Genetic and environmental influences in obstructive sleep apnoea hypopnoea syndrome

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SUMMARY. Obstructive sleep apnoea hypopnoea syndrome (OSAHS) is a multifactorial and complex disease. There is a growing body of evidence demonstrating that genetic factors influence the expression of OSAHS. Lack of a consistent definition of the OSAHS phenotype and incomplete understanding of the environmental influences on its expression hinder progress in determination of the OSAHS genotype. In order to elucidate its genetic basis, the OSAHS phenotype can be separated into intermediate phenotypes, based on craniofacial morphology, obesity, susceptibility to sleepiness, ventilatory parameters and upper airway control. Identification of the genetic systems that influence more than one of the intermediate phenotypes may facilitate better understanding of mechanisms underlying OSAHS and lead to formulation of pharmacological interventions. *Pneumon 2012, 25(1):114-119.*

The obstructive sleep apnoea hypopnoea syndrome (OSAHS) is a sleep disorder characterized by recurrent episodes of upper airway collapse during sleep. These episodes are most often associated with recurrent sleep arousals and recurrent oxygen desaturation[1]. OSAHS is a complex disease with multiple adverse consequences, including increased risk of driving accidents, cognitive impairment, and cerebrovascular and cardiovascular morbidity and mortality, and it therefore represents a significant public health concern.

OSAHS is an increasingly prevalent condition in modern society. Data from the Wisconsin Cohort Study indicate that the prevalence of OSAHS in people aged 30-60 years is 9-24% for men and 4-9% for women[2]. Studies with similar design and methodology have found similar rates in populations in Pennsylvania[3,4] and Spain[5]. The male-to-female ratio in community-based studies is 2-3:1[2,6], but the prevalence of OSAHS in women appears to increase after menopause[7-9]. OSAHS increases with age[10] with an estimated rate of as high as 65% in a community sample of people aged above 65 years[11].

Increasing awareness of high prevalence and consequences of OSASH

has directed research towards exploration of a potential genetic basis for this disorder. A familial basis for OSAHS was first postulated in 1978[12], since when it has become clear that OSAHS commonly clusters within families[13,14], probably due to the familial aggregation of risk factors involved in the pathophysiology of OSAHS, such as obesity. Even after accounting for these risk factors, the over-representation of OSAHS among family members persists, suggesting that genetic susceptibility plays an important role in OSAHS pathogenesis[13,15]. Elucidation of the patterns of gene or protein expression in cells or tissues related to OSAHS, or the molecular signature, may provide to the basis for better understanding of individual predisposition to the disease and its consequences. Approaches to the assessment of molecular signatures are depicted in Figure 1[16]. Currently, two general approaches have been used to explore the genetic components of OSAHS, namely, linkage studies, which study single-gene disorders, and association studies, which identify genes involved in polygenic disorders[17,18].

This is a short review of the most clinically relevant information on genetic and environmental influences in OSAHS. It does not judge all the newly-available information, but summarizes that considered to be of greatest general interest.

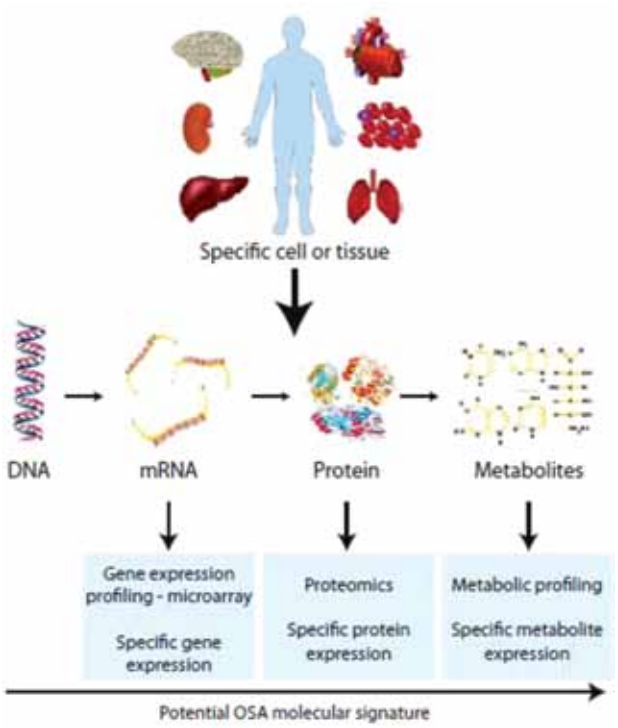

FIGURE 1. Possible ways of assessing molecular signatures in specific cells or tissues. Adapted with permission from: Arnardottir *et al.* Sleep 2009;32:447-70.[16]

