Genetics Aspects of the Obstructive Sleep Apnea/Hypopnea Syndrome

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Abstract

Obstructive sleep apnea/hypopnea syndrome is a common condition affecting approximately 0.3–4% of the middle-aged population. A hereditary component to the condition has long been identified but the genetic basis has been difficult to elucidate. Not least of the difficulties resides in a single definition of the phenotype. In an attempt to unravel some of the components, which might contribute to the expression of the syndrome, ‘intermediate phenotypes’ such as craniofacial structure, obesity and upper airway control have been utilized. A number of gene polymorphisms have been explored in association with these and two genome-wide scans have identified potential regions, which may be of interest in further defining the ‘intermediate phenotypes’. This chapter focuses largely on human studies with an update on the most recent work in the area.

Obstructive sleep apnea/hypopnea syndrome (OSAHS) affects approximately 0.3–4% of the middle-aged population and is defined on the basis of symptoms of daytime sleepiness and objective measures of disordered breathing during sleep [1]. OSAHS occurs throughout the entire lifespan, from neonates to the elderly. In adults, the frequency of disordered breathing during sleep increases with age and is poorly associated with an increased incidence of daytime sleepiness or other symptoms of OSAHS [2, 3].

A number of studies have shown that OSAHS runs in families. Mechanisms contributing to the etiology of OSAHS include genetically and environmentally induced changes in craniofacial dimensions, differential deposition of adipose tissue, abnormalities in upper airway control and differential susceptibility to sleepiness. All of these potential co-etiologies have come under increasing scrutiny on a genetic level. With the completion of the Human Genome Project and the establishment of a single nucleotide polymorphism (SNP) gene map, enormous progress has been made in clarifying the genetic causes of phenotypic differences in the human population.

Here, we will deal with current knowledge regarding OSAHS and genetic factors with a focus on human studies.

OSAHS Phenotype

A precise characterization of the OSAHS phenotype is difficult. Therein lies the primary problem in conducting genetic studies on this disorder.

There is no one specific human morphology that is typical such as is the case in mendelian (single gene) disorders, e.g. Duchenne’s muscular dystrophy. OSAHS remains a condition that must be classified on a physiological basis and on objective or subjective evaluation of sleepiness manifest as a daytime symptom. Currently, the most widely accepted definition of OSAHS is provided by The American Academy of Sleep Medicine Task Force [4]. Although this constitutes a good general working definition of the disorder and can be applied satisfactorily in a research setting, it is pragmatic rather than soundly evidence based and does not take into
account age-related or gender-related changes in sleepiness and sleep-disordered breathing. There are very few normative data for either in the population and the results obtained are highly dependent on the technology used to measure breathing during sleep or sleepiness [2, 3, 5].

Variations in definitions hinder comparison between studies and may make replication studies examining genetic factors difficult to evaluate.

Owing to the inherent nosological problems with the definition of OSAHS, genetic studies have largely focused on its component parts, the ‘intermediate phenotypes’, which contribute to its clinical expression such as craniofacial changes, obesity, fat distribution, metabolic derangements and control of ventilation.

**Is Obstructive Sleep Apnea/Hypopnea Syndrome Hereditary?**

It has been suggested that hereditary factors invoke 40% of the variance in the occurrence of OSAHS in the population [6].

Initially, case reports were suggestive of a familial link for OSAHS, but they were not representative of the population at large (e.g. [7]).

Douglas [8] performed a prospective study of first-degree relatives of 20 consecutive nonobese patients with OSAHS. In studying a total of 40 relatives, they found that 10 of them had more than 15 apneas/hypopneas per hour of sleep and 8 had more than five 4% desaturations per hour. A further study using cephalometry suggested that relatives of probands with OSAHS had more backset maxillae and mandibles compared to age and sex-matched controls [9]. Twin studies have found greater concordance for snoring among monozygotic compared to dizygotic twins [10]. Familial aggregation and segregation analysis of snoring and symptoms of OSAHS applied to 584 pedigrees with 2,019 cases enrolled in the Tucson Epidemiologic Study of Obstructive Airways disease demonstrated mendelian dominant or co-dominant transmission [11]. However, this analysis also found that a non-genetic model would fit the data equally well, suggesting that environmental factors probably contribute to the development of OSAHS. More recently, Buxbaum et al. [12] performed a segregation analysis on a sample of 177 Caucasian families and 125 African-American families. This demonstrated transmission of a putative candidate gene for OSAHS (defined solely by apnea/hypopnea index, AHI) that was variable depending on whether the mathematical/statistical model was age- or BMI-adjusted for the Caucasians and independent of BMI for African-Americans.

