Obstructive sleep apnoea syndrome and genes

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ABSTRACT

Obstructive sleep apnoea (OSA) is a complex disease entity strongly influenced by genetic factors, especially those that affect obesity and fat distribution, upper airway muscle tone, craniofacial morphology, ventilatory control and sleep, giving rise to the OSA phenotype. OSA can also be considered a metabolic syndrome which adversely affects multiple organ systems, especially the cardiovascular system and the brain. The most widely used clinical marker for the diagnosis of OSA is the apnoea-hypopnoea index, calculated by polysomnography. A percentage of 35 to 40% of its variance can be attributed to genetic factors. Therefore, the identification and elucidation of the genes implicated in the pathogenesis of OSA becomes a matter of extensive research and could lead to the development of therapeutic agents that can have a beneficial effect on the natural course of OSA.

KEYWORDS

Genetic susceptibility, OSA, polymorphism

INTRODUCTION

Obstructive sleep apnoea (OSA) is defined by a constellation of signs and symptoms; specifically, 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-oesophageal reflux. The patient frequently wakes in the morning with a headache and dry mouth or throat. OSA is now recognised 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 apnoea-hypopnoea index (AHI) of ≥5.[2] Its association with several chronic health conditions, particularly obesity, hypertension, diabetes, and cardiovascular diseases,[5-7] has underscored the broad public health importance of this condition. An elucidation of the aetiology of OSA, and the extent to which the disorder is due to genetic factors, is needed to better develop screening and treatment approaches. Very important is the role of apnoea-hypopnoea index (AHI), which is simply a count of the number of apnoeas and hypopnoeas per hour of sleep.[8] Apnoea is defined as a pause of at least ten seconds in the oral-nasal flow of air, despite the movement of the chest or abdomen, which leads to a reduction in O_2 saturation (≥2.5%) and awakening, while hypopnoea occurs when mild obstruction leads to a decrease in air flow by 50%. This index may be moderately correlated with various indices of night-time oxygen desaturation and sleep fragmentation measured using overnight polysomnography, which includes recording of oronasal flow (thermocouples), thoraco-abdominal movements (strain gauges), electrocardiogram, submental electromyogram, electro-oculogram, electroencephalogram (C4-A1, C3-A2) and transcutaneous SaO_2. Subjects are often considered 'diseased' if the AHI exceeds the threshold value of 5.[9]

As with blood pressure, increasing values of AHI indicate increasing disease severity.[10] Most studies of the genetics of OSA have used the AHI as the major disease-defining variable, and these studies have demonstrated significant familial aggregation. Advantages of the use of AHI are simplicity and high night-to-night reproducibility,[11] whereas its major disadvantages include the between-laboratory variability in measurement technique, the lack of information it provides on the severity of individual events (duration, associated hypoxaemia and arousal) and its uniformity regarding the functional and physiological impact of the disorder.[10] OSA seems to be a complex disorder that includes multiple genes, environmental influences, and developmental factors. Specific gene

products may more directly influence lower level phenotypes than higher level phenotypes. Traits such as facial and head form, ventilatory chemosensitivity, load compensation, sympathetic nervous system activity, connective tissue laxity, muscle fatigability and central obesity are possible intermediate phenotypes for OSA. Examples of low level phenotypes include hormone levels or receptor subtypes.[10]

Inheritance and observed aggregation within families

Descriptive reports of families with multiple affected members[12,13] show that there is likely to be role for inheritance apart from familial influences related to obesity. Preliminary results from segregation analysis have further defined the likely magnitude of genetic influences. Relatives of patients with the sleep apnoea-hypopnoea syndrome reported snoring, daytime sleepiness and had more apnoeas and hypopnoeas, arousals from sleep, poorer sleep quality and more oxygen desaturations compared with relatives of controls.[14] Another study[15] calculated the estimated risk ratios for relatives of patients with OSA and found that they were increased. The risk ratio for first-degree relatives was 2.0 for parents and 1.9 for siblings. For second-degree relatives (half-sibs, uncles/ aunts, grandparents) the estimated risk ratios were 1.9, 1.3 and 1.3, respectively, with the first two being significant. The estimated risk ratio for cousins was 1.3, which was also statistically significant. The more severely affected group (continuous positive airway pressure (CPAP)-treated) shows, in general, somewhat higher risk ratios. OSA was reported in members of the same and different generations. It was found in children as well as adults, and in obese and nonobese family members. One report cited the co-occurrence of OSA, seizures and anosmia in affected family members as suggesting an inherited syndrome.[16]

