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The genetics of obstructive sleep apnea.

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Abstract

Obstructive sleep apnea (OSA) is a common chronic disease, and is associated with high social and economic costs. OSA is heritable, and there is evidence of both direct genetic contributions to OSA susceptibility and indirect contributions via ‘intermediate’ phenotypes such as obesity, craniofacial structure, neurological control of upper airway muscles, and of sleep and circadian rhythm. Investigation of the genetics of OSA is an important research area, and may lead to improved understanding of disease etiology, pathogenesis, adverse health consequences, and new preventive strategies and treatments. Genetic studies of OSA have lagged behind other chronic diseases, however recent gene discovery efforts have been successful in finding genetic loci contributing to OSA-associated intermediate phenotypes. Nevertheless, many of the seminal questions relating to the genetic epidemiology of OSA and associated factors remain unanswered. This paper reviews the current state of knowledge of the genetics of OSA, with a focus on genomic approaches to understanding sleep apnea.

Keywords

Genetics; obstructive sleep apnea; epidemiology

1. Introduction

Obstructive sleep apnea (OSA) is a genetically complex disease that likely results from multiple interacting genetic and environmental factors[1]. Obesity is a major risk factor and is present in approximately 70% of patients with OSA[2, 3]. OSA affects up to 15% of middle-aged adults[4-7], with a prevalence that increases rapidly with age and is higher in men. OSA is associated with substantial social and economic costs globally due to its high prevalence

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in the community, the profound clinical effects on an individual's cognitive and general functioning, and the increased risk of adverse health complications[8].

Concurrent with increased clinical recognition of OSA and importance as a chronic disease, there have been major advances in genetic methodologies to discover genetic susceptibility loci for many conditions. For example, 97 validated loci have been discovered by genome wide association studies (GWAS) for obesity[9]. Relative to many other common, chronic disorders, the genetic understanding of OSA has lagged behind. In part this is due to a lack of large collections of well-characterized OSA cases with DNA. Much remains unknown regarding the genetic basis of OSA. Understanding the genetic basis of OSA susceptibility, disease progression, and response to therapy are all important goals. In particular, such understanding may prove critical to the development of better ways of targeting efficacious treatments for OSA (i.e., 'precision medicine'[10]).

In this review we discuss the definition of adult OSA as a disorder, biomarkers of OSA, what is known about the genetic epidemiology of OSA and different analytic approaches to detect genes for OSA, and the importance of intermediate phenotypes of OSA. Finally, we discuss future genomic approaches in OSA research.

2. Definition of obstructive sleep apnoea

OSA is a syndrome where reduced patency of the upper airway results in repetitive upper airway obstruction, either in the form of reduced airflow (hypopnea) or complete cessation of airflow (apnea), as the soft tissue structures of the upper airway, behind the tongue and soft palate, collapse in upon one another[11]. Obstructive events lead to hypoxemia and are usually terminated by a cortical arousal from sleep resulting in muscle activation and recovery of airway patency[12]. The primary measure that is used to define disease in both clinical and research settings is the apnea hypopnea index (AHI). This is calculated from overnight polysomnography (PSG) and is a count of the number of episodes of breathing obstruction per hour of sleep. Male and female subjects are often considered to have OSA if the AHI exceeds a certain level, usually 5-10 events per hour. Other factors enter into the clinical diagnostic decision than AHI, but it remains the primary biomarker of OSA.

3. Biomarkers of obstructive sleep apnea

The use of the AHI to determine disease status in clinical practice and research studies is advantageous because of its simple calculation from PSG and its high night-to-night reproducibility[13]. Most genetic studies of OSA have thus far used the AHI as the sole disease-defining variable[14]. The major disadvantages of using the AHI as the only biomarker of disease include: 1) the between-laboratory and within-laboratory variability in measurement and scoring of PSG[15]; 2) the loss of important information regarding the severity of individual obstructive events (duration, intensity and frequency of hypoxemia and arousal); and 3) the absence of information on the functional impact of the disease on an individual. Additionally, the AHI may include both obstructive and central events, and obstructed breaths may or may not occur in a background of periodic breathing. Since central events and Cheyne-Stokes respiration may occur in association with cardiac failure,

central nervous system disease, and with use of certain medications (e.g., opiates)[16], the AHI may not accurately reflect the physiological nature of the disease process in an individual.