AHI is variable within subjects on a nightly basis and subject to recording and scoring error. Therefore, it is not an immutable characteristic that substitutes for phenotype. Furthermore, a previous study showed that BMI is just as important in the etiology of OSAHS in African Americans as it is in American Caucasians [13].

Although there may be racial differences in the presentation of OSAHS [14], it is often taken for granted that the human species is divided into homogeneous groups or races among which biological differences are large [15]. Studies of allele frequencies do not support this view, as differences between members of the same population account for 85% of the total diversity. Differences among continents represent roughly 1/10 of human molecular diversity, which does not suggest that racial subdivision of our species reflects any major discontinuity in our genome [15].

**Craniofacial Morphology**

The craniofacial complex is probably one of the most important heritable determinants of OSAHS. A number of morphological features have been described including changes in cranial base dimensions, displacement of the hyoid bone inferiorly, macroglossia, adenotonsillar hypertrophy, bulkier soft tissue in the upper airway resulting in narrowing and increases in lower facial height [16–18].

Retroposed maxillae and specifically short mandibles have been consistently shown to predispose to OSAHS [17, 18]. Such differences in jaw size can be inherited or acquired – e.g., following nasal occlusion in childhood [19]. There are also a number of syndromes such as the Carpenter syndrome and Apert’s syndrome, which are associated with craniofacial anomalies leading to OSAHS. Here the genetic locus has been identified but the confounder remains the multitude of associated anomalies, which characterize these syndromes.

The craniofacial complex is comprised of a number of components which are interdependent in their growth patterns and which are so closely linked, that the growth and shape of one component will influence the rest.

A hierarchy of control genes is activated in sequence, which specifies how the cells in a domain should develop. These controls are influenced by local feedback and intercommunication mechanisms between cells and tissues. The effect of other genes on contiguous tissue will also influence expression of the gene of interest with resultant effects on each other. Genes have been identified through animal studies (mouse mutants), human craniofacial syndromes and expression studies of signaling molecules during facial growth.
development [20]. It is now well recognized that growth of the craniofacial complex continues throughout adulthood; that significant sexual dimorphism exists with men being larger at all ages with more growth; that women have periods of increased growth often associated with pregnancy; and that mandibular orientation and occlusal relations change throughout the life cycle [21].

Environmental mechanisms affecting growth include deleterious orofacial muscle habits such as thumb-sucking and abnormal tongue posturing; nasopharyngeal disease and disturbed respiratory function which may produce mouth-breathing; oral/gingival tumors; dental caries with loss of teeth and loss of permanent teeth. Polymorphisms in genes controlling final adult height and stature may affect craniofacial growth. These include the vitamin D receptor, beta-2-adrenergic receptor, growth hormone, insulin-like growth factor (IGF-1), insulin-like growth factor receptor and growth hormone receptor (GHR). Specifically, IGF-1 has been shown to be an important and independent regulator of maxillofacial and mandibular growth postnatally [22].

GHR gene SNPs have been associated with postnatal bone and soft tissue growth as well as with obesity [23]. A recent study aimed to quantitatively evaluate the relationship between craniofacial morphology and the Pro561Thr (P561T) variant in the GHR gene in a normal Japanese population [24]. Subjects without P561T had a significantly longer mandibular ramus as measured cephalometrically suggesting that the GHR gene P561T variant may be associated with mandibular height growth as well as being a genetic marker for it. Riha et al. [unpubl.] examined the GHR P561T polymorphism (within 10 kb of the +561 T/G SNP) in 400 subjects and found no association with cephalometric variables in those with OSAHS compared to those without it.

Studies using genome-wide linkage to look at mandibular structure and size have so far not been undertaken in humans.

**Obesity**

Obesity is the most commonly identified risk factor for OSAHS [25]. Obesity is thought to contribute to the development/expression of OSAHS due to reduction in nasopharyngeal caliber secondary to fat deposition or as a result of hypoventilation due to a decrease in chest wall compliance. Heritability for Body Mass Index (BMI) in large sample sizes has been estimated to lie between 25 and 40% [26].

The susceptibility to becoming obese therefore seems to be determined significantly by genetic factors, but a favorable ‘obesogenic’ environment is necessary for phenotypic expression [27].