Twin studies and familial clustering of snoring

First of all, the concordance for snoring was greater between monozygotic (MZ) twins than between dizygotic (DZ) twins, suggesting a role for inheritance.[17] Recent twin studies have also shown higher concordance in monozygotic than in dizygotic twins for habitual snoring.[18] Furthermore, habitual snoring, excessive daytime sleepiness, and snorting, gasping, or apnoeas were reported two or four times more frequently among the first-degree relatives of patients with OSA than among control subjects.[19] In another study a significant relationship was demonstrated between family history of snoring and self-reported snoring.[20] Risk of snoring was increased approximately threefold when at least one first-degree relative was reported to be a snorer, and increased fourfold when both parents were reportedly snorers. First-degree relatives of patients with OSA have consistently been shown to be at increased risk. Familial aggregation is generally explained by the fact that most risk factors involved in the pathophysiology of OSA are, to a large extent, genetically

determined.[16,21-24] The major risk factors for OSA include obesity, ventilatory control abnormalities, and craniofacial dysmorphism (disproportionate craniofacial anatomy).

AHI and reported frequency within families

There were studies in which the definition of the disease was based on various threshold values of the AHI. In the studies the prevalence of OSA among first-degree relatives of probands with OSA varied from 21% (in the Cleveland Family Study) to as high as 84%.[21] When OSA was defined by an AHI >5 occurring with daytime tiredness or sleepiness and one other symptom, prevalence among first-degree relatives was 84%.[21] Changing the definition by requiring an AHI >15 and the occurrence of daytime sleepiness reduced the prevalence to 13%. This remark emphasises the importance of carefully considering how phenotype is defined. The Cleveland study also found an association between sudden unexpected death in infancy and OSA, suggesting that there are some families that may be predisposed to both syndromes.[25]

Results of racial, sex and ethnic variation in AHI and BMI

Obesity is the most characteristic feature of OSA in both European-American and African-American adults, and is most commonly measured by an elevated body mass index (BMI). Although relatively little is known about OSA in non-European populations, emerging data from the United States suggest that both old and young African-Americans have higher levels of AHI than European-Americans. Obesity is more prevalent and is more epidemic in African-Americans than in European-Americans, with the greatest ethnic differences observed for females. OSA appears to present at a younger age in African-Americans than European-Americans, and may also be more severe. Hypertensive end organ disease (kidney and cerebral vascular disease) and cardiovascular mortality are two- to threefold more prevalent among African-Americans than European-Americans. Higher levels of AHI are seen in African-Americans than Caucasians, particularly among case families.[26] Elderly African-Americans were at an approximately twofold increased risk for sleep apnoea compared with elderly Caucasians, and also had more severe sleep apnoea. In the Cleveland family study, racial differences were most prominent in individuals <25 years of age and even higher among children <13 years (odds ratio >3.0).[27] Racial variations may be due to variations in upper airway anatomy and other physiological factors. Anatomic risk factors in African-Americans appeared to be related to increased upper airway soft tissue rather than bony features that reduce airway size. It has also been shown that the familial aggregation of OSA in Caucasian males may be largely determined by influences related to obesity. Another observed difference was that Pacific Islanders and Maori living in New Zealand suffer from more severe OSA compared with individuals of European descent.[28] These racial effects were attributed

Kaparianos, et al. Obstructive sleep apnoea syndrome and genes.

SEPTEMBER 2006, VOL. 64, NO. 8

281

to group differences in neck size and body mass. Further light needs to be shed on the extent to which environmental or cultural *vs* genetic factors explain such difference in underlying pathogenetic mechanisms for OSA.

Strong genetic effects underlying the BMI have been shown by studies conducted on Nigerian, Jamaican, and African-American families, with the heritability of adult BMI ranging from 48 to 58%.[29] The heritability for AHI has also been shown to have a strong genetic predisposition, in a study conducted in African-American families it was around 32%.[26] A wide genomic scan showed some evidence of linkage for both AHI and BMI to a broad region on chromosome 8q, namely 8q24. It could represent a locus affecting AHI and BMI independently. Other regions showing linkage with obesity-related phenotypes include chromosome 4q23, connected with abdominal subcutaneous fat and trunk-to-extremity skinfold ratio. The 4q23 region contains the intestinal fatty acid-binding protein 2 (*FABP2*) and uncoupling protein 1 (*UCP1*) genes, which have been associated with BMI, percentage of body fat, abdominal fat, and weight loss.[26] The 8q21 region linked BMI and leptin levels, and the 10q26 region associated BMI levels with measures of abdominal fat. The chromosome 8q22 region also contains a core-binding factor (runt domain, P subunit) gene (*CBFA2T1*), which has been previously associated with BMI, percentage of body fat, and waist-and-hip circumference in a study of Pima Indians.[26] The 10q24–26 region contains the ponsin (*SH3D5*) and P-2A-adrenergic receptor (*ADRA2A*) genes, which have been associated with measures of obesity or fat distribution. QRS was also linked with loci on chromosomes 2p, 7p, and 12p. Regions that showed strong linkage with AHI were located on chromosomes 1p, 2p, 12p, and 19p.[26] It therefore seems that although they appear to be independent parameters, two important markers associated with OSA (AHI and BMI) have both shared and unshared genetic determinants and the analysis of the various genetic loci linked with them, through mapping efforts, could give more information on the genetics of OSA and its phenotypes