Other biomarkers used for epidemiologic studies include measures of hypoxemia (e.g., the oxygen desaturation index, which measures the number of episodes of oxygen desaturation of greater than 3 or 4% per hour of sleep or time spent with oxygen saturation below a certain threshold), measures of sleep disruption (e.g., the arousal index), and duration of obstructive events.

Another important biomarker is obesity, as epidemiological, molecular, and physiological studies demonstrate substantial evidence for shared pathogenic pathways for obesity and OSA. Fat located in the intra-abdominal cavity and surrounding vital organs (visceral fat) predicts insulin resistance and other cardiometabolic consequences and is biochemically active. OSA induced hypoxia, sleep fragmentation and sleep loss contributes to further metabolic abnormalities[17], which predisposes to obesity. However, total fat (visceral and subcutaneous) around the neck and abdomen is also likely to exert a direct mechanical load on the upper airway. Therefore better characterization of body fat distribution rather than reliance upon the body mass index (BMI) and anthropometry is necessary to define obesity and its impact on OSA. Novel methods to characterize fat deposition such as dual energy X-ray absorptiometry (DEXA) imaging have begun to be used[18-20].

New objective biomarkers are necessary for OSA. Future investigations should consider biomarkers of hypoxic stress or arousal, central ventilatory control, and sleep homeostasis. There is a need to utilize other physiological, biochemical and/or anatomic measures to optimally characterize the OSA phenotype, and to couple this work with genetic studies. Recent advances in physiological methodology to measure anatomic (magnetic resonance imaging, CT scans, optical coherence tomography, 3D scanning) and non-anatomic/physiological causes of OSA with simple testing (passive critical closing pressure of the upper airway, arousal threshold, loop gain and muscle responsiveness)[21] are likely to play a major role in this area moving forward.

4. The genetic epidemiology of OSA and associated traits

Complex genetic diseases such as OSA do not follow Mendelian patterns of inheritance and characteristically involve many genes that interact with many environmental factors.

4.1 Analytic approaches to detect genes for complex diseases such as OSA

Heritability studies measure the covariance of OSA or OSA-related phenotypes among family members and estimate the proportion of phenotypic variance attributable to genetic factors. Candidate gene studies examine associations between selected single nucleotide polymorphisms (SNPs) and OSA phenotypes in case-control or cohort studies. The SNPs are selected based upon a known or presumed contribution of the variant to a functional change in biochemistry, or on the basis of reasonable biological plausibility for a role of the gene in disease etiology. In contrast, the intention of genome-wide linkage studies and GWAS is to find causal genes without having *a priori* knowledge of functionality or position within the

genome – a 'hypothesis free' discovery paradigm[22]. Genome-wide linkage studies use genotyped familial data to identify regions of the genome statistically associated (co-segregating) with the disease or disease-associated phenotype[23, 24]. GWAS generally genotype a dense set of markers in large samples of unrelated individuals to identify genomic regions containing common genetic variants causally associated with disease phenotypes[22, 25]. Figure 1 summarizes the GWAS process in more detail for Crohn's disease (The text and figure reprinted with permission from the American Association for the Advancement of Science).

In sharp contrast to linkage or candidate gene studies, GWAS of large, unrelated samples investigating complex diseases have so far discovered >10,000 robust associations with diseases and disease associated phenotypes over the last decade for complex chronic diseases such as type 2 diabetes, autoimmune diseases, and common cancers[26].

