OBSTRUCTIVE SLEEP APNEA (OSA), a disorder characterized by repetitive collapse of the upper airway during sleep, is one of the most common respiratory disorders, with an estimated prevalence of 24% and 9% among middle-aged American men and women, respectively (92). Obesity in modern Western society is also extremely common. As of 2002, nearly one-third of US adults met clinical criteria for obesity, and this prevalence appears to only be increasing (27).

That obesity and OSA often colocalize is of no surprise. Other than perhaps male gender, obesity is the strongest risk factor for the development of OSA. Relative to those with a stable weight, a 10% increase in weight over 4 yr is associated with a sixfold increase in the risk of developing moderate to severe OSA (58). Weight loss trials have found significant reductions in apnea severity with moderate weight loss (69, 74). However, the mechanisms by which obesity causes OSA are not completely defined, with many potential pathways hypothesized (93). 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 (37). Another possible mechanism relating obesity with sleep apnea is via the hormonal effects of adipose tissue. Leptin, a hormone produced by adipose tissue, has important effects on weight regulation by stimulating hypothalamic satiety centers (6, 34, 57). Human obesity is typically associated with elevated leptin levels, suggesting a state of leptin resistance (15). Besides regulating weight, leptin may have important effects on ventilatory drive. Leptin-deficient mice hyperventilate and have a blunted response to hypercapnia (53, 84). Administration of leptin corrects these abnormalities independent of changes in weight (53). 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.

It is also possible that OSA may play a causal role in the development of obesity. OSA patients have elevated leptin levels compared with weight-matched controls, and OSA treatment lowers these levels (39, 53, 55). These findings suggest OSA may be a cause of leptin resistance and thus a propensity for further weight gain. Not only does sleep disruption, a common result of OSA, reduce serum leptin levels, it also increases levels of the appetite-stimulating hormone ghrelin (76, 82). These findings were associated with increases in hunger and appetite scores (76). Epidemiological studies consistently implicate reduced sleep as a risk factor for the development of obesity (36, 47, 70, 82, 87, 89). Although overall weight does not appear to fall with treatment of OSA, one study did find the amount of fat inside the abdominal cavity (visceral fat) diminishes (10). This fat compartment appears to have unique hormonal effects as the amount of visceral adipose tissue is more strongly associated with metabolic complications of obesity such as insulin resistance and dyslipidemia than measures of subcutaneous fat or overall obesity (28, 29).
FAMILIAL AGGREGATION OF OBESITY AND SLEEP APNEA

That obesity is in large part genetically determined has been known for almost three decades (26). A large twin study estimated the heritability of weight to be 78% (79). That is to say, 78% of the variability in weight across a population is explained by shared intrafamilial factors. Subsequent studies demonstrated that adopted children have a body size more closely resembling their biological parents than their adopted parents (80). Studies in Finland and the United Kingdom have estimated the heritability of body mass index (BMI) to be 60–80% (42, 61). Linkage to obesity-related phenotypes has been investigated in some 50 genomewide scans to date with dozens of candidate loci and genes identified (3, 59).

Similarly, familial factors have been known to influence OSA risk for nearly 25 years (77). Since then, several groups have quantified the familial risk of OSA by studying widely different populations. All of these studies have identified a strong heritable component to OSA (30, 32, 49, 62, 66). Family-based studies suggest that the risk of OSA is approximately twice as great among relatives of apneic persons (30, 66). In addition, a dose-response relationship exists such that the risk of OSA increases with increasing number of apneic relatives (66). 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% (7).

SHARED SUSCEPTIBILITY GENES

Given the strong genetic components to 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. This is clearly not the case. Even after controlling for BMI, significant familial aggregation for OSA persists (32, 66). Furthermore, a study of nonobese apneic patients also demonstrated strong heritability of OSA (49). That this should be the case should be of no surprise given that other pathophysiological pathways to apnea development such as craniofacial structure and ventilatory control have also been demonstrated to have a heritable component (13, 32, 49, 63, 65). Thus the susceptibility genes for OSA are not exclusively the same genes as those modulating obesity. That does not mean, however, that no overlap exists.

