Pleiotropic genetic effects influencing sleep and neurological disorders

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Research evidence increasingly points to the large impact of sleep disturbances on public health. Many aspects of sleep are heritable and genes influencing traits such as timing, EEG characteristics, sleep duration, and response to sleep loss have been identified. Notably, large-scale genome-wide analyses have implicated numerous genes with small effects on sleep timing. Additionally, there has been considerable progress in the identification of genes influencing risk for some neurological sleep disorders. For restless legs syndrome, implicated variants are typically in genes associated with neuronal development. By contrast, genes conferring risk for narcolepsy function in the immune system. Many genetic variants associated with sleep disorders are also implicated in neurological disorders in which sleep abnormalities are common; for example, variation in genes involved in synaptic homoeostasis are implicated in autism spectrum disorder and sleep–wake control. Further investigation into pleiotropic roles of genes influencing both sleep and neurological disorders could lead to new treatment strategies for a variety of sleep disturbances.

Introduction

Sleep disturbances and disorders represent a substantial global health burden: they are prevalent worldwide and have various negative sequelae.[1–3] Adults are recommended to sleep for 7–9 h per night for optimum health,[3,4] yet many individuals sleep for less than 7 h per night.[1,5] Sleeping too little (eg, ≤6 h) is associated with impaired cognition, vigilance, memory, mood, behaviour, and learning ability, as well as depression and mortality.[3] In the USA alone, 50–70 million individuals have a disorder of sleep and wakefulness.[2] Substantial evidence implicates genetic factors in these disorders, and studies have identified genes that influence circadian rhythm disorders and individual preferences in sleep timing.[6–8] Furthermore, research indicates that genetic factors affect variability in EEG-measured sleep.[9–20] Sleep duration and response to sleep loss also vary substantially from person to person, and although environmental factors underlie much of this variability, genetic determinants also exist.[18,19,21–33]

This Review offers a broad overview of key findings from candidate gene and genome-wide investigations (panel 1) of sleep traits in human beings (panel 2). Results from studies of more common, well studied sleep disorders are discussed, including circadian rhythm disorders (prevalence ~7%), insomnia (~13%), restless legs syndrome (~6%), and narcolepsy (~0·04%); prevalence estimates vary depending on the studied population and diagnostic criteria.[34] Also discussed are the overlapping genetic mechanisms of sleep disturbances and neurological disorders (appendix).[35] Characterising pleiotropic genetic effects could improve understanding of disease mechanisms and inform treatment for sleep disturbances in individuals with neurological disorders. Research focused on obstructive sleep apnoea, less common sleep disorders, and animal studies of sleep is considered outside the scope of this Review.

See Online for appendix

Chronotype and circadian rhythm sleep disorders

The genetic basis of the molecular circadian clock inherent to all cells is a well defined autoregulatory feedback loop. The clock circadian regulator (*CLOCK*) and aryl hydrocarbon receptor nuclear translocator-like (*ARNTL* [*BMAL1*] and *ARNTL2* [*BMAL2*]) genes encode the positive component, and the cryptochrome circadian clock (*CRY1* and *CRY2*) and period circadian clock (*PER1*, *PER2*, and *PER3*) genes encode the negative component.[36] Numerous other genes also encode proteins that regulate circadian rhythms, making circadian rhythm sleep disorders and the behavioural manifestation of the internal clock (chronotype) promising phenotypes for genetic studies. Indeed, variants conferring risk for circadian rhythm sleep disorders and chronotype have been identified (figure 1, appendix).

Many circadian rhythm sleep disorders exist, two of which have strong evidence for genetic influences: advanced sleep phase and delayed sleep phase disorders (table). Advanced sleep phase disorder is characterised by difficulty staying awake until the desired bedtime and early morning awakening, whereas delayed sleep phase disorder denotes difficulty falling asleep at the desired bedtime and waking later.[37] Familial aggregation of advanced sleep phase disorder suggests genetic influences,[20] and missense mutations in the *PER2* and casein kinase 1 delta (*CSNK1D*) genes have been implicated in human beings.[37] Notably, in-vivo studies of the *CSNK1D* mutation showed effects on circadian period; however, conflicting evidence of longer circadian periods in *Drosophila* versus shorter periods in mice has been reported.[37] This suggests that although individual components of the circadian clock are highly conserved, there could be different interactions among circadian genes across species. For delayed sleep phase disorder, evidence from small candidate gene studies varies, but a 54-nucleotide variable number tandem repeat in *PER3* and variation in *CLOCK* might have a role.[37]

Chronotype, often assessed by use of self-report, ranges from morningness (feeling sleepy early in the evening and waking early) to eveningness (not feeling sleepy until late at night and waking later; panel 2). Genetic analyses of chronotype have received attention because evidence indicates that when the sleep–wake cycle is not in tune with the circadian clock, there is an increased risk for a number of health problems, including neurological issues—eg, shift work has been associated with impaired cognitive ability.[38] Results from three genome-wide studies of chronotype, done using recreational and public datasets, indicate that multiple genes contribute small effects (figure 1, appendix).