4.2. Heritability studies of OSA and related phenotypes

OSA is a heritable disease [27, 28]. First degree relatives of an individual with OSA are more likely to snore or have observed apneas, after controlling for obesity, age, and gender[28, 29]. Around 40% of the variance in AHI has been shown to be explained by genetic factors[27]. Twin and family studies suggest that ventilatory responsiveness to either hypoxemia or hypercapnia, obesity, and craniofacial morphology are also under a high degree of genetic control, with 30-70% of phenotypic variance being explained by shared familial factors[30,31-33]. The genetic basis of sleep duration and quality is poorly defined. Heritability has been estimated at ~40% for measures of sleep duration[34], 25-45% for insomnia[35], and 17% for excessive daytime sleepiness[35], but few genetic factors are known. Sleep timing is an essential component of the sleep-wake cycle with twin studies suggesting a genetic component in diurnal types (chronotype), with preference for time to bed and wake time estimated to be about 50% heritable[36]. Chronotype has a strong genetic basis but is also influenced by light exposure, age and gender[37]. These observations suggest that genetic factors likely contribute to OSA disease severity.

4.3. Genome-wide linkage studies of OSA

Three genome-wide linkage studies of the Cleveland Family Study (a longitudinal study of cases of OSA, their family members, and control families) were conducted in both Caucasians and African Americans[38-40]. In common with genome-wide linkage scans for most other common complex diseases, linkage proved to be under-powered for gene discovery in the context of a complex, multifactorial disease, and the results were inconclusive[41].

A more recent genome wide linkage analysis from the Cleveland Family study and follow-up association identified a clear link between a polymorphism in the angiopoietin-2 gene (*ANGPT2*), an endothelial factor which modulates vascular and inflammatory responses, and mean nocturnal oxygen saturation, a surrogate marker of the severity of OSA[42]. Biological/functional follow-up of the *ANGPT2* candidate gene and associated variants is now warranted.

4.4. Candidate gene association studies of OSA

Many candidate gene studies of OSA have examined polymorphisms in genes known to encode biomarkers of inflammatory response and insulin resistance[43]. Most have been of small sample size and have investigated polymorphic variation in genes with strong biological plausibility in disease risk. As for linkage analysis, it is generally true that most candidate gene studies of complex human diseases and phenotypes have been difficult to replicate and most are likely to be spurious. This failure relates to issues of problematic study design and concomitant low statistical power, and to a failure to replicate findings[44]. Applied to OSA, the majority of the candidate gene association studies conducted to date have either failed to replicate or replication has yet to attempted. Notably, the majority of candidate genes studied have not been significantly associated with OSA phenotypes in newer GWA studies.

Nevertheless, a few candidate gene association studies of OSA have been independently replicated (Table 1). Some of these suggest a relationship between polymorphic variation in the pro-inflammatory cytokine, tumor necrosis factor-α (TNFα) gene and OSA. The *−308G/A* polymorphism has been associated with increased levels of TNF-α, which is involved in intermittent hypoxia. Amongst OSA cases, the *A* allele, in comparison with those homozygous for the *G* allele, was significantly associated with AHI[45, 46], oxygen saturation, and serum TNF-α levels[45]. However, controls with the *A* 'risk' allele had smaller waists and necks, and lower levels of TNF-α in comparison with cases who had the same genotype, suggesting that factors other than the TNF-α *(−308G/A)* polymorphism are associated with raised TNF-α levels and obesity in OSA. Meta-analysis of these three studies estimated that the *TNF-α (−308G/A)* polymorphism is a risk factor for OSA (OR=1.82, 95% CI 1.26-2.61)[47].

Several larger studies have investigated the *APOE ε4* locus. The *APOE ε4* locus encodes a lipoprotein that influences lipid metabolism, ventilatory stability during sleep, and the development of cardiovascular disease[48]. Reported associations between OSA and variation at this locus have been conflicting, however a recent meta-analysis of eight studies reviewed data on 1,901 cases of OSA and 4,607 controls and concluded that there was not enough evidence to suggest a causal relationship between the *APOE ε4* locus and OSA[49] (Table 1).

