, Lowe WL, Luke A, Blangero J, Cooper RS. The quantitative trait locus on chromosome 2 for serum leptin levels is confirmed in African- Americans. Diabetes 2003;48:643–644.*

5. *Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir CritCareMed 2002;165:677-82.*

6. *Linkowski P. EEG sleep patterns in twins. J Sleep Res 8 Suppl 1993;1:11–13.*

7. *Ohman M, Oksanen L, Kaprio J, et al. Genome-wide linkage scan of obesity in Finnish sibpairs reveals linkage to chromosome Xq24. J Clin Endocrinol Metab 2000;85: 3183–3190.*

8. *Peppard PE, Young T, Palta M, Dempsey J, and Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA 284: 3015–3021,2000.*

9. *Leung RS, Bradley TD. Sleep apnea and cardiovascular disease. Am J Respir Crit Care Med 2001;164:2147-65.*

10. Newman AB, Nieto FJ, Guidry U, et al. Relation of sleep-disordered breathing to cardiovascular disease risk factors: the Sleep Heart Health Study. Am J Epidemiol 2001;154:50-9.

11. Schwartz AR, Gold AR, Schubert N, et al.. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. Am Rev Respir Dis 1991;144: 494–498.

12. Smith PL, Gold AR, Meyers DA, Haponik EF, and Bleecker ER. Weight loss in mildly to moderately obese patients with obstructive sleep apnea. Ann Intern Med 1985;103: 850–855.

13. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002;165:1217-39.

14. Kadotani H, Kadotani T, Young T, et al. Association between apolipoprotein E e4 and sleep-disordered breathing in adults. JAMA 2001;285:2888–2890.

15. Clodagh M. Ryan and T. Douglas Bradley. Pathogenesis of obstructive sleep apnea. J Appl Physiol 2005;99: 2440-2450.

16. Feinleib M, Garrison RJ, Fabsitz R, et al. The NHLBI twin study of cardiovascular disease risk factors: methodology and summary of results. Am J Epidemiol 1977;106: 284–285.

17. Stunkard AJ, Foch TT, and Hrubec Z. A twin study of human obesity. JAMA 1986;256: 51–54.

18. Ferini-Strambi L, Calori G, Oldani A, et al. Snoring in twins. Respir Med 1995;89:337–340.

19. Redline S, Tishler PV, Tosteson TD, et al. The familial aggregation of obstructive sleep apnea. Am J Respir Crit Care Med 1995;151:682–687.

20. Heath AC, Eaves LJ, Kirk KM, Martin NG. Effects of lifestyle, personality, symptoms of anxiety and depression, and genetic predisposition on subjective sleep disturbance and sleep pattern. Twin Res 1998;1:176–188.

21. Buxbaum SG, Elston RC, Tishler PV, Redline S. Genetics of the apnea hypopnea index in Caucasians and African Americans. I. Segregation analysis. Genet Epidemiol 2002;22: 243–253.

22. Redline SR, Tishler PV. The genetics of sleep apnea. Sleep Med Rev 2001;4:583–602.

23. Allison DB, Kaprio J, Korkeila M, Koskenvuo M, Neale MC, Hayakawa K. The heritability of body mass index among an international sample of monozygotic twins reared apart. Int J Obes Relat Metab Disord 1996;20:501–506.

24. Maes HH, Neale MC, Eaves LJ. Genetic and environmental factors in relative body weight and human adiposity. Behav Genet 1997;27:325–351.

25. Koeppen-Schomerus G, Wardle J, and Plomin R. A genetic analysis of weight and overweight in 4-year-old twin pairs. Int J Obes Relat Metab Disord 2001;25: 838–844,.

26. Pietilainen KH, Kaprio J, Rissanen A, et al. Distribution and heritability of BMI in Finnish adolescents aged 16y and 17y: a study of 4884 twins and 2509 singletons. Int J Obes Relat Metab Disord 1999;23: 107–115,.

27. Bell CG, Walley AJ, and Froguel P. The genetics of human obesity. Nat Rev Gen 2005;6: 221–234.

28. Perusse L, Rankinen T, Zuberi A, et al. The human obesity gene map: the 2004 update. Obes Res 2005;13: 381–490.

29. Mathur R, Douglas NJ. Family studies in patients with the sleep apnea-hypopnea syndrome. Ann Intern Med 1995;122:174–178.

30. Gottlieb DJ, DeStefano AL, Foley DJ, et al. APOE epsilon4 is associated with obstructive sleep apnea/hypopnea: the Sleep Heart Health Study. Neurology 2004;63: 664–668.