A genome-wide association study (GWAS) in a 23andMe dataset (n=89 283) identified 15 loci associated with self-report of being a morning person.[6] Follow-up analyses indicated enrichment in this population for genes involved in circadian and phototransduction pathways. Notably, the effects for each individual variant were relatively small; the large dataset required to detect small effects on chronotype potentially reflects variability inherent in self-reported phenotypes. Three of the 15 loci associated with morningness in the 23andMe dataset[6] reached genome-wide significance for associations with chronotype in a UK Biobank dataset (n=100 420).[7] Follow-up analyses indicated enrichment for genes involved in CNS function and neurological disorders, including dementia and affective disorders. Potential reasons that many loci associated with chronotype in the 23andMe dataset were not associated with chronotype in the UK Biobank include the use of different phenotype definitions, the described limitations of self-report, or different genetic effects influencing chronotype in the two datasets. Analysis of self-reported chronotype in a larger UK Biobank dataset (n=128 266) observed additional signals when chronotype categories were adjusted for age, gender, and study centre.[8] Many previously reported loci also showed a trend towards significance ($p<0·05$), with consistent directions of effect—ie, results were either positive or negative in both analyses. Seven of the loci identified in the analysis remained significant after conditioning on the 15 loci from 23andMe,[6] suggesting 22 independent chronotype-associated loci from the two studies.[8]

Notably, single nucleotide variations near the coding sequence of the regulator of G-protein signalling 16 (*RGS16*) and adenylate kinase 5 (*AK5*) genes reached genome-wide significance in all three GWAS (figure 1). *RGS16* inactivates G-protein alpha subunits, and *RGS16* knock-out mice had a longer circadian period.[6] *AK5* is expressed exclusively in the brain and regulates adenine nucleotide metabolism.[6] Furthermore, in the larger UK Biobank GWAS,[8] associations reported near *PRPF3* and *TARS2*, and *ORAI2* and *RASA4* represented the same signals as associations near anterior pharynx defective 1 (aph-1 homologue A, gamma-secretase subunit; *APH1A*) and f-box and leucine rich repeat 13 (*FBXL13*) observed in the 23andMe[6] and smaller UK Biobank GWAS.[7] Although the precise function is unknown, *APH1A* is regulated by orexin, the neurotransmitter that regulates arousal.[6] *FBXL13* has a role in circadian rhythms by ubiquitinating and mediating the degradation of cryptochrome proteins, and mutant *FBXL3* mice have an extended circadian period.[6] Variation near *PER2* was associated with morningness in the 23andMe[6] and larger UK Biobank GWAS,[8] with a trend towards significance in the smaller UK Biobank analysis.[7] A polymorphism in the 5′-UTR of *PER2* was also implicated in a smaller candidate gene study.[39] *PER2* represses the CLOCK-BMAL2 protein

For more on **23andMe** see https://www.23andme.com

For more on the **UK Biobank** see http://www.ukbiobank.ac.uk

Panel 1: Definitions of key terms

Association (disorder)
Significantly increased frequency of a genomic variant in unrelated (no familial relationship) individuals with a disorder, compared with unrelated, unaffected controls.

Linkage (disorder)
Co-segregation of a genomic locus and a disorder from parents to offspring.

Familial aggregation
Evidence that a disorder or trait runs in families, as a result of common genes, environment, or both.

Heritability
The proportion of the phenotypic variability in a disorder or trait that can be explained by additive (narrow-sense) or dominant (broad-sense) genetic factors, or both, not environmental effects.

Genome-wide significance
A p-value threshold of $5·0 \times 10^{-8}$, indicating the probability that the observed test statistic, or one more extreme, occurs by chance. This threshold is based on Bonferroni multiple testing correction of p=0·05 for 1 000 000 independent common variants across the European ancestral genome, as estimated by the International HapMap Consortium.

Panel 2: Definitions of sleep traits with genetic influences

Chronotype
The circadian clock promotes sleeping and waking which manifests as chronotype. Sleeping and waking outside of the times set by the internal clock has been observed to cause global changes in gene expression.