THE COMPLEXITY OF OSAHS

OSAHS is a heterogeneous disorder, the critical pathophysiological feature of which is sleep-related collapse of the upper airway at the level of pharynx. The pathophysiology of OSAHS cannot be considered in isolation as a dysfunction of the upper airway alone, but rather as the consequence of a number of interrelated risk factors, such as obesity and ageing[19,20] (Figure 2). It has been estimated that up to 40% of the variance in the occurrence of OSAHS is attributable to familial factors, with the remaining 60% attributable to environmental factors[21].

It has been suggested that the development of OSAHS begins with snoring, which progresses to increased resistance of the upper airways, to sleep disordered breathing and, finally, to OSAHS. There have been no studies to verify this model over time or studies of paediatric patients followed into adulthood to determine whether OSAHS improves, worsens or recurs after treatment. The development and progression of OSAHS are different in older than in younger adults[22], and the clinical phenotype also changes, with older subjects reporting less daytime sleepiness than younger subjects with an equivalent

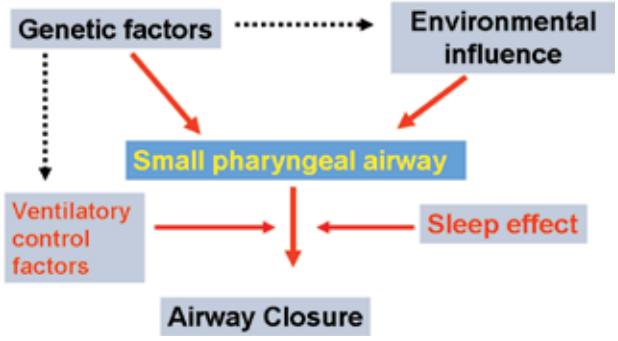

FIGURE 2. The pathogenesis of obstructive sleep apnoea hypopnoea syndrome.

severity of OSAHS[23].

OSAHS Phenotypes

According to the definition of OSAHS, severity is based on the degree of daytime sleepiness and overnight monitoring of breathing[24]. Clinicians, however, do not always agree on how specific respiratory events are identified, or on the threshold level of the apnoea hypopnoea index (AHI) that should be judged pathological, or even on what

symptoms are considered necessary for determining disease status. There is no universally accepted strategy for accounting for age or sex-related changes, and AHI has been shown to be only moderately correlated with other physiological measurements of OSAHS severity, such as nocturnal hypoxaemia and sleep fragmentation. For these reasons the OSAHS definition is not particularly useful for phenotyping OSAHS.

OSAHS appears to be to be polygenic and a suitable environment may be required for the OSAHS phenotype to emerge. Because OSAHS phenotype is difficult to define, it can be separated into intermediate phenotypes, which may facilitate the identification of genetic polymorphisms[25]. These phenotypes may be based on factors including craniofacial morphology, obesity and susceptibility to sleepiness, ventilatory parameters and upper airway control.

Craniofacial morphology

Craniofacial morphology determines the anatomy, including the diameter of the upper airways, which is reduced in OSAHS[26]. It of note that growth of the craniofacial skeleton continues throughout adulthood and that the sex of the individual plays a significant role, as women show increased growth of the craniofacial skeleton during pregnancy and with other hormonal changes[27]. Studies suggest that certain inherited craniofacial abnormalities are linked with the development of OSAHS[28-31]. Such anomalies include the cranial base dimensions being more obtuse, inferior displacement of the hyoid bone, macroglossia, adenotonsillar hypertrophy, increase in lower facial height, a retroposed maxilla and a short mandible[32]. Of these, mandibular position and size appear to play the greatest role in predisposition to OSAHS [25]. Inherited craniofacial abnormalities appear to explain at least a part of the familial clustering of OSAHS.