Obesity, fat distribution and implicated genes

Obesity appears to increase risk of OSA approximately 10 to 14-fold.[30,31] In contrast, weight loss may reduce the severity of the condition.[32] Obesity may lead to OSA through fat deposition in upper airway tissues, reducing nasopharyngeal caliber and/or from hypoventilation occurring in association with reduced chest wall compliance. Twin studies also showed that 70% of the variance in obesity within the general population can be attributed to genetic factors.[23,24] Familial studies of abdominal visceral fat reveal that the familial transmission reaches >50% of the age, sex and total body fat adjusted variance.[24] Obesity is believed to be secondary to abnormalities in autonomic, endocrine, and hypothalamic function which, in turn, are associated with genetic factors that influence metabolic rate, fat storage, and eating behaviour. About a quarter of the between-twin variability in regional body fat distribution may be influenced by genetic factors.[24] Hence, upper-body obesity may be a relatively greater risk factor for OSA than total body fat mass. The heritability of the amount of upper body fat or the level of upper body fat relative to lower body fat ranges from approximately 30 to 50% of the phenotype's age, sex and total body fat adjusted variance.[24] Even relatively nonobese individuals with OSA may have regional excess fat deposition, especially in the anterolateral upper airway.[33]

The coaggregation of OSA, central obesity, hypertension, and type 2 diabetes suggests that OSA may be part of a 'metabolic' syndrome, which may be largely influenced by genes that have an effect on insulin resistance and body fat distribution. Candidate genes for obesity are therefore relevant for studies of the genetics of OSA both because of the prominence of obesity in the OSA phenotype, and because of the potential impact of these genes on the expression of other traits of potential relevance to OSA. Previous genetic studies of obesity have not evaluated OSA, which may occur in as many as 66% of obese individuals. The term 'syndrome Z' has been introduced for the combination of hypertension, central obesity, insulin resistance, hyperlipidaemia, and OSA.[34] Some studies have shown combined metabolic abnormalities in patients with obesity (metabolic syndrome or syndrome X), and sleep deprivation itself has been shown to have metabolic consequences.[35] It is plausible that OSA may increase the risk of obesity. For example, OSA causes sleep fragmentation and sleepiness, effects that may promote weight gain through reduced physical activity and hypercytokinaemia.[36]

There are a number of studies showing the pleiotropic effects of leptin (an adipose-derived circulating hormone), not only in appetite regulation but also in lung growth and respiratory control as well as in sleep architecture. A genome wide scan conducted on ten extended Mexican-American families showed an established linkage between serum leptin levels and areas on chromosomes 2 and 8.[37] These regions respectively encompass genes encoding for pro-opiomelanocortin (POMC), which may be important in appetite regulation, and for X-3-adrenergic receptor (ADRB3), which may influence the regulation of energy expenditure. A more recent family study in Germany has additionally implicated mutations in the melanocortin-4 receptor gene (MC4-R) in extreme and moderate obesity.[38] A number of candidate genes for obesity (e.g. leptin, adenosine deaminase and melanocortin-4 receptor) are expressed in a variety of tissues and brain sites important in the regulation of breathing.[39,40] In knockout mice models leptin deficiency causes depressed ventilatory responses to hypercapnia in both wakefulness and sleep.[41] Finally, leptin administration also influences sleep architecture in rats.[42]

Craniofacial morphology in the aetiology of OSA

Craniofacial morphology is very important since it determines the anatomy and the diameter of the upper

Kaparianos, et al. Obstructive sleep apnoea syndrome and genes.