The regulation of appetite and energy expenditure comprises an extremely complex system with a large number of redundant pathways biased towards weight gain. Obesity develops when energy intake exceeds energy expenditure over time. Accumulated information regarding obesity susceptibility genes is so extensive, that it is currently published in updated form on an annual basis as The Human Obesity Gene Map and is now available as a website (http://obesitygene.pbrc.edu). The most current update [27] incorporates published results on single-gene mutation obesity cases, Mendelian disorders exhibiting obesity as a feature, quantitative trait loci (QTLs) from human genome-wide scans and animal crossbreeding experiments as well as association and linkage studies with candidate genes and other markers. In total, more than 300 genes, markers and chromosomal regions have been associated or linked with human obesity phenotypes.

So far, only a few single gene mutations causally related to obesity have been convincingly detected in a small number of people. These include the leptin receptor gene, the leptin gene, the pro-opiomelanocortin gene, the prohormone convertase 1 gene and the melanocortin MC4 receptor gene. A recent meta-analytic review of the linkage association of the 3 currently known leptin receptor gene polymorphisms in a total of 3,263 individuals (>74% Caucasian) showed no statistically significant association with waist circumference or body mass index at the p = 0.05 level [28]. The role of leptin in OSAHS has been emphasized in recent sleep research. However, its role in normal and obese physiology has not been elucidated. Because of its pleiotropic effects on metabolic and appetite regulation, control of ventilation and sleep homeostasis, it cannot be fully integrated in a single pathway that results in OSAHS alone. Other genes that have been sequenced and screened in the search for what predisposes to obesity include the agouti gene, the uncoupling proteins (UCP1–3), all the melanocortin receptor genes, the neuropeptide Y receptor 1 and 5 genes, TNF-α, peroxisome proliferation-activated receptor-gamma (PPAR-γ) and the β3-adrenocceptor genes among many others. None of the genetic associations reported so far has been proven to be the consequence of a mutation affecting the function or amount of a gene product. Many of the studies reporting single gene polymorphisms associations also need to be supported by cellular work identifying the functional consequences of the reported polymorphisms and it would be of greater clinical relevance if the environmental circumstances necessary for the full phenotypic consequence of these genes and their expression were identified.
**Upper Airway in OSAHS**

Sleep-related reductions in pharyngeal muscle activity lead to snoring and upper airway obstruction, which in turn lead to arousal from asleep. These arousals in turn activate the pharyngeal muscles thereby restoring airway patency and more effective breathing.

The genioglossus muscle, innervated by the hypoglossal nerve, is considered to be the major upper airway dilator. NREM sleep and especially REM sleep are associated with the withdrawal of tonic excitation of the hypoglossal motor neurons via reduced firing of predominantly serotonergic medullar raphe neurons and less so by noradrenergic locus coeruleus neurons [40].

Molecular dissection techniques have most recently shown the 5HT2A receptor to be the predominant receptor subtype in hypoglossal motor neurons [41] and pharmacologic trials support this receptor subtype as well as 5-HT2c (found in much smaller quantities) as the predominant post-synaptic facilitator of hypoglossal motor neurons, thereby being instrumental to the regulation of upper airway tone [42].

Clinically, attempts have been made to alleviate obstructive apneas by using selective serotonin reuptake inhibitors (SSRI) [43]. The results have been mixed, with incomplete responses to the SSRIs despite demonstration of increased genioglossal activity as measured by EMG in the awake state.

In light of current knowledge in this area, it would be of potential value to explore whether gene polymorphisms in the 5-HT2A receptor may play a role in the modulation of serotonin metabolism affecting upper airway responsiveness. A preliminary study by Riha [unpubl.] showed no difference in a population of over 400 subjects in the distribution of the T102C SNP in the 5HTR2A gene between those with and without OSAHS compared to those without it [37].

**Control of Ventilation**

Genetic influences may play a role in determining the wide variability in the magnitude of response to hypoxia and hypercapnia in the adult human. Studies in
adult monozygotic twins have shown concordance in responses to hypoxia, but not consistently to hypercapnia [45, 46]. A high degree of heritability of peripheral chemoreceptor response to hypoxia and hyperoxia in monozygotic twins during infancy compared with dizygotic twins exposed to similar environmental conditions has also been shown [47].

An examination of the ventilatory drive in OSAHS patients and their healthy relatives as well as healthy unrelated controls has been undertaken by a number of investigators with no convincing differences demonstrated [48, 49]. Based on this information, it is difficult to conclude that there is one single abnormality in ventilation in sleep disordered breathing, making search for a candidate gene currently untenable. Knowledge with regard to neural control of breathing in vertebrates is still in its infancy. Gene deletion models and their effects on ventilatory responses in transgenic mice have been investigated at length but the genes examined potentially play their most important role during early embryonic development and for a brief and transient period only, e.g. Hox and Krox-20 [50].