Clearly, given the strong effect of obesity on OSA pathogenesis, any genetic variant that predisposes to obesity will secondarily also lead to the development of OSA. Thus any obesity gene might also be considered to be an apnea gene. However, obesity is not a monolithic process. Clearly, there are some forms of obesity that have a more important role in the pathogenesis of sleep apnea. For example, fat deposition in the neck is much more important than fat deposition in the limbs (17). An android fat deposition pattern (excess subcutaneous truncal-abdominal fat) and visceral adiposity have also been found to more closely predict OSA than overall obesity (31, 72). Therefore genetic polymorphisms that influence fat deposition in these sites will be more important OSA genes. There is a wealth of evidence that these fat distribution pattern phenotypes are genetically driven. Large differences in the patterns of fat deposition exist across inbred strains of cattle, suggesting an important role for genetics (83). Among humans, even after correction for overall obesity, measures of fat deposition pattern aggregate within families. The ratio of subscapular skinfold thickness to subscapular plus suprailliac thicknesses, a measure of the android fat pattern, has been reported to have a heritability of 43% (71). Measures of central obesity such as BMI-adjusted waist circumference and ratio of trunk to extremity skinfold ratio have heritabilities of 29–48% (40). These findings strongly support the hypothesis that there are genetic polymorphisms that specifically promote fat deposition in the subcutaneous regions of the torso or around the abdominal viscera. Through this mechanism, these variants would promote the development of both obesity and OSA.

Another type of 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). For example, by impacting leptin function, a genetic polymorphism may reduce satiety and also increase ventilatory instability. This is what is referred to as genetic pleiotropy. Pleiotropic genetic effects have clearly been described in other situations. A well known example is at the APOE locus, which codes for apolipoprotein E. The ε4 allele of APOE is an important risk factor for both atherosclerotic heart disease as well as Alzheimer’s dementia (24, 91). The circadian regulatory gene, CLOCK, also appears to influence multiple biological systems. CLOCK-knockout mice have profound disruptions in circadian rhythmicity, and so it is not surprising that these animals would have abnormal timings for feeding and activity (88). In addition, however, these mutant animals demonstrate an overall increase in caloric intake associated with a phenotype of obesity and metabolic syndrome (85). Similarly, given the large number of neurological, metabolic, and mechanical overlaps 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. Orenergic neurons in the lateral hypothalamus play an important role in sustaining wakefulness with projections to all of the wake-promoting areas of the brain (21). Loss of these neurons is associated with a narcolepsy phenotype (60). These neurons, as the name

![Fig. 1. Both obesity and sleep apnea are heavily influenced by underlying genotype. Some susceptibility genes act directly on one phenotype and through the causal relationships between obesity and sleep apnea have indirect effects on the other. Other loci have pleiotropic effects, impacting susceptibility to both obesity and sleep apnea via independent mechanisms.](http://jap.physiology.org/10.1152/jappl.00703.2004)
orexin implies, also play an important role in stimulating appetite, projecting on to the arcuate nucleus of the hypothalamus (68). 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.

The recently reported linkage scans from the Cleveland Family Study represent the first genomewide linkage studies of OSA phenotypes (54, 55). 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 (56). 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 LOD score, a measure of the odds ratio of linkage to no linkage was found at the short arm of chromosome 2. 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 without 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 (54). 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 anorexigenic activity is mediated via depolarization of these neurons, and use of an MSH agonist decreases both body fat and leptin levels in humans (16, 25). Obesity phenotypes have been consistently linked to the POMC locus (14, 33, 38, 67), haplotypes in this gene have been associated with leptin levels (38, 50), and severe mutations in this gene produce a severe childhood obesity phenotype (44). 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 (64).

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 (55). 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 (43). Severe mutations in this gene have been associated with Cohen syndrome, an autosomal recessive condition characterized by truncal obesity (9). Other findings include facial dysmorphism, mental retardation, and ocular anomalies. 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.

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 (5). In addition, serotonin potentiates hypoglossal neural output, which increases upper airway dilator muscle activity (45, 75). Thus reductions in serotoninergic activity, by increasing appetite, could promote obesity and, by lowering muscle tone in the

Table 1. Candidate genes that might link the genetic mechanisms of obesity with sleep apnea through either pleiotropy or gene × environment interactions

<table>
<thead>
<tr>
<th>Candidate Gene</th>
<th>Relationship to Obesity</th>
<th>Relationship to Sleep Apnea</th>
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</thead>
<tbody>
<tr>
<td>Pleiotropy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POMC</td>
<td>Mediator of leptin effects on appetite</td>
<td>Mediator of leptin effects on ventilatory drive</td>
</tr>
<tr>
<td>COH1</td>
<td>Regulation of fat deposition pattern</td>
<td>Regulation of craniofacial development</td>
</tr>
<tr>
<td>SLC6A14</td>
<td>Serotonergic regulation of weight</td>
<td>Serotonergic control of upper airway muscle activity</td>
</tr>
<tr>
<td>Gene × environment interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPARG</td>
<td>Regulation of adipocyte differentiation</td>
<td>Downregulated by hypoxia</td>
</tr>
<tr>
<td>UCP1, UCP2</td>
<td>Regulation of thermogenesis</td>
<td>Uregulated by sleep deprivation</td>
</tr>
</tbody>
</table>

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

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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 (51, 81). 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 (73). A French study has confirmed the association of this polymorphism with obesity, and an association with hunger and satiety scores was also found (19). Whether this polymorphism is associated with OSA (via or independent of any obesity effects) has not yet been studied, as the OSA linkage scans reported thus far have not included the sex chromosomes.