SEPTEMBER 2006, VOL. 64, NO. 8

282

airways. OSA occurs when the size of the upper airway is reduced.[43] Structural abnormalities that cause this are reduction of the anteroposterior dimension of the cranial base,[44] reduction of the size of the posterior and superior airway spaces,[45] inferior displacement of the hyoid,[46] elongation of the soft palate, macroglossia, adenoidotonsillar hypertrophy and increased vertical facial dimension, with a disproportionate increase in the lower facial height.[44] Retrognathia and micrognathia have also been linked with OSA, although the link was not as strong.[47] Also a brachycephalic head form often creates a problem since it is associated with sudden unexpected death in infancy and an increased risk of OSA in Caucasians while in people of African descent, this head form is uncommon, and therefore does not appear to increase risk of OSA. Finally, OSA is common in individuals with Down's syndrome, which is commonly associated with a number of craniofacial dysmorphisms, a clue that provides another link between genes affecting craniofacial morphology and OSA. Another study in 60 MZ and 40 DZ twins estimated the heritability of a number of measures of craniofacial structure. The heritability of one of these, the cephalic index, was extremely high (0.90 in males, 0.70 in females). Heredity appeared to account for 40% of the variability of dental and facial characteristics associated with malocclusions. In humans, micrognathia can be found in a myriad of chromosomal deletion syndromes, suggesting that genes affect and alter normal craniofacial growth.

Studies in mice have shown that deficiency in transforming growth factor-X2,[46] endothelin-1,[47] retinoic acid receptor-aZ[48] and collagen gene mutations (types II and XI) leads to various craniofacial abnormalities, including retrognathia and micrognathia. Various other genetic syndromes are known to cause problems in the organisation of the extracellular matrix and are associated with craniofacial dysmorphism and upper airway connective tissue laxity. One of these syndromes, the Marfan syndrome, causes abnormalities in fibrillin and may contribute to both.[49] A recent[50] study showed the volume of the lateral pharyngeal walls, tongue and total soft tissue demonstrated significant levels of heritability and that heritability of the upper airway soft tissue structures is found in normal subjects and patients with apnoea.

Ventilatory control and chemoreceptor sensitivity

Inherited abnormalities of ventilatory control may predispose to obstructive or central sleep apnoea or both by influencing ventilation during sleep and increasing the propensity to upper airway collapse. Altered ventilatory drive may participate in sleep apnoea and periodic breathing, while ventilatory control instability could cause blunted or augmented chemosensitivity.[51,52] This notion is supported by the demonstration that the degree of oxygen desaturation is the greatest and the duration of apnoeas the longest in subjects with OSA in whom ventilation in response to hypoxia during wakefulness is the most

blunted. A study by El Bayadi *et al.* demonstrated blunted ventilatory responses to progressive eucapneic hypoxia ventilatory challenges in all five of the affected subjects studied.[16] Thus, in this family, the underpinnings of OSA may have been associated with inherited abnormalities in the control of ventilation. A genetic basis for the chemoresponse to blood oxygen saturation is suggested by several twin studies that have demonstrated similarities in ventilatory responses to hypoxia or hyperoxia to be greater in monozygotic than in dizygotic twins.[53,54] The variance of responses using a single-breath hypoxic stimulus was greater within dizygotic pairs than in monozygotic twins.[54] Heritability estimates for chemoresponsivity to oxygen saturation levels vary between approximately 30 and 75%, suggesting a substantial contribution of inheritance to this trait.[54] Evidence for a role for genetics in the ventilatory response to hypercapnia in humans is less consistent. Members of OSA families significantly demonstrated a reduced ventilatory response to progressive eucapnic hypoxia measured during wakefulness compared with members of control families.[55] The finding was a significantly greater increase in ventilatory impedance with inspiratory resistive loading in OSA family members compared with control subjects. The familial aggregation of OSA may in some instances be based on inherited abnormalities in ventilatory control, perhaps related to chemoregulation and/or load compensation. The upper airway of genetically susceptible individuals appears vulnerable to excess collapsibility during conditions of mild inspiratory loading. This may occur especially during sleep as the balance between upper airway and chest wall activation changes or intrathoracic airway pressure during inspiration becomes more negative. Also, it has been shown that tidal volume is reduced in relatives of apnoea sufferers under resistive loading.[56]

There are numerous case reports of children with frequent apnoeas and daytime hypoventilation that appear attributable to severe chemoregulatory dysfunction, manifest as profound blunting of the hypercapnic and hypoxic ventilatory responses.[57] Developmental abnormalities of the brainstem or cerebral cortex have been found in some of these cases. It is worth noting that Hirschsprungs disease, a congenital disorder characterised by intestinal dysmotility and absence of myenteric and submucosal ganglia in the distal bowel, may occur in as many as 50% of cases of idiopathic congenital central hypoventilation (CCH), known as Ondine's curse.[58] Mutations of both the RET proto-oncogene, encoding a receptor tyrosine kinase thought to be involved in neural crest migration and proliferation, and the RET ligand, glial cell line-derived neurotrophic factor (GDNF),[59] have been described in children with Hirschsprungs disease, and in CCH occurring in association with Hirschsprungs disease.[60,61] More recent studies, however, implicate the PHOX2b gene as the most important cause of this syndrome. PHOX2b is mapped to chromosome

Kaparianos, et al. Obstructive sleep apnoea syndrome and genes.