EEG characteristics
Sleep EEG can be deconstructed into specific frequency bands ranging from delta to gamma frequencies. The relative contribution of each band in the sleep EEG (ie, their power or spectral density) has been linked to sleep physiological variables, changes in which can be linked to EEG abnormalities, however, little is know about their health effects.

Quantity and quality
Healthy sleep includes onset within 30 min of lying down and consolidated sleep for 7–9 h. Observed neurological consequences of reduced quantities and poor quality of sleep include reduced psychomotor responses, attention lapses, memory lapses, reduction in short-term and working memory, impaired cognitive function, difficulty concentrating, and increased pain sensitivity.

Response to sleep loss
Typical response includes daytime sleepiness, and increased periods of slow-wave sleep during subsequent recovery sleep.

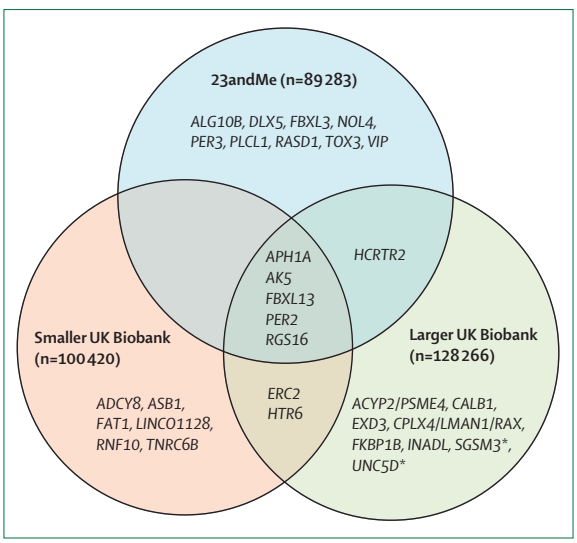

Figure 1: **Genes harbouring loci significantly associated with chronotype**
Venn diagram plotting the overlap among genes to which loci that reached genome-wide significant associations with chronotype in at least one of the genome-wide association studies[6-8] were assigned. *Implicated genes in which loci were observed to reach significance ($p<5{\cdot}0\times10^{-8}$) in discovery analyses but not in a meta-analysis of the combined larger UK Biobank[8] and 23andMe[6] datasets. Where two or more genes are separated with /, associated variants were near coding regions of multiple genes.

	Clinical features	Related neurological conditions
Circadian rhythm sleep disorders	A mismatch between endogenous circadian rhythms and the sleep–wake schedule preferred by the individual; advanced sleep phase syndrome involves difficulty staying awake until the desired bedtime and waking early; delayed sleep phase syndrome involves difficulty falling asleep at the desired bedtime and waking later	Abnormal circadian rhythms are potentially risk factors for neurodegenerative diseases; other comorbid conditions include major depression, bipolar disorder, obsessive-compulsive disorder, schizophrenia, and substance misuse
Insomnia	Difficulty initiating or maintaining sleep, associated with significant daytime consequences or distress	Comorbid conditions include headache, stroke, seizures, dementia, Parkinson's disease, mood disorders (eg, major depressive disorder), anxiety disorders (eg, post-traumatic stress disorder), schizophrenia, eating disorders, attention deficit hyperactivity disorder, adjustment disorder, and personality disorders
Restless legs syndrome	Unpleasant sensations in the legs during periods of rest, creating an irresistible urge to move the legs and, consequently, sleep disruptions	Comorbid conditions include Parkinson's disease, multiple sclerosis, migraine, stiff-man syndrome, Huntington's chorea, essential tremor, amyotrophic lateral sclerosis, generalised anxiety disorder, major depressive disorder, and obsessive-compulsive disorder
Narcolepsy	Irresistible and excessive sleepiness typically associated with cataplexy (bilateral loss of muscle tone provoked by emotion) or other sleep phenomena (eg, paralysis or hypnagogic hallucinations)	Comorbid conditions include increased migraine frequency, increased pain threshold, chronic pain, suicide risk, major depressive disorder, bipolar disorder, post-traumatic stress disorder, social anxiety, agoraphobia, panic disorder, schizophrenia, and obsessive-compulsive disorder

Clinical features of the more common sleep disorders included in this Review are described. Examples of neurological symptoms or comorbid conditions commonly observed in individuals with these sleep disorders are listed.