The outstanding issue remains whether respiratory control is implicated in the pathogenesis of OSAHS. Although there are abnormalities of respiratory control in OSAHS, these reverse with CPAP [51, 52]. Thus, the changes may be secondary rather than causative. This makes search for a genetic abnormality in respiratory control likely to be low yield.

**Apolipoprotein E – A Role in OSAHS?**

Apolipoprotein E (APOE = gene; ApoE = protein) occurs in all lipoproteins and its major role is thought to be the conversion of LDL proteins to IDLs [53]. The 3 major isoforms of human apo E (apoE2; apoE3 and apoE4) are coded for by 3 alleles (epsilon 2, 3, 4). The APOE3 allele is the most frequent, especially in populations with a long-established agricultural economy such as those in the Mediterranean basin where the frequency of the allele is 0.849–0.898. The APOE4 allele frequency remains higher in populations such as the Pygmies (0.407), Aborigines of Malaysia (0.240) and Australia (0.260) [54].

Allelic variants in APOE were first examined on the basis of its role as an ‘injury-response’ macromolecule in peripheral nerves and neuromuscular junctions in the context of pharyngeal dilator muscle patency in OSAHS [55]. In this Finnish population, there was no significant difference in distribution of either APOE alleles or genotypes between cases and controls. A second study in an American population looked exclusively at the presence or absence of apolipoprotein E4 alleles in a group of patients who had all undergone polysomnography and were classified as all having sleep apnea (AHI >5) [56]. A normal control group was not used and subjects were grouped as either APOE4-positive (n = 222) or APOE4-negative (n = 569). There was a significantly higher mean AHI in the E4-positive group (6.5±0.6 vs. 4.8±0.3) and there was a higher percentage of patients with AHI >15 in the E4-positive group (12 vs. 7%). However, the median values between groups were not significantly different: 1.3 (0–121) in the E4-negative group vs. 2 (0–81) in the E4-positive group. A third study in 718 Japanese-American men in Hawaii aged between 79 and 97 years demonstrated a prevalence of 18% of the E4 allele [57]. Moderate to severe sleep disordered breathing (AHI >15) was present in 42% of this sample of men and adjustment for age, BMI, smoking and use of antihypertensive medication did not reveal an association between E4 and an AHI >15. The most recent study in 1,775 American subjects aged between 40 and 100 years, showed one APOE e4 allele present in 25% of subjects with only 1.3% being E4/E4 homozygotes [58]. Only 19% of the population had an AHI >15 events/h. The strongest association of APOE e4 was found in subjects aged less than 65 years (OR 3.08, CI 1.43–6.64) and was stronger with hypertension or cardiovascular disease.

Apo E is inconsistently associated with the presence of atherosclerosis, Alzheimer’s disease and potentially neuropathy and the association with sleep apnea is even more problematic. No controls without OSAHS have been examined in the positive studies. Furthermore, OSAHS is associated with a number of comorbidities that have independently been shown to associate with increased frequency of the E4 allele, such as atherosclerosis, and coronary artery disease. There also appears to be no biologically plausible mechanism currently under consideration that would link ApoE with the development of OSAHS.

**OSAHS as a Complex Trait**

OSAHS appears to be a polygenic disorder with a complex phenotype, so it is not surprising that there have been relatively few studies investigating genetic markers in association with global phenotype per se.

Early studies looked at HLA markers. A Japanese study [59] showed an association of the HLA-A2 antigen with OSAHS. Another study in an American population showed no association of HLA-DR2, commonly found in the narcoleptic population, with OSAHS [60]. Numbers in both studies were very small. A more recent study examining
HLA antigens in 41 children with OSAHS found HLA-B65 to be significantly more frequently expressed in this group compared to controls [61]. Overall, however, the data did not suggest that HLA played a key role in the pathogenesis of OSAHS.

More recently, attempts have been made to associate various gene polymorphisms with OSAHS. Data from a Han Chinese population was examined for an association of the angiotensin system genes (modulation of hypoxic responses at altitude; effects on hypertension) with OSAHS [62]. Findings suggested that the angiotensin G/T polymorphism was potentially involved in the development of central obesity and thereby may have contributed to the expression of OSAHS and hypertension. Application of this result to over a thousand American subjects in the Wisconsin Sleep Cohort revealed that the ACE gene insertion/deletion polymorphism was dose-dependently associated only with the degree of blood pressure recorded and not with sleep-disordered breathing [63].