In 2012, the first multiple cohort candidate gene study of OSA including subjects of both European and African-American ancestry was performed[50]. European ancestry subjects came from subsets of the Atherosclerosis Risk in Communities study, Framingham Heart Study, and the Cleveland Family Study with a total of 963 cases of OSA and 1,965 controls. Subjects of African American ancestry came from the Cleveland Family Study (233 OSA cases, 414 controls). Unlike previous candidate gene studies of OSA, the CARe study considered a broader spectrum of the genome (>2000 genes) and selected candidate genes implicated in heart, lung, blood, and sleep disorders[51]. In European ancestry subjects, the rs1409986 SNP in the prostaglandin E2 receptor (*PTGER3*) gene was significantly associated with OSA. In African-American ancestry subjects, the rs11126184 SNP in the pleckstrin (*PLEK*) gene was associated with OSA and the rs7030789 SNP in the lysophosphatidic acid receptor 1 (*LPAR1*) gene was associated with AHI. The authors then sought to replicate these findings in further independent samples. The association of OSA

with rs1409986 (*PTGER3*) was replicated in a sub-sample of European Caucasians (n=1795) from the Western Australian Sleep Health Study[52]. In a replication study of the findings in African American subjects, 459 clinical cases of OSA from the Case Sleep Apnoea study were compared with 551 controls from the Case Transdisciplinary Research in Energetics and Cancer Colon Polyps Study. The findings with rs7030789 (*LPAR1*) but not rs11126184 (*PLEK*) were replicated (Table 1).

4.5. Genome-wide association studies of OSA

Consistent with genetic research in OSA being an under-explored area, the first GWAS for OSA phenotypes have only recently been conducted.

A recent study reported a GWAS on 12,558 Hispanic American ancestry participants where a number of OSA-associated phenotypic traits were investigated, including AHI, mean oxygen saturation, and mean apnea and hypopnea duration[53]. AHI was associated with a polymorphism in the G-protein receptor gene (*GPR83*), which is expressed in several areas of the brain including the hypoglossal nucleus, dorsal motor nucleus of the vagus, and the nucleus of the solitary tract. Measures of sensitivity to hypoxia and respiratory arousability as reflected in the average apnea and hypopnea duration in females were suggestively associated with variants in the β-arrestin 1 (*ARRB1*) gene, which is an important regulator of hypoxia inducible factor 1 alpha (HIF-1α) and influences the expression of HIF-1α target genes, including vascular endothelial growth factor. HIF-1α plays a role in hypoxic sensitivity in the carotid bodies and therefore the causal variant at this locus may be intimately involved in the etiology of OSA through hypoxic sensitivity and control. The duration of apneas and hypopneas was also associated with variation in several loci associated with an important lipid biosynthesis transcription factor, sterol regulatory element binding protein (SREBP). While independent replication of these findings may be difficult due to the lack of independent cohorts of Hispanic/Latino ancestry with AHI measures and genetic data, future studies should investigate association of independent common or rare variants in these gene regions in other ethnic groups.

The International Sleep Genetic Epidemiology Consortium (ISGEC)[54] was formed in 2011 and has recently completed the first of a series of planned GWAS meta-analyses for OSA phenotypes. The first ISGEC study has investigated risk of moderate/severe OSA by conducting a GWAS in case and control samples from 9 independent European ancestry cohorts. Replication was undertaken in 5 mixed ancestry cohorts. In total, 8,336 cases and 76,663 controls were investigated. Analyses were stratified by obesity in order to examine associations with OSA risk in obese and non-obese patients. Results have been presented at international scientific meetings but have yet to be published.

4.6. Genetics of OSA related traits: Intermediate phenotypes

In OSA a number of risk factors interact to increase the likelihood for repetitive upper airway collapse during sleep. In any individual, this is determined by anatomic and non-anatomic factors that influence upper airway size and collapsibility. Recognized risk factors include: obesity, male gender, small upper airway size, ventilatory control mechanisms, and control of sleep and circadian rhythm. Identification of genes that determine ‘intermediate’

phenotypes that are potentially on a causal pathway leading to OSA may be helpful to determine susceptibility genes.