SEPTEMBER 2006, VOL. 64, NO. 8

283

4p12 and encodes a highly conserved homeobox domain transcription factor (314 amino acids), with two short and stable polyalanine repeats of nine and 20 residues.[62] It has an early embryological function as a transcriptional activator in promotion of pan-neuronal differentiation including upregulation of proneural gene and mammalian achaete-scute homologue-1 (MASH1) expression, and expression of motoneural differentiation.[63] Likewise, genes pertinent to early embryological development of the autonomic nervous system (ANS) and their effect on respiratory drive are now a major area of interest and active research, such as mammalian achaete-scute homologue-1 (MASH1), bone morphogenic protein-2 (BMP2), engrailed-1 (EN1) TLX3, endothelin-converting enzyme-1 (ECE1), endothelin-1 (EDN1), PHOX2a and PHOX2b.[63] Two studies[62,63] showed that children with CCH are heterozygous for the PHOX2b polyalanine expansion mutation, although the frequency observed in the incidence of this mutation as well as in the incidence of any PHOX2b mutation differed (97 and 98.5% in the Weese-Mayer *et al.* study, 62 and 69% in the Amiel *et al.* study). Association between the polyalanine repeat mutation length and severity was also found,[63] while the Amiel *et al.* study found no such association.[62] The Amiel *et al.* study suggested that the mutation arises *de novo* while the later study suggests that it is heritable, in an autosomal dominant fashion. These associations suggest that CCH syndromes may sometimes be caused by abnormalities in migration of neural crest cells to central respiratory control centres and can provide critical information concerning the effect of genes on respiratory drive and its dysfunction. Other genes involved in the endothelin signalling pathway (endothelin B receptor gene, EDNRB and endothelin 3 gene, EDN3) have also been implicated in Hirschsprungs disease and could be considered candidate genes for CCH syndromes and sleep apnoea.[64] Other loci of interest may be identified on chromosome 15, mutations of which may result in a number of somatic abnormalities (e.g. Prader–Willi syndrome) as well as OSA.

Heterozygous and homozygous RET knockout mice, who survived only briefly, demonstrated reductions in hypercapnic ventilatory responses.[65] Endothelin-1 (ET-1), a potent vasoactive peptide, may also participate in control of ventilation. In a knockout mouse model, absence of ET-1 results in respiratory failure, ventilatory control abnormalities, craniofacial abnormalities and hypertension, characteristics remarkably similar to traits found in OSA. Mutant mice deficient in ET-1 have impaired ventilatory responses to both hypoxia and hypercapnia.[66] A zinc finger protein, namely Krox-20, has been identified which affects the development of the hindbrain. If deleted by homologous recombination in mice, they demonstrate slow respiratory frequencies and long apnoeas.[67] Loss of another factor, brain-derived neurotrophic factor (BDNF), results in reduced survival of neurons in the nodosepetrosal ganglion.[68] Homozygous mice demonstrated irregular and depressed ventilation, including spontaneous apnoeas, and abnormalities in chemoregulation specifically related to hyperoxia but not to hypercapnia. Nonlethal alterations in the genetic control of neural growth factors may contribute to phenotypic variations in ventilatory traits.[67] A small cluster of genes seem to play the major role in inheritance. These are candidate genes that encode neuroreceptors (e.g. glycine receptor, glutamate receptor) and genes that influence the postnatal development of the lung (e.g. basic fibroblast growth factor, bFGF), in the mouse model described by Tankersley.[68] Another link made between respiratory control and genetic loci was one pointing to the 8q22 chromosomal region. It contains three genes for carbonic anhydrase (CA) isoenzymes: CA1, CA2, and CA3. The roles of CA in modulating respiratory control, and the role of CA inhibitors as potential treatment for conditions with underlying respiratory instability, including sleep periodic breathing and sleep apnoea, have been the subjects of numerous animal and human studies.[69-71]

Sleep regulation, REM sleep, orexins and OSA

Some of the most exciting work on sleep-wake control has come from recent studies of narcolepsy (cataplexy, REM-onset sleep and hypersomnolence). Studies resulted in the discovery that canine narcolepsy, which is transmitted as a single autosomal recessive trait with full penetrance, is caused by mutations in one of the receptors for the newly discovered lateral hypothalamic neuropeptides, the hypocretin-1 (HCRT-1) and hypocretin-2 (HCRT-2) (also called orexins A and B, respectively),[72] two polypeptides that are ligands for two G protein-coupled receptors in the brain. At around the same time, mice with targeted disruption of the hypocretin precursor (preprohypocretin) gene were shown to have periods of behavioural arrest and EEG patterns that resemble human narcolepsy.[73] These findings in animals have now been extended to human beings and most of the narcolepsy-cataplexy patients studied have been shown to have low or undetectable hypocretin in their CSF.[74,75] Few post-mortem studies of the human brain have been conducted, but these studies have shown that patients with narcolepsy have much lower than normal hypocretin levels in the brain.[76,77]