Table: **Clinical features and related neurological conditions of sleep disorders with genetic influences**

complex and some individuals with familial advanced sleep phase disorder and *PER2* mutations have a 4-h advance of the sleep–wake rhythm.[6,40] Figure 1 illustrates the implicated genes and overlap across these GWAS.

Evidence for genes influencing circadian rhythm sleep disorders is lacking and additional research is needed. Furthermore, very large sample sizes have been required to identify small genetic influences on chronotype. Notably, the smaller UK Biobank study observed larger effects when comparing extreme chronotype groups of individuals reporting "definitely morning" (n=26 948) versus "definitely evening" (n=8724).[7] Future work aimed at refining the sources of genetic signals in large datasets could improve understanding of genetic contributions to this complex trait. Since circadian rhythm and sleep disruptions are prevalent in individuals with neurological disorders—eg, circadian rhythms might influence susceptibility to depression[37]—effective treatment of these issues might help to minimise symptom severity. Although the extent to which circadian rhythm genes influence neurological disorders is unclear, many are implicated in a range of neurological conditions (figure 2, appendix).

Characteristics of EEG during sleep

Some features of sleep defined by EEG potentially contribute to negative health outcomes—eg, reduced periods of slow-wave or rapid eye movement (REM) sleep (panel 2). Understanding genetic contributions to sleep EEG variability might help to reduce risk for negative outcomes.

A well studied gene that influences EEG variability is *PER3*. Research has focused on a 54-nucleotide variable number tandem repeat in exon 18. Homozygosity for five repeats, *PER3(5/5)*, affects sleep structure and homoeostasis (including increased slow-wave sleep, theta and frontal delta activity, and decreased frontal sigma activity) compared with homozygosity for four repeats, *PER3(4/4)*.[9,10] Furthermore, sleep-deprived *PER3(5/5)* individuals have greater slow-wave energy increases (ie, increased sleep drive) during so-called recovery sleep, and show a greater detrimental effect of sleep deprivation than sleep-deprived *PER3(4/4)* and *PER3(4/5)* individuals.[11,12,28] *PER3(5/5)* also relates to earlier age of onset of bipolar disorder (figure 2, appendix) than in those with bipolar disorder who do not have this genotype. Moreover, treatment for depressive episodes in bipolar disorder includes total sleep deprivation with light therapy, which is less effective in *PER3(5/5)* individuals.[41] Additionally, a symptom of manic episodes is decreased sleep drive; thus, expression of sleep disturbances in bipolar disorder might be modified by pleiotropic effects of *PER3*. *PER2* might also have effects on sleep homoeostasis, as *PER2* variants were associated with less time spent in slow-wave sleep (n=84; $p<0{\cdot}046$).[42]

A rare variant near melatonin receptor 1B (*MTNR1B*) was associated with longer REM sleep latency (n=82; $p<0{\cdot}046$) than that in people without the variant;[42] on