4.6.1. Obesity and Body Fat Distribution.—Obesity increases the risk of OSA 10-14 fold, with the most profound impact observed in middle-age. Obesity, measured as BMI, is expected to explain up to 40% of the genetic variance in AHI[55]. Regulation of body weight and fat distribution are genetically modulated. Recent GWAS in up to 339,224 individuals have identified 97 loci that contribute to normal variation in BMI, implicating genes and pathways related to synaptic function, glutamate signaling, insulin action and secretion, energy metabolism, lipid biology, and adipogenesis[9]. In support of the importance of the genetic contribution of BMI to OSA, a recent study tested for association of variation in the BMI-associated *FTO/IRX3* locus with >1,000 Electronic Health Record ascertained diagnoses and found significant evidence of association with OSA (2,335 cases and 21,863 controls[56]). The effect of the *FTO/IRX3* region variant was attenuated upon adjustment for BMI. GWAS of body fat distribution in up to 224,459 individuals have identified 49 genetic loci for waist-to-hip ratio adjusted for BMI, with sex-specific associations identified at approximately half of the loci, highlighting the considerable sexual dimorphism in this trait[57]. Nineteen additional loci for related measures of waist and hip circumference have been identified. Together, these loci highlight adipogenesis, angiogenesis and insulin resistance as important processes contributing to inter-individual differences in body fat distribution[9].

4.6.2. Craniofacial Morphology.—Craniofacial morphology, affecting both bony and soft tissues, predisposes to OSA by reducing the size of the upper airway. Commonly identified craniofacial abnormalities in OSA include mandibular deficiency, an inferiorly placed hyoid bone relative to the mandibular plane, a narrow posterior air space, a greater flexion of the cranial base, and elongation of the soft palate. When these abnormalities are coupled with obesity the degree of craniofacial abnormality may determine the extent of obesity required to produce OSA in a given individual[58].

Recent GWAS of 20 quantitative traits of normal facial morphology based on 3D surface images have thus far identified and in some cases, replicated, genome-wide significant associations for cranial base width, intercanthal width, nasal width, nasal ala length, and upper facial depth[59-61], implicating the genes *CACNA2D3*, *PRDM16*, *MAFB*, *PAX9*, *MIPOL1*, *ALX3*, *HDAC8*, *PAX3,* and *PAX1*. Interestingly, many newly discovered regions harbor genes that are known to play a role in craniofacial development or are mutated in rare syndromes affecting the face, suggesting that larger studies of specific craniofacial abnormalities associated with OSA may be fruitful.

4.6.3. Ventilatory Control—No genetic studies investigating ventilatory control in OSA have been performed. Measurement of loop gain, muscle responsiveness, and passive critical closing pressure of the upper airway will assist in better phenotyping of OSA patients and will be important for future genetic studies[21].

4.6.4. Control of sleep and circadian rhythm—Sleep and circadian rhythm are complex, multifactorial traits with sleep being controlled and influenced by many

environmental and genetic factors, with the genes regulating sleep-wake control and circadian rhythm[62] likely having particular importance. Evidence of a genetic component in the regulation of human sleep is suggested by the heritability of sleep traits, the identification of specific genetic polymorphisms that affect these traits, and known familial sleep disorders[63].

Many candidate gene studies have targeted circadian genes, based on the detailed understanding of the molecular nature of the circadian clock and the connection with sleep regulation in humans[64]. Thirty years after the seminal work on Period gene mutants in *Drosophila*[65], it was discovered that familial advanced sleep phase syndrome is caused by mutations in analogous human clock-related genes. A mutation in Period 2 results in individuals having a 4-6 hour phase advance in sleep and wake times, on a background of normal sleep architecture[66]. Subsequently, several associations between clock genes and circadian rhythm disorders have been reported. The core set of clock genes involved in the generation of circadian rhythmicity are known[67]. A Mendelian short sleep mutation in *BHLHE41* (P385R) has been identified, and confirmed in a mouse model[68].