31. Gislason T, Johannsson JH, Haraldsson A, et al. Familial predisposition and cosegregation analysis of adult obstructive sleep apnea and the sudden infant death syndrome. Am J Respir Crit Care Med 2002;166: 833–838.

32. Carmelli D, Colrain IM, Swan GE, and Bliwise DL. Genetic and environmental influences in sleep-disordered breathing in older male twins. Sleep 2004;27: 917–922.

33. Boston BA Pro-opiomelanocortin and weight regulation: from mice to men. J Pediatr Endocrinol Metab 2001;14: 1409–1416.

34. Tsuchiya T, Shimizu H, Horie T, Mori M. Expression of leptin receptors in lung: leptin as a growth factor. Eur J Pharmacol 1999;365:273–279.

35. Palmer, L J, Buxbaum, S G, Larkin, E, et al. A Whole-Genome Scan for Obstructive Sleep Apnea and Obesity. Am. J. Hum. Genet 2003;72:340–350.

36. Comuzzie AG, Hixson JE, Almasy L, et al. A major quantitative trait locus determining serum leptin levels and fat mass is located on human chromosome 2. Nat Genet 1997;15:273–276.

37. Hixson JE, Almasy L, Cole S, et al. Normal variation in leptin levels is associated with polymorphisms in the proopiomelanocortin gene POMC. J Clin Endocrinol Metab 1999;84: 3187–3191.

38. Delplanque J, Barat-Houari M, Dina C, et al. Linkage and association studies between the proopiomelanocortin (POMC) gene and obesity in Caucasian families. Diabetologia 2000; 43:1554–1557.

39. Miraglia del Giudice E, Cirillo G, Santoro N, et al. Molecular screening of the proopiomelanocortin (POMC) gene in Italian obese children: report of three new mutations. Int J Obes Relat Metab Disord 2001;25: 61–67.

40. Larkin EK, Elston RC, Patel SR, et al. Linkage of serum leptin levels in families with sleep apnea. Int J Obes Relat Metab Disord 2005;29(3):260-7.

41. Collins DD, Scoggin CH, Zwillich CW, and Weil JV. Hereditary aspects of decreased hypoxic response. J Clin Invest 1978;62: 105–110.

42. Pillar G, Schnall RP, Peled N, Oliven A, and Lavie P. Impaired respiratory response to resistive loading during sleep in healthy offspring of patients with obstructive sleep apnea. Am J Respir Crit Care Med 1997;155: 1602–1608.

43. Polotsky VY, Smaldone MC, Scharf MT, et al. CP. Impact of interrupted leptin pathways on ventilatory control. J Appl Physiol 2004;96: 991–998.

44. Patel S J. Shared genetic risk factors for Obstructive Sleep Apnea and obesity J Appl Physiol 2005;99: 1600-1606.

45. Espana RA and Scammell TE. Sleep neurobiology for the clinician. Sleep 2004;27: 811–820.

46. Peyron C, Faraco J, Rogers W, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nat Med 2000;6: 991–997.

47. Sakurai T, Amemiya A, Ishii M, et al.. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 1998;92: 573–585.

48. Rankinen T, Perusse L,Weisnagel SJ, Snyder EE, Chagnon YC, Bouchard C.The human obesity gene map: the 2001 update. Obes Res 2002;10:196–243.

49. Wilson AF, Elston RC, Tran LD, Siervogel RM. Use of the robust sib-pair method to screen for single-locus, multiple- locus, and pleiotropic effects: application to traits related to hypertension. Am J Hum Genet 1999;48:862–872.

50. Bailey-Wilson JE, Wilson AF, Bamba V. Linkage analysis in a large pedigree ascertained due to essential familial hypercholesterolemia. Genet Epidemiol 1993;10:665–669.

51. Bray MS, Boerwinkle E, Hanis CL. Linkage analysis of candidate obesity genes among the Mexican-American population of Starr County, Texas. Genet Epidemiol 1999;16:397– 411.

52. Chagnon YC, Borecki IB, Perusse L, et al. Genome-wide search for genes related to the fat-free body mass in the Quebec family study. Metabolism 2000;49:203–207.

53. Sun G, Gagnon J, Chagnon YC, et al. Association and linkage between an insulin-like growth factor-1 gene polymorphism and fat free mass in the Heritage Family Study. Int J Obes Relat Metab Disord. 1999;23:929–935.

54. Palmer LJ, Buxbaum SG, Larkin E, et al. whole-genome scan for obstructive sleep apnea and obesity. Am J Hum Genet 2003;72: 340–350.