**GENE × ENVIRONMENT INTERACTION**

Another potential method of genetic interaction between obesity and OSA is a form of gene-by-environment effect where the adverse effects of obesity or OSA can be thought of as environmental stressors (Fig. 2). Each of the methods by which obesity predisposes to OSA can be influenced by an individual's underlying genetic susceptibility. An increase in fat deposition around the upper airway will be more likely to produce apnea in individuals with a lower ability to respond to this stressor due to reduced 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.

The peroxisome proliferator-activated receptor-γ (PPARG) gene located on chromosome 3p25 encodes a protein that is a key component of a nuclear transcription factor important in adipocyte differentiation (4). Variants in this gene have been implicated as risk factors for the development of obesity (4, 18, 20, 48, 86). Because hypoxia is known to suppress PPARG gene transcription (94, 95), the importance of a mild defect in PPARG function may become magnified in the setting of recurrent exposure to hypoxia from OSA. Thus PPARG allelic variants may play a much more important role in determining obesity phenotypes in individuals with OSA, and OSA may play a much more important role in promoting weight gain among those with a mutation in PPARG.

Similarly, the effects of uncoupling protein-1 (UCP1) and UCP2, two other obesity candidate genes, may be influenced by OSA. These genes encode for uncoupling proteins, mitochondrial proton channels that divert energy from ATP synthesis to thermogenesis (2). In so doing, their activation increases energy consumption. Polymorphisms in both genes have been associated with obesity phenotypes (8, 12, 22–23, 52). Interestingly, sleep deprivation in rodent models has been shown to increase expression of both UCP1 and UCP2 (11, 41), suggesting the sleep disruption of OSA may influence expression of these genes and thus the relative importance of a variant at these loci in determining obesity risk.

**FUTURE DIRECTIONS**

There appear to be multiple causal pathways linking obesity with sleep apnea. Although obesity is clearly a strong risk factor for OSA, further research is needed to better define any potential risk OSA carries for promoting weight gain. Both diseases also clearly have a strong genetic basis. Although work has begun to identify the specific genetic polymorphisms that confer risk to the development of these disorders, clearly much more needs to be accomplished in this arena. A recent workshop sponsored by the American Thoracic Society laid out recommendations for future research aimed at dissecting the genetic bases for sleep-disordered breathing (78). A chief objective was the development of novel phenotypes, including biomarkers, that more closely reflect only one or a few molecular pathways rather than the overarching syndrome defined with the AHI. These simpler phenotypes could be more amenable to genetic analysis because of the fewer sources of variance than a global measure of apnea. The same holds true for obesity research, where the use of more specific phenotypes of fat deposition patterns would provide not only better insight into the molecular mechanisms underlying obesity but also a better understanding of how obesity and OSA interrelate.

The use of dense single nucleotide polymorphism maps will allow for better resolution of linkage findings so as to narrow down candidate loci. A better understanding of the neurobiology and molecular pathways underlying obesity and sleep apnea will also allow for a more rational selection of candidate genes to test for association with these disorders. Ultimately, the use of gene-knockout animal models will be important to establish causality of any identified associations. In performing these genetic studies, it will be important to simultaneously consider both disorders given their close relationship. Methodology for conducting bivariate linkage scans has already been developed, and there is evidence to suggest that such a strategy is more powerful than traditional univariate approaches (1). Not only will many genetic variants influence the development of OSA by causing obesity or vice versa but it is likely that there are also variants with pleiotropic effects predisposing to
obesity and OSA via independent mechanisms. Identifying such genes and understanding their function will provide novel insights into the shared pathogenesis of these diseases. Finally, the possibility that genetic polymorphisms may affect the susceptibility that each disease confers toward the other should not be ignored. Incorporating such a model of gene × environment interaction into future study designs along with an understanding of the effects of obesity on OSA can allow for a better delineation of OSA susceptibility genes and vice versa. Similarly, use of such a model along with information about the genetics of obesity would allow for a more complete understanding of how OSA may impact obesity.

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