So far, only one case of narcolepsy has been associated with a mutation in the gene that encodes preprohypocretin.[76] This case is unusual in that the onset of narcolepsy was at a very early age (cataplexy at age 6 months). The mutation in the preprohypocretin gene (a polar substitution in the hydrophobic core of its molecule, specifically arginine insertion in the polyleucine stretch of neutral, hydrophobic amino acids) results in abnormal trafficking of the mutant peptide precursor.[76] Mutations in the hypocretin 2 receptor have been identified in canine narcolepsy and disruption of the prepro-orexin /hypocretin ligand gene results in both an animal model of narcolepsy and sporadic cases of the human disease. Orexin neurons have been demonstrated to have widespread projections to areas

Kaparianos, et al. Obstructive sleep apnoea syndrome and genes.

SEPTEMBER 2006, VOL. 64, NO. 8

284

in the ascending cortical activating system, including the tuberomamillary nucleus, locus ceruleus, the dorsal and median raphe and pedunculopontine nuclei.[73] The pedunculopontine nuclei are thought to be especially critical to the control of REM sleep. Abnormalities in orexin genes, or genes coding for their receptors, could be relevant to studies of OSA because of the potential impact of these neuropeptides on arousal and muscle tone, both of which influence the behaviour of respiratory systems, and/ or because of the close proximity of these neurons to central respiratory control centres, with potential interactions between arousal and respiratory centres.

An alternative way to access the molecular biology of respiration is to characterise the genetic variation involved in individual differences in the control of respiratory behaviour. A large twin-sibling study[77] tested the heritability of 24-hour respiration rate and its genetic linkage through a whole genome scan. Four genomic regions were identified as having a high likelihood of harbouring loci that influence respiration rate, in particular loci 10q26, 22q12, 3q27 and 7p22. Positional candidate genes with the strongest evidence of linkage that are implicated in this study are the glial cell line-derived neurotrophic factor family receptor alpha-1 gene (GRFA-1, implicated in CCH), fibroblast growth factor receptor 2 gene (with its major role in craniosynostosis syndromes) and the homeobox genes HMX2 and EMX2 (with an as yet unknown function in respiratory rhythmogenesis) in the proximity of 10q, the adenosine A_{2A} and A_2 receptor genes (ADORA2A and ADORA2L respectively, known to affect REM sleep and respiratory drive) in the proximity of 22q12 and the 5-HT receptor 3C gene (HTR3C, the role of serotonin is discussed further below). It should also be noted that another finding of this study is that the heritability of respiration rate was found to be moderate during the daytime (41 to 50%), but to sharply increase at night (81%).[77] This shift in genetic architecture suggests that respiration rate is under more control during sleep than during awake periods. This makes sense since many environmental factors such as speech or physical activity impact respiration during the daytime, whereas, during sleep, respiratory frequency will be a more pure reflection of intrinsic rhythmogenesis by the brain stem.

Polymorphisms in serotonin receptor, transporter genes and OSA

Patency of the human upper airway is mostly maintained by muscle activation and soft tissue structures. The activity of the muscles responsible for maintaining patency of the upper airway is increased during inspiration, thus stiffening and dilating the upper airway and acting to counteract the collapsing influence of negative airway pressure.[78] During sleep there is a loss of both tonic premotor input (and neuromuscular compensation) and reflex-driven muscle activation leading to a large decrement in electromyogram

and ultimately airway collapse. 5-HT plays an important role in the patency of the upper airway. 5-HT excites upper airway dilator motor neurons in adults[79,80] and provides intrinsic excitation of brainstem motor neurons in un-anaesthetised animals.[81] The activity of neurons supplying 5-HT to motor neurons declines during sleep.[82,83] Furthermore, pretreatment of upper airway dilator motor neurons with 5-HT reduces sleep state-dependent suppression in upper airway dilator muscle activity.[84]