Three recent GWAS of self-reported morningness/eveningness preference in large-scale populations of European ancestry with >100,000 individuals (the UK Biobank resource and 23andMe company database) identified over 20 genome-wide significant associations, implicating known circadian clock genes and providing new opportunities for enhanced molecular understanding of chronotype and its impact on health outcomes[69-71]. Future studies require GWAS in large samples with better measures of chronotype, and objective measures of sleep timing to fully characterize the genetic architecture of chronotype.

GWAS for sleep duration have been reported[70, 72, 73] but only associations at the thyroid expressed *PAX8* locus and schizophrenia linked *VRK2* locus have reached genome-wide significance in well-powered studies with >40,000 individuals[70, 72, 73]. Suggestive association is seen for dopamine D2 receptor gene (*DRD2*) variation in a multi-ethnic study[74]. In UK Biobank (n=112,586), genetic associations with insomnia symptoms (near *MEIS1*, *TMEM132E*, *CYCL1*, *TGFBI* in females and *WDR27* in males) and excessive daytime sleepiness (near *AR/OPHN1*) have been identified[72, 75] that should be useful for understanding of the contribution of sleep quantity and quality to the etiology of OSA. Further studies in this important area are needed.

5. Genetic links between sleep apnea and adverse health outcomes

OSA has an established independent association with CVD, metabolic syndrome, and hypertension. More severe OSA is more frequently associated with adverse cardiovascular, metabolic, and neuropsychiatric outcomes[76, 77]. Observational studies have consistently shown significantly fewer cardiovascular events, reduced vascular endothelial dysfunction, inflammation, and oxidative stress, and reduced HbA1c levels in patients adherent to CPAP therapy compared to those who are not adherent[77-80]. OSA is associated with cognitive dysfunction, which can be at least partially reversed with CPAP therapy, and with accelerated cognitive decline and dementia[81-88].

All of these traits associated with OSA are themselves genetically determined, and therefore, a key question for future studies is to examine if genetic factors are shared between OSA and these adverse health outcomes. If genetic variants are found to associate both with OSA and a co-morbid disorder, Mendelian Randomization[89, 90], a technique that uses inherited genetic effects as instrumental variables to elucidate if a trait is causally linked to another trait, can be used to determine whether pathways disrupted in the pathogenesis of OSA causally contribute to these outcomes, or whether genetic effects are pleiotropic, i.e. the genetic variants contribute simultaneously to both phenotypes through different mechanistic effects.

6. New *in silico* and genomic approaches to understanding OSA

Online databases containing sequencing and functional data have improved dramatically over the last decade, and such *'in silico'* resources greatly aid identification of the causal variant and biological interpretation of findings from GWAS discovery efforts[26, 91]. For instance, the ongoing accrual of data on coding variants (via exome sequencing and/or exome array genotyping) has been extremely useful in assigning correct causal coding variants to GWAS peaks[92, 93]. Additionally, given that GWAS findings have largely implicated non-coding variation, sequence annotation of tissue-specific chromatin states and protein binding (e.g., from the Roadmap Epigenomics[94] and ENCODE projects[95]), promoter, enhancer, and transcriptomic atlases that assess combinatorial gene regulation (e.g., the FANTOM project[96]), and databases that enable assessment of the effect of SNPs on tissue-specific gene expression (e.g., the gTEX consortium[97]) have been particularly useful to identify functional variants and to generate hypotheses about their mechanism of action.