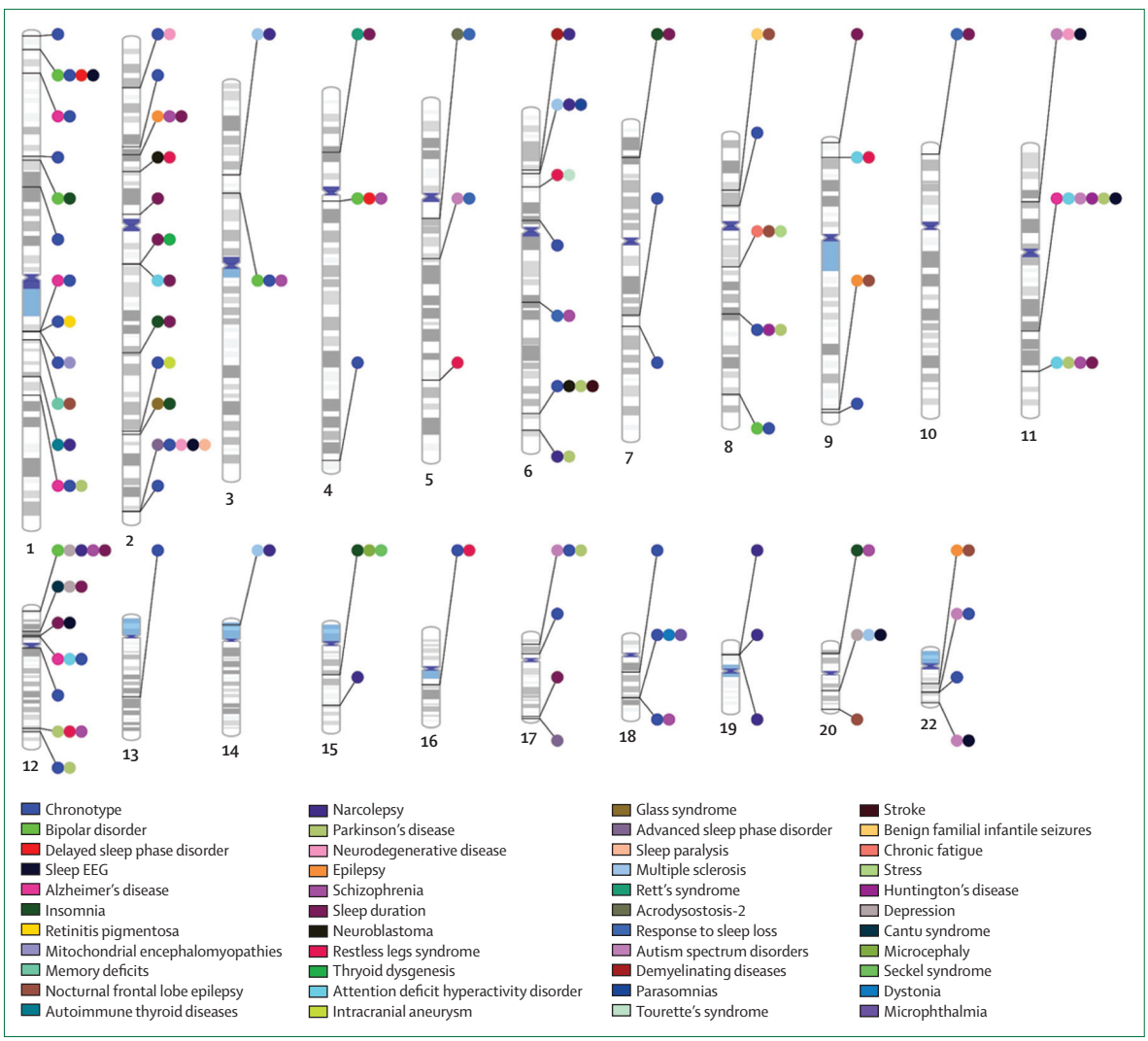

Figure 2: **Pleiotropic effects of genes implicated in sleep**
Idiogram mapping genes that have been implicated in various sleep traits to chromosomal locations. Included are neurological disorders in which the same gene is implicated, and phenotypes are colour coded. The number of different phenotypes that have been observed associated with the same variant suggests pleiotropy. This figure was generated using PhenoGram software

For **PhenoGram software** see http://visualization.ritchielab.psu.edu/phenograms/plot

average, time from sleep onset to REM sleep was 65 min longer in people with this rare variant in the *MTNR1B* gene (n=6). Melatonin receptors were reported to modulate sleep architecture in-vivo studies.[43] Furthermore, non-synonymous mutations in *MTNR1B* were observed in individuals with attention deficit hyperactivity disorder and autism spectrum disorder, and altered expression of melatonin receptors is frequently reported in autism spectrum disorder and neurodegenerative diseases (figure 2, appendix).

Brain derived neurotrophic factor (BDNF) also regulates EEG activity. A Val66Met mutation in the encoded protein results in impaired dendritic trafficking and synaptic localisation of BDNF, and a reduction in activity-dependent BDNF secretion.[44] Mutation carriers might have reduced slow-wave sleep[13] and decreased spectral power in specific bands and stages of sleep.[14] The Val66Met polymorphism is also implicated in neurodegenerative diseases, and associated with altered memory-related hippocampal regional cerebral blood flow and impaired neuronal integrity and synaptic activity (figure 2, appendix). BDNF-based synaptic repair is a proposed treatment strategy for neurodegeneration, and both reduced and elevated BDNF concentrations are implicated in neurodevelopmental disorders (figure 2, appendix). Thus, BDNF is a strong candidate for future research investigating the developmental and age-related connection between sleep and neurological problems.