5-HT acts through a large family of receptors.[85] The 5-HT 2A/2C receptor subtype plays an important role in the maintenance of upper airway stability and normal breathing in obesity. 5-HT 2A is the predominant excitatory 5-HT receptor subtype at the hypoglossal motor neurons.[86] The excitatory effects of the 5-HT 2C receptor are of a lower magnitude.[86] Based on these data, polymorphisms in the 5-HT 2A/2C receptor genes were studied in order to investigate whether or not they are associated with OSA, but the results showed no significant relationship.[87] Synaptic 5-HT is inactivated by presynaptic reuptake, which is mediated by the serotonin transporter. The aim of another study was the polymorphism of the serotonin transporter gene, the associated alterations in serotonin level and their importance in OSA.[88] The serotonin transporters are coded by the serotonin transporter gene (STG) that is located on chromosome 17q12. A polymorphism of the gene coding for the serotonin transporter has been identified,[89,90] and two polymorphisms, VNTR (variable-number-tandem-repeats of 17 bp sequence in the second intron and has several alleles) and 5-HTTLPR, have been described. The function of VTNR is thought to affect enhancer function and thus transcription of the gene. 5-HTTLPR (5-HTT gene-linked polymorphic region) is a deletion insertion polymorphism located at the 5'-flanking regulatory region of the STG and creates short (S) and long (L) alleles. The uptake of serotonin in cells homozygous for the L form (or L/L) of the promoter polymorphism was found to be 1.9 to 2.2 times greater than that in cells carrying one or two endogenous copies of the S (or S/L, or S/S) allele. That is, S allele corresponds to low serotonin uptake activity.[91]

Although the study did not reveal any significant difference between the patients and controls regarding the genotypes and allele frequencies, there were significant differences between the results of male and female patients as well as between male patients and male controls.[88] These findings may suggest a genetic predisposition to OSA, especially in male patients, which results in an alteration in the activity of serotonergic system. These results are supported with the finding that there is a five- or sixfold increased risk of obstructive sleep apnoea in men compared with women according to sleep laboratory data, and two- or threefold increased risk in men *vs* women according to community-based studies.[92,93]

The presence of the S allele is associated with decreased 5-HT reuptake, which, in turn, results in longer serotonergic

Kaparianos, et al. Obstructive sleep apnoea syndrome and genes.

SEPTEMBER 2006, VOL. 64, NO. 8

285

activity. The frequency of S allele and S/S genotype was less frequent in male patients than in male controls and female patients. This condition may result in increased serotonin reuptake and shorter serotonergic activity in male patients with OSA.[88] On the other hand, the presence of the L allele results in shorter serotonin activity because of the relatively faster reuptake of 5-HT. The L/L genotype was more frequent in male patients than in female patients. This genotype difference between the sexes may also be associated with serotonin depletion in male patients. On the basis of these genotype differences, serotonin depletion caused by fast 5-HT reuptake appears to predispose male patients to OSA. The L/S genotype was more frequent in male OSA patients than in male controls.[88] This genotype results in a moderate serotonin reuptake activity and appears to be associated with the occurrence of OSA in male patients. It was suggested that the S allele of the 5HTTLPR may identify patients at risk for developing insomnia with fluoxetine (a serotonin reuptake inhibitor drug) treatment. This is also an indirect support of the finding of this study that the presence of S allele is protective against OSA.[88] Despite the fact that functional results of VNTR polymorphism are unclear, the genotype differences found in this study suggest that polymorphism of 5-HT transporter gene may be associated with OSA.

The use of serotonergic antidepressants may cause sleep disorder.[94] However, many of the drugs tested to evaluate the effects of 5-HT receptor antagonists have not produced significant improvement in sleep apnoea.[95] Serotonin receptor subtypes may affect efficiency of the 5-HT receptor antagonists. Systemic administration of serotonin 2A and 2C receptor agonists were shown to improve upper airway collapsibility, at least in rats.[96] It is possible that the serotonergic activity is shorter in male patients because of STG polymorphism. Further studies are necessary to discover the affect of serotonergic antagonists in male OSA patients.

OSA in children and leukotriene receptor genes

Cysteinyl leukotriene receptors 1 and 2 (LT1-R and LT2-R) are expressed in human tonsils, and are deeply involved in inflammatory and allergic responses.[97] Tissue damage through inflammation during respiratory infection or through recurrent vibratory trauma will in turn promote the development of an inflammatory response. This could lead to mucosal swelling and subsequently to upper airway obstruction, suggesting that LT1-R and LT2-R gene upregulation may underlie components of the pathophysiological mechanisms linking the enlargement of the tonsillar tissue to the emergence of sleep apnoea in snoring children. This may possibly occur through enhanced upper airway inflammation linked to mechanical irritation of the upper airway mucosa due to snoring.[98] Therefore, upregulation of LT-R expression would occur, leading ultimately to accelerated growth of the tonsillar tissue and to upper airway obstruction during sleep.