Many congenital and genetic syndromes are associated with craniofacial abnormalities, and consequently with respiratory problems or upper airway obstruction. Among the commoner of these are Pierre–Robin syndrome and Treacher–Collins syndrome, both of which are characterized by marked retrognathia and a predisposition to OSAHS[33]. Environmental influences, such as thumb-sucking and abnormal tongue posturing, nasopharyngeal disease, mouth breathing, tumours, loss of teeth, malnutrition and certain forms of endocrinopathy may significantly alter the skeletal morphology and subsequently the phenotypic expression[34]. There is continuous interaction between genetic and environmental factors in the development of the upper airway region[30] (Figure 3), but the number of studies evaluating specific genetic polymorphisms that contribute to craniofacial abnormalities is very limited[35,36]. In mice, craniofacial abnormalities such as retrognathia and micrognathia were observed in mice deficient in endothelin-1[37], with mutations of the retinoic acid receptors (RARs)[38] and of transforming growth factor-β2 (TGFβ2)[39].

Obesity

Not all forms of obesity play the same role in the development of OSAHS. Fat deposition in the neck reduces nasopharyngeal calibre and may lead to hypoventilation due to reduced chest wall compliance[40]. The typical pattern of fat depositionof the male sex in the subcutaneous regions of the torso and abdomen could be considered as predictors of OSAHS[41]. Katzmarzyk and co-workers found heritability rates of 29–48% for various indicators of fat distribution, specifically, body mass index (BMI)-adjusted waist circumference and ratio of trunk to extremity skinfold thickness[42]. Although susceptibility to obesity is largely genetically determined, with BMI heritability ranging from 25% to 40%[43], an obesogenic environment must be present for its phenotypic expression. Currently, more than 300 markers, genes and chromosomal regions have been documented to be associated with human obesity phenotypes[44]. As obesity and OSAHS are closely related[45] (Figure 4), any genetic risk factor for obesity can also be considered a risk factor for OSAHS. Obesity increases the risk of OSAHS 10 to 14-fold[46,47], while weight loss may reduce the severity of the condition[48]. The causal pathways involved in the relationship between obesity and OSAHS have not been completely delineated. Considine and co-workers suggested that there may be a state of leptin resistance in obese subjects[49], as adipose tissue produces leptin, a hormone that not only has an important effect on

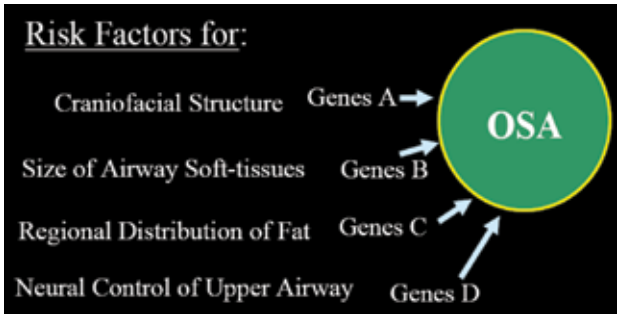

FIGURE 3. The interaction between genetic and environmental factors in the development of the upper airway region and obstructive sleep apnoeahypopnoea syndrome (OSA).

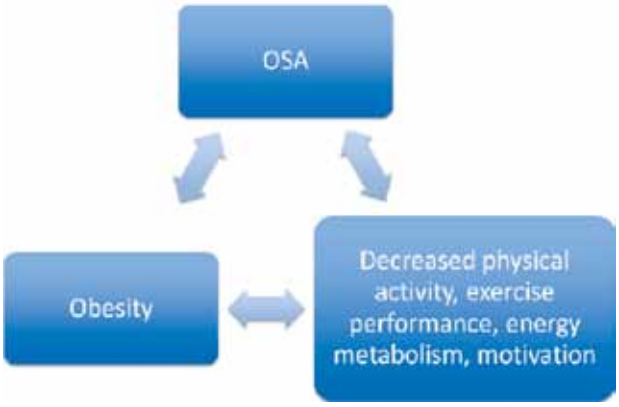

FIGURE 4. The interaction between obesity and obstructive sleep apnoea hypopnoea syndrome (OSA).