Furthermore, two studies (n=14[15] and n=22[16]) reported that individuals heterozygous for an adenosine deaminase (*ADA*) mutation (p.Asp8Asn), which correlated with

reduced enzymatic activity of the protein product, had more slow-wave sleep and higher power in non-REM sleep in the delta and low-theta bands, indicating elevated need to sleep. A population-based study[17] (n=800) corroborated some of these findings; however, mutation carriers did not have more slow-wave sleep. One potential explanation for this discrepancy is that only the smaller studies[15,16] controlled for caffeine intake, which affects adenosine. ADA deficiency has been implicated in neurological and psychiatric disorders, including multiple sclerosis and depression, and neurological abnormalities, such as seizures and developmental delay (figure 2, appendix). Variation in *ADA* potentially contributes to abnormal sleep patterns in individuals with these neurological disorders, making ADA a useful target protein for drug development.[45]

Finally, one study[18] observed EEG effects associated with basic helix-loop-helix family member e41 (*BHLHE41* or *DEC2*); a rare mutation (p.Tyr362His) in exon 5 was identified in one dizygotic twin with higher delta power during non-REM and less REM sleep compared with his twin without the mutation. *DEC2* encodes a component of the circadian clock[36] and is related to sleep durations and response to sleep loss.[18,19]

Overall, sleep EEG genetics is a promising area of research. Evidence of major genetic contributions to sleep EEG exists; however, studies are limited to candidate gene approaches within small samples. Many genes implicated in EEG variability and neurological disorders overlap, but more research is needed on the clinical relevance of identified genes.

Sleep quantity and quality

Sleep duration and response to sleep loss

Defining normal sleep duration (panel 2) is difficult because of high interindividual and night-to-night variability and the influence of a myriad of factors. Sleep time is typically longest during early development and decreases with age.[46] Furthermore, the response to sleep loss typically includes longer and deeper sleep during subsequent recovery sleep.[46] Although sleep duration is strongly influenced by the environment, twin studies also indicate a genetic contribution[20] and genetic variants that influence this trait have been identified (figure 2, appendix). Because sleep duration is a highly variable trait that is usually measured via self-report, identifying genes with appreciable influence has been difficult, and large GWAS sample sizes have been needed to detect associations. Nevertheless, a few genes show substantial evidence for involvement in the regulation of sleep duration and response to sleep loss.

One gene is ATP binding cassette subfamily C member 9 (*ABCC9*), which encodes a pore-forming subunit of an ATP-sensitive potassium channel involved in energy metabolism. Potential *ABCC9* involvement is important because a suspected function of sleep is energy conservation.[47] A genome-wide significant association (panel 1) was observed (n=4251) between *ABCC9* variation and self-reported sleep duration.[21] Furthermore, experimental downregulation of an *ABCC9* homologue in *Drosophila* neurons reduced night-time sleep duration, but this association was not observed in independent datasets.[8,21–23] However, in one dataset (n=5249) it was noted that the effect of *ABCC9* depended on season and phase of entrainment,[21] and a pathway-based GWAS identified the ATP transporter-binding cassette pathway as enriched for variants nominally associated ($p<0\cdot05$) with sleep duration.[22] Additional evidence for *ABCC9* in sleep duration includes results that were either non-significant after correction for multiple testing[25] or observed only in a rare, recessive model (two of 947 individuals with a homozygous recessive genotype).[24] Notably, pleiotropic effects for *ABCC9* and depressive symptoms were observed in one study (n=901), with fewer symptoms reported in 33 individuals with a homozygous recessive *ABCC9* genotype.[24]

Another GWAS (n=1941) implicated both protocadherin 7 (*PCDH7*) and kruppel like factor 6 (*KLF6*) in sleep duration.[22] Suggestively associated alleles ($p<0\cdot0001$) were related to increased expression of both genes; increased *KLF6* expression correlated with shorter sleep durations and *KLF6* expression increased after five nights of sleep restriction.[22] *KLF6* encodes a transcription factor that activates the promoter for inducible nitric oxidase, and nitric oxide increases during sleep deprivation in rats.[48]

Another study (n=738) reported a significant genome-wide association (although not corrected for multiple phenotypes or analyses; panel 1) between phosphodiesterase 4D (*PDE4D*) variation and ratings of subjective sleepiness based on the Epworth Sleepiness Scale.[27] The putative effects of *PDE4D* variants are compelling, because *PDE4D* is implicated in memory consolidation,[49] which is a suspected function of sleep.[47] Pleiotropic effects of *PDE4D* were observed in patients with acrodysostosis-2, a rare developmental disorder causing intellectual disability (figure 2, appendix).