The rapidly accumulating body of evidence in adult OSA patients lends credible support to the theory that the recurrent vibration of the air column in the upper airway due to snoring will induce mechanical trauma. The study showed no expression of these receptors in cells located in germinal centres of the tonsillar lymphoid tissue and one possible explanation is that these cells have migrated from the vasculature to occupy their sites within the tonsils.[99] LT1-R antagonists such as montelukast have found their application in the treatment of asthma and allergic rhinitis in children, while no antagonist for the LT2-R has been developed thus far. The use of LT-R antagonists may be a potential future therapeutic consideration in treating children with OSA. This has been shown by a recent study that demonstrated improved breathing during sleep in children with sleep-disordered breathing after oral therapy with montelukast.[100]

OSA and other associations

OSA has been linked with various loci of the major histocompatibility complex (MHC) complex. A study showed a twofold increase in the HLA-A2 antigen.[101] HLA-A2 positive subjects with OSA were more obese than OSA patients negative for this antigen, suggesting a relationship between this genetic marker and obesity. Another study[102] implicated HLA-A33, HLA-DRB1*03, DQB1*02 with OSA and HLA-B7, B65, B63, B73 with primary snoring, although the significance was not consistent.

An increased frequency for the Lewis blood group phenotype Le (a+b-) is also seen in snorers compared with non-snorers, although the implications of this finding have not yet been clarified.

Also conflicting are the findings regarding the possible link between apolipoprotein E genotype 4, and OSA. Apolipoprotein E is a polymorphic protein arising from three alleles at a single gene locus on chromosome 19q13. Although no difference was found in the apolipoprotein E levels between OSA patients and controls, a higher proportion of homozygotes for the E4 genotype was observed in the sleep apnoea group, although the finding was not statistically significant.[103] Another study showed that the risk for AHI >15 was doubled among homozygotes, independently of sex and BMI.[104] In a third study no association was found.[105] A recent paper showed that there is a disease susceptibility locus for obstructive sleep apnoea in the region of ApoE (chromosome 19), but ApoE itself is unlikely to be the causative locus.[106]

A study reported an association between angiotensin-converting enzyme (ACE) gene polymorphism and severity of sleep apnoea, something that shows a potential link between this gene and severity of OSA.[107] Another study compared ACE activity in patients with OSA and control subjects and showed that ACE activity is increased in patients with OSA, a finding independent of the presence of arterial hypertension, but the distribution of ACE genotypes and of allelic frequency in OSA patients did

Kaparianos, et al. Obstructive sleep apnoea syndrome and genes.

SEPTEMBER 2006, VOL. 64, NO. 8

286

not differ from that determined in healthy subjects.[108] Therefore, although the increased ACE activity would seriously jeopardise the endothelial function and vascular structure, increasing the prevalence for cardiovascular events, no significant correlation was found between AHI and ACE activity in OSA patients. A more recent study found no association between ACE and OSA.[109]

Elevations in various factors have been found in serum from patients with OSA, and could also serve as biological markers. Increased levels of circulating endothelin-1,[110,111] a peptide with vasoconstrictor effects, have been demonstrated in OSA subjects as compared with control subjects and its levels declined after therapy with CPAP. Another study, however, showed that plasma endothelin-1 precursor but not endothelin-1 levels are elevated and decline after therapy with nasal CPAP.[112] The inflammatory cytokine, tumour necrosis factor (TNF)-α, has also been shown to be elevated in OSA patients when compared to controls.[113,114] Plasma fibrinogen concentration and whole blood viscosity have been reported to be higher in the morning than afternoon in a small number of untreated OSA patients, with no such diurnal change in OSA patients treated with CPAP.[115] Also, variations in the levels of heat shock proteins, proteins thought to respond to stresses such as hypoxia, have been examined in small numbers of OSA patients, with results that were ambivalent.[116]

CONCLUSION

OSA is a multifactorial entity and only recently the complex genetical and environmental links begun to be elucidated. Racial studies and chromosomal mapping, familial studies and twin studies have provided evidence for the possible link between the OSA phenotypes and genetic loci that could prove to be markers for further research, including obesity, fat distribution, snoring, and sleep regulation. Also, the potential role of serotonin and the regulation of upper airway tone during sleep could prove a field of pharmaceutical intervention. Tissue damage, through recurrent vibratory trauma induced by snoring, and the role of inflammatory mediators could also be a target for drug therapy. On the other hand, if their exact significance is clarified, the importance of the increased levels of certain molecules, such as TNF-α, ET-1 and plasminogen, could give physicians a quantitative tool, apart from the AHI index, for determining the severity of OSA and the risk for adverse cardiovascular effects, making it possible for a scoring system to be developed.

ACKNOWLEDGEMENTS

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SEPTEMBER 2006, VOL. 64, NO. 8

287

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288

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SEPTEMBER 2006, VOL. 64, NO. 8

289