weight regulation, but may also affect regulation of the respiratory centre[50]. Furthermore, a causative relationship between leptin levels and OSAS has been suggested[51]. It has been argued that the genetics of obesity cannot be separated from the genetics of OSAHS, but the findings of genetic studies suggest both common and independent genetic determinants of obesity and OSAHS[52]. Future targets for intervention will be provided by the discovery of genes that influence OSAHS through independent pathways of obesity.

Sleepiness

Although sleepiness is a criterion required for OSAHS definition, the two are not necessarily correlated, as there is a differential susceptibility to somnolence among individuals. Cytokines that promote sleep and are also implicated in the sequelae of OSAHS, particularly inflammation, are interleukin (IL)-1, tumour necrosis factor-a (TNF-a), IL-10, IL-6, interferon, IL-2, IL-4, granulocyte-macrophage colony-stimulating factor, colony-stimulating factor and fibroblast growth factor[53,54].

Upper airway control

Reduction in airway muscle tone during sleep leaves patients with OSAHS more vulnerable to airway obstruction[55]. Figure 5 depicts the major parameters contributing to airway collapse/patency. Although serotonin appears to be a key neurotransmitter in upper airway dilator muscle activity, few studies have investigated serotonin gene polymorphisms in OSAHS[52,56,57]. Selective serotonin reuptake inhibitors (SSRIs) have undergone trials as possible pharmacological treatment for increasing upper

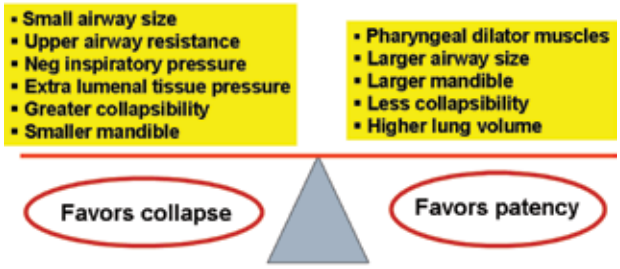

FIGURE 5. The major parameters contributing to airway collapse/patency.

airway tone, but the results were mixed[58].

Ventilatory control

Inherited abnormalities of ventilatory control may predispose to OSAHS by influencing ventilation during sleep and increasing the propensity to upper airway collapse[59]. An inherited basis for ventilatory responsiveness to hypoxaemia or hypercapnia has been suggested, but few studies have evaluated ventilatory control in OSAHS and the results were conflicting[60,61]. The question as to whether respiratory control problems are implicated in the pathogenesis of OSAHS is debatable, but abnormalities of respiratory control have been attenuated with treatment with continuous positive airway pressure (CPAP)[62]. The observed ventilatory instability may be acquired and not necessarily the primary manifestation of the genotype related to OSAHS.

ENVIRONMENTAL INFLUENCES

Although environmental influences may be significant, it is difficult to estimate the degree of their contribution. Recent evidence indicates a higher prevalence of smoking in patients diagnosed as having OSAHS, and it appears that cigarette smoke may be an independent risk factor for OSAHS[63,64]. Exacerbation of OSAHS may occur as a result of alcohol ingestion, through reduction of the activity of the genioglossus muscle, leading to upper airway collapse[65], sedative use, sleep deprivation and sleeping in the supine posture. Nasal congestion or anatomical defects resulting in reduced nasal patency, and respiratory allergies, may all contribute significantly to OSAHS[66].

In conclusion, there is growing evidence that genetic factors influence the expression of OSAHS. Identification of genetic systems that influence more than one of the intermediate phenotypes of OSAHS may facilitate

better understanding of the underlying mechanisms. It should then be possible to use this information to identify individuals at increased risk for the disorder, allowing for design of more efficient prevention and screening programmes. In addition, the elucidation of pathways to disease development or pathways that are protective may lead to novel treatment strategies that target the specific molecular defects.

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