Two loci had genome-wide significant associations with sleep duration in another GWAS (n=47 180).[23] One locus fell between paired box 8 (*PAX8*) and COBW domain containing 2 (*CBWD2*). *PAX8* encodes a transcription factor involved in thyroid development, whereas *CBWD2* is expressed in the brain with an unknown function. The second locus was in a non-coding RNA (*LOC101927400*) that is important in regulating the expression of multiple genes. Thus, functional effects could include altered expression of protein-coding genes without any DNA sequence variation, suggesting that epigenetic studies are warranted. Another GWAS of sleep duration (n=128 266) observed genome-wide significant associations between variants near *PAX8*, as well as vaccinia related kinase 2 (*VRK2*), which encodes a serine/threonine kinase.[8] All of the variants associated with sleep duration in the

discovery dataset showed suggestive association (p≤0·01) in an independent dataset (n=47 180). Using publically available GWAS statistics, this study also found a genetic correlation between sleep duration and schizophrenia. Specifically, *VRK2* variants have been associated with schizophrenia (figure 2, appendix).[8]

Variants (ie, a single base-pair change or single nucleotide variant) in dopamine receptor D2 (*DRD2*) is associated with both shorter self-reported sleep durations (n=25 465) and objectively measured shorter sleep-onset latency.[26] Suggesting pleiotropy, *DRD2* variation has been shown to increase the risk for attention deficit hyperactivity disorder, schizophrenia, and Parkinson's disease (figure 2, appendix). Additionally, defects in the dopaminergic system are implicated in sleep–wake cycle regulation, restless legs syndrome, and other neurological disorders.[50]

RNA binding protein, fox-1 homologue 3 (*RBFOX3*) potentially influences sleep duration, given its expression in the brain and coexpression with genes associated with the release cycle of neurotransmitters involved in sleep onset. A meta-analysis of seven GWAS (n=4242) identified associations approaching significance (p<0·0001) between *RBFOX3* variants and self-reported sleep latency.[51] *RBFOX3* was also associated with sleep latency (p≤0·015) in a meta-analysis of 12 datasets (n=30 377).[51]

A GWAS (n=956) of actigraphic measures of night and daytime sleep[52] replicated previously observed associations between aryl hydrocarbon receptor (*AHR*) and number of awakenings, wake after sleep onset and sleep efficiency,[33] and uridine phosphorylase 2 (*UPP2*) and sleep duration.[23] Furthermore, genome-wide significant associations were observed between variants upstream of UFM1-specific ligase 1 (*UFL1*) and sleep efficiency on weekdays, between doublesex and mab-3 related transcription factor 1 (*DMRT1*) and sleep latency, and between SET and MYND domain containing 1 (*SMYD1*) and sleep offset.[52] *UFL1* is a ubiquitin-like modifier involved in the regulation of apoptosis and trafficking of vesicles. Ubiquitin and ubiquitin-like pathways have been found to be upregulated after partial sleep restriction and are implicated in schizophrenia (figure 2, appendix). Neither *DMRT1* nor *SMYD1* have other reported effects on sleep. *DMRT1* has an important role in embryonic development and sexual differentiation, and *SMYD1* is implicated in myogenesis and cardiogenesis.[52] Additional studies are needed to further characterise these genes in relation to sleep, particularly because this GWAS did not correct for multiple phenotypes. Finally, a variant in calcium voltage-gated channel subunit alpha1 C (*CACNA1C*) was nominally associated (p=0·00038) with sleep onset irregularity. Another GWAS (n=2323) observed trending associations (ie, p<0·05, but not genome-wide significance) between *CACNA1C* variants and both increased sleep latency (p<0·0001) and poorer sleep quality (p<0·0001).[33] Another study found no significant association between variants and sleep latency (n=2034);[33] however, a candidate gene study observed associations between *CACNA1C* variants and poor sleep quality (p<0·017).[24] Furthermore, the rare, homozygous recessive genotype (three of 932 individuals) for this *CACNA1C* variant was associated with reduced sleep latency (p<0·005) and higher reports of depressive symptoms (p<0·001).[24] *CACNA1C* encodes an L-type voltage-dependent calcium channel activated by the wake-promoting neuropeptide orexin, and has been implicated in depression, bipolar disorder, schizophrenia, and one small (n=602) candidate gene study of narcolepsy (figure 2, appendix).

In addition to genome-wide studies, candidate gene sequencing has offered insight into the genetics of sleep duration and response to sleep deprivation. By selecting individuals with well defined extreme phenotypes, sequencing can identify rare variants with large effects that can be characterised through in-vitro and in-vivo studies. A rare variant analysis was done in two participants with no evidence of daytime impairment, despite sleeping only 6 h per night.[19] Targeted sequencing of circadian genes identified a mutation in exon 5 (p.Pro384Arg) of *DEC2*. In *Drosophila* and mice, the mutation resulted in shortened sleep durations, and reduced recovery sleep following sleep deprivation in mice.[19] A different mutation in the same codon (p.Pro384Gln) had no clear effects on sleep duration in another study.[18] Another *DEC2* mutation (p.Tyr362His), which has effects on sleep EEG, also influenced sleep duration and response to sleep loss.[18] In-vitro studies observed that p.Tyr362His and p.Pro384Arg, but not p.Pro384Gln, reduced the ability of *DEC2* to suppress CLOCK or BMAL1 transactivation.[18] These studies show the power of rare variant analyses with well characterised phenotypes and subsequent functional assessment.