Another factor potentially accelerating the development of cardiovascular disease is haptoglobin, an antioxidant and immunomodulatory protein encoded by 2 alleles. A study examining 465 subjects with OSAHS compared to 757 controls showed the risk of cardiovascular disease in sleep apnea patients <55 years with haptoglobin 2–2 was greater than 2.32-fold compared to haptoglobin 2–1 [64].

The first study to look at cytokine gene polymorphisms in OSAHS has shown that the (−308A) TNF-α polymorphism occurs significantly more frequently in subjects with OSAHS compared to population controls and in siblings with OSAHS compared to siblings without OSAHS [37]. To date, 2 genome-wide scans in a population with OSAHS have been published. Palmer et al. [65] performed a 9-cM genome scan for OSAHS and obesity in 66 European-American pedigrees comprising 349 subjects. OSAHS was phenotyped on the basis of AHI alone. The pedigrees were chosen on the basis of either an affected individual with overnight, in-home measurement of breathing using a portable monitor (Edentec®) or a proband who was a neighborhood control individual. Multipoint variance-component linkage analysis was performed for the OSAHS-associated quantitative phenotypes of AHI and BMI. The analysis identified candidate regions on chromosomes 1p (LOD score 1.39), 2p (LOD score 1.64), 12p (LOD score 1.43) and 19p (LOD score 1.40) for linkage with AHI. BMI was linked to the following regions: chromosome 2p (LOD score 3.08), 7p (LOD score 2.53) and 12p (LOD score 3.41). Further statistical modeling indicated that evidence for linkage to AHI was removed after adjustment for BMI, excepting regions on chromosomes 2p (adjusted LOD score 1.33) and 19p (adjusted LOD score 1.45). When BMI linkages were adjusted for AHI the LOD scores were roughly halved.

A further 9-cM whole genome scan was conducted in 59 African-American pedigrees [66]. Once again, OSAHS was defined on AHI alone and analysis identified linkage on chromosome 8q (LOD score 1.29) [64]. Body mass index was linked to chromosomes 4q (LOD = 2.63) and 8q (LOD = 2.56). Adjustment for AHI greatly reduced linkages to BMI and vice versa.

Why findings between the two studies differ is difficult to explain. It should also be noted that LOD scores of less than 2 are not considered to demonstrate significant linkage under most circumstances so the results must be interpreted with caution.

**Conclusions**

OSAHS is a complex, polygenic disease with a number of etiologies interacting to produce a single phenotype. OSAHS is not just a sporadic, but also a familial condition. The degree of environmental influence on its development is currently unknown but is almost certainly considerable including effects on obesity and craniofacial structure.

The major factor affecting progress in genetic studies remains a solid definition of the OSAHS phenotype. Further investigation should be undertaken into whether the OSAHS phenotype remains static throughout life, or whether it changes with time and under different environmental conditions. At present, we are limited to studying the phenotype at a single point in time – when it calls itself to clinical attention, generally in middle age.

Longitudinal studies, firstly identifying those who have OSAHS in childhood and following them through and secondly, continuing to follow those with sleep disordered breathing identified in adult life could be useful in clarifying this issue. There may be large differences in underlying genotype, for instance, between those progressing into old age with asymptomatic sleep disordered breathing, compared to those who develop symptoms and require treatment. We may discover that we are dealing with a range of diseases that manifest as a single phenotype at a particular point in time in the individual’s life rather than a single disorder (genotype). Further study is needed to determine the best variables to be used to define phenotype, including age and gender related cut-offs to be used.

Perhaps it is premature at present to utilize genome-wide scans in OSAHS owing to phenotype complexity. Choosing candidate genes for OSAHS in case-control
studies is also difficult because a large number of disparate co-etiologies need to be considered. These include obesity, craniofacial structure, upper airway control and sleepiness. Each of these etiologies in turn is regulated by a wide variety of genes and mechanisms that may be pleiotropic and may interact and influence each other. The role of epigenetic phenomena is underestimated and highlights influences that are difficult to measure with accuracy. OSAHS is a complex disorder and future work attempting to unravel its genetic basis may be better served by utilizing a combination of investigative methods. At present, much remains to be done in elucidating the precise role of genes involved in the regulation of craniofacial growth as well as upper airway control. Once the basic biochemical and physiological processes have been completely understood, then the underlying genetic factors will be rapidly identified.

References