Current technologies such as exome or whole genome sequencing[92], epigenetic analysis (that measures DNA methylation and chromatin modification[98]), and transcriptomics, proteomics, and metabolomics (measuring changes in levels of gene expression, protein or metabolite levels)[99] have only recently begun to be applied to OSA. Such technologies are promising, and have accelerated the understanding of other diseases[100, 101]. Rare variants may play an important role in chronic disease[102]. Indeed, discovery of rare, protective variants for cardiovascular disease has already resulted in successful development of cholesterol-lowering drugs that mimic human mutations[103]. Analytically, genome sequencing simply results in a very dense GWAS, but novel methods that aggregate the effect of putatively functional rare variants across genes or genomic windows increase power[98]. Epigenome-wide association studies (EWAS) assess DNA methylation across diseased and normal individuals to identify differentially methylated sites that could be environmental or genetic causal contributors to OSA or may be a consequence of the disease process. Initial studies have reported altered transcriptomic signatures in OSA patients versus controls in blood leukocytes[104, 105] and visceral fat[106], and suppression of cancer-associated gene expression signatures in cases after treatment with CPAP[106], but future research in transcriptomics, proteomics and metabolomics and integrative genomics analysis will be important to derive biological insights into the causes and consequences of sleep apnea.

7. Conclusions

OSA is a complex disease genetically with many potential genetic and environmental factors combining to produce the disease. The future for gene discovery in complex diseases such as OSA will likely involve hundreds of thousands of samples with whole-genome sequencing data. New approaches involving *in silico* research and advanced sequencing technologies together with ongoing efforts in GWAS and international cooperation and collaboration[54] are causes for optimism that the genetic basis of OSA will be defined over the coming decade. Such knowledge will lead to better understanding of the pathogenesis of the disease and potentially to better therapies and to 'precision medicine'. Ongoing work on model organisms for OSA will also be important to fully understand causative pathways.

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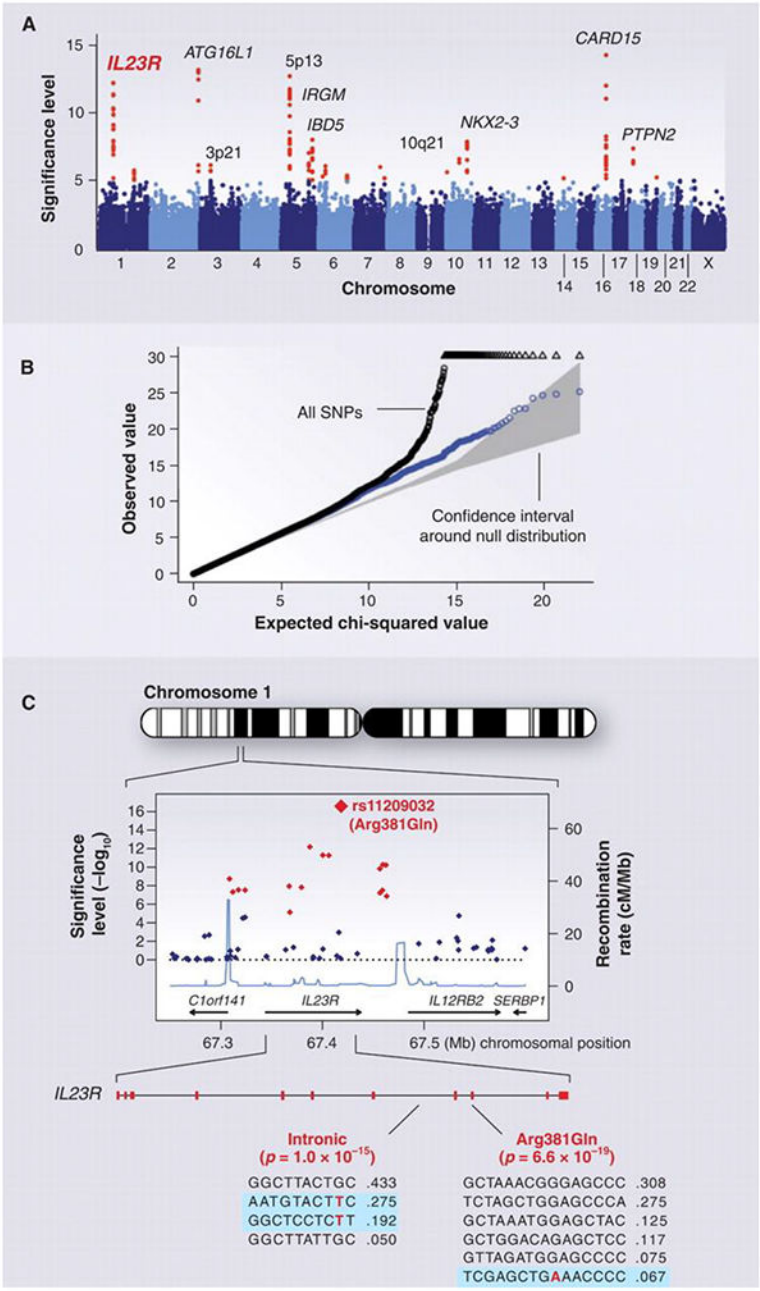