55. Cowley MA, Smart JL, Rubinstein M, et al. Leptin activates anorixegenic POMC neurons through a neural network in the arcuate nucleus. Nature 2001;411: 480–484.

56. Pelleymounter MA, Cullen MJ, Baker MB, et al. Effects of the obese gene product on body weight regulation in ob/ob mice. Science 1995;269: 540–543.

57. Fehm HL, Smolnik R, Kern W, McGregor GP, Bickel U, and Born J. The melanocortin melanocyte-stimulating hormone/adrenocorticotropin(4–10) decreases body fat in humans. J Clin Endocrinol Metab 2001;86: 1144–1148.

58. Comuzzie AG, Hixson JE, Almasy L, et al. A major quantitative trait locus determining serum leptin levels and fat mass is located on human chromosome 2. Nat Genet 1997;15: 273–276.

59. Hager J, Dina C, Francke S, et al. A genome-wide scan for human obesity genes reveals a major susceptibility locus on chromosome 10. Nat Genet 1998;20: 304–308.

60. Sloan JL and Mager S. Cloning and functional expression of a human Na+ and Cl–-dependent neutral and cationic amino acid transporter B0+. J Biol Chem 1999;274: 23740–23745.

61. Krude H, Biebermann H, Luck W, Horn R, Brabant G, and Gruters A. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. Nat Genet 1998;19: 155–157.

62. Kolehmainen J, Black GC, Saarinen A, et al. Cohen syndrome is caused by mutations in a novel gene, COH1, encoding a transmembrane protein with a presumed role in vesicle-mediated sorting and intracellular protein transport. Am J Hum Genet 2003;72: 1359–1369.

63. Chandler KE, Kidd A, Al-Gazali L, et al. Diagnostic criteria, clinical characteristics, and natural history of Cohen syndrome. J Med Genet 2003;40: 233–241.

64. Blundell JE, Goodson S, and Halford JC. Regulation of appetite: role of leptin in signalling systems for drive and satiety. Int J Obes Relat Metab Disord 25, Suppl 2001;1: S29–S34.

65. Kubin L, Tojima H, Davies RO, and Pack AI. Serotonergic excitatory drive to hypoglossal motoneurons in the decerebrate cat. Neurosci Lett 1992;139: 243–248.

66. Sood S, Liu X, Liu H, Nolan P, and Horner RL. 5-HT at hypoglossal motor nucleus and respiratory control of genioglossus muscle in anesthetized rats. Respir Physiol Neurobiol 2003;138: 205–221.

67. Durand E, Boutin P, Meyre D, et al. Polymorphisms in the amino acid transporter solute carrier family 6 (neurotransmitter transporter) member 14 gene contribute to polygenic obesity in French Caucasians. Diabetes 2004;53: 2483–2486.

68. Zhang LQ, Yao WZ, He QY, Wang YZ, Ren B, Lin YP. Polymorphisms in the ß2 and ß3 adrenergic receptor genes in obstructive sleep apnoea/hypopnoea syndrome. Zhonghua Nei Ke Za Zhi 2005;44:333–336.

69. Barley J, Blackwood A, Carter ND, et al. Angiotensin converting enzyme insertion/deletion polymorphism: association with ethnic origin. J Hypertens 1994;12(8):955-7.

70. Xiao Y, Huang X, Qiu C, et al. Angiotensin I-converting enzyme gene polymorphism in Chinese patients with obstructive sleep apnea syndrome. Chin Med 1999;J.112(8):701-4.

71. 1 Isono S, Remmers JE, Tanaka A, et al. Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects. J Appl Physiol 1997;82:1319–26.

72. Donnelly LF, Shott SR, LaRose CR, et al. Causes of persistent obstructive sleep apnea despite previous tonsillectomy and adenoidectomy in children with down syndrome as depicted on static and dynamic cine MRI. AJR Am J Roentgenol 2004;183(1):175-81.

73. Lam B, Ip MS, Tench E, Ryan CF. Craniofacial profile in Asian and white subjects with obstructive sleep apnoea. Thorax. 2005;60(6):504-10.

74. Ozturk L. The Association of the Severity of Obstructive Sleep Apnea with Plasma Leptin Levels. Arch Otolaryngol Head Neck Surg 2003;129:538-540.

75. Turek FW, Joshu C, Kohsaka A, et al. Obesity and metabolic syndrome in circadian clock mutant mice. Science 2005;308:1043–1045.

76. Patel SR, Larkin EK, Palmer LJ, et al. Shared genetic variance of sleep apnea and related metabolic traits. Am J Respir Crit Care Med 169: A759, 2004.