Figure 1. (Figure and text reprinted with permission from D. Altshuler, M.J. Daly, E.S. Lander Genetic Mapping in Human Disease. Science 2008; 322(5903): 881-888).

GWAS for Crohn's disease. The panels show data from the study of Crohn's disease by the Wellcome Trust Case Control Consortium. (**A**) Significance level (*P* value on $\log_{10}$ scale) for each of the 500,000 SNPs tested across the genome. SNP locations reflect their positions across the 23 human chromosomes. SNPs with significance levels exceeding 10^{-5}(corresponding to 5 on the *y* axis) are colored red; the remaining SNPs are in blue. Ten regions with multiple significant SNPs are shown, labeled by their location or by the likely disease-related gene (e.g., *IL23R* on chromosome 1). (**B**) The fact that the SNPs in red are extreme outliers is made clear from a so-called Q-Q plot. A Q-Q plot is made as follows:

The SNPs are ordered (from 1 to *n*) according to their observed *P* values; observed and expected *P* values are plotted for each SNP. Under the null distribution, the expected *P* value for the *i*th SNP is *i*/*n*. If there are no significant associations, the Q-Q plot will lie along the 45° line; the gray region corresponds to a 95% confidence region around this null expectation. Black points correspond to all 500,000 SNPs studied that passed strict quality control; they diverge strongly from the null expectation. Blue points reflect the *P* values that remain when the SNPs in the 10 most significant regions are removed; there is still some excess of significant *P* values, indicating the presence of additional loci of more modest effect. (**C**) Close-up of the region around the IL23R locus on chromosome 1. The first part shows the significance levels for SNPs in a region of ~400 kb, with colors as in (A). The highest significance level occurs at a SNP in the coding region of the *IL23R* gene (causing an $Arg^{381} \rightarrow Gln$ change). The light blue curve shows the inferred local rate of recombination across the region. There are two clear hotspots of recombination, with SNPs lying between these hotspots being strongly correlated in a few haplotypes. The second part shows that the IL23R locus harbors at least two independent, highly significant disease-associated alleles. The first site is the $Arg^{381} \rightarrow Gln$ polymorphism, which has a single disease-associated haplotype (shaded in blue) with frequency of 6.7%. The second site is in the intron between exons 7 and 8; it tags two disease-associated haplotypes with frequencies of 27.5% and 19.2%.

Table 1:

Replicated candidate gene association studies of OSA

Gene (publication)	Abbreviation	Chromosome	Year	Cases/controls	Findings:
Tumor necrosis factor-α[47]	*TNF-α*	6	2014	1369/1064	*TNF-α (−308G/A)* polymorphism is a risk factor for OSA
Apolipoprotein E Epsilon 4[49]	*APOE ε4*	19	2009	1901/4607	no causal relationship between the *APOE ε4* locus and OSA
Prostaglandin E2 receptor EP3 subtype[50]	*PTGER3*	1	2012	963/1965 European ancestry	rs1409986 SNP in the *PTGER3* gene was significantly associated with OSA
Lysophosphatidic acid receptor 1[50]	*LPAR1*	9	2012	233/414 African Americans	rs7030789 SNP in the *LPAR1* gene was associated with OSA