Overall, numerous studies have identified potential candidate genes influencing sleep duration or response to sleep loss, but for many of these genes, substantiated evidence is scarce. Future research with a focus on understanding the connection between sleep and implicated genes is warranted.

Insomnia

Insomnia, defined as difficulty initiating or maintaining sleep that is associated with substantial daytime consequences or distress, is one of the most prevalent sleep disorders (table). Although studies have suggested that heritable insomnia-related traits exist,[20] insomnia can be substantially influenced by non-genetic factors (eg, environmental stimuli, medications, concomitant medical conditions). Furthermore, although insomnia can be measured objectively through actigraphy, potentially biased self-reports are usually used. Genetic studies are scarce, and this is probably because of uncertainty about the optimum insomnia phenotype.

Two insomnia GWAS have been done,[32,33] neither of which yielded genome-wide significant associations

(panel 1). One GWAS[32] (n=10 038) observed suggestive associations for variation in receptor tyrosine kinase like orphan receptor 1 (*ROR1*; p<0·0001), which has been associated with bipolar disorder, and phospholipase C beta 1 (*PLCB1*; p<0·0001), which has been associated with schizophrenia (figure 2, appendix). This observation suggests pleiotropy or confounding, or both, because insomnia is prevalent in bipolar disorder and schizophrenia[35] and this analysis did not correct for comorbid psychiatric conditions. *ROR1* encodes a protein known to modulate synapse formation and *PLCB1* encodes a protein important for the intracellular transduction of many extracellular signals. Follow-up analyses indicated enrichment of variants nominally associated with sleep duration (p<0·005) in synaptic and neuronal differentiation genes, and genes involved in cerebellar long-term depression, hippocampal long-term potentiation, and calcium signalling.[32]

Another GWAS evaluated insomnia factor scores (n=2267) and observed suggestive associations with variants near *CEP152* (p<0·0001) and *SATB2* (p<0·0001).[33] Centrosomal protein 152 (*CEP152*) encodes a core protein of the centrosome with a crucial role in cell division, which is upregulated in response to supplemental melatonin.[53] Mutations in *CEP152* are also causal factors for Seckel syndrome and microcephaly (figure 2, appendix). Another gene, SATB homeobox 2 (*SATB2*), encodes a protein involved in transcription regulation and protein remodelling. *SATB2* is a causal factor for Glass syndrome, in which severe sleep disturbances are common (figure 2, appendix).

Although more large-scale studies with robust phenotyping are necessary to elucidate the mechanisms underlying complex insomnia, genetic mechanisms have been shown for the rare condition fatal familial insomnia, which causes severe and progressive insomnia, autonomic nervous system malfunction, motor disturbances, and eventual death.[54,55] Fatal familial insomnia is a prion disease caused by mutations in the prion protein gene (*PRNP*).[54,55] Despite its name, fatal familial insomnia is distinct from complex insomnia, with no evidence of shared clinical or pathophysiological features.

Neurological sleep disorders

Considerable progress has been made towards understanding genetic contributions to neurological sleep disorders such as restless legs syndrome and narcolepsy (figure 2, appendix), potentially reflecting a stronger influence of underlying biological mechanisms and less influence from external environmental factors than in sleep disorders such as insomnia.

Restless legs syndrome

Restless legs syndrome is a sleep-related movement disorder characterised by unpleasant sensations in the legs during periods of rest, creating an irresistible urge to move the legs and, consequently, sleep disruptions (table).[56] Findings from studies of restless legs syndrome represent a major accomplishment in elucidating genes associated with sleep disorders; observations of strong genetic effects influencing a phenotype largely defined via questionnaires are particularly notable. Initial studies were motivated by familial aggregation (panel 1) of restless legs syndrome. The pattern of inheritance of early-onset restless legs syndrome appears to be autosomal dominant,[57,58] although a causal gene has not been identified.

Variants in nitric oxide synthase 1 (*NOS1*) were associated with restless legs syndrome (n=918; p<0·05) in a European population following fine-mapping of a previously reported linkage region.[59] Although a follow-up analysis in a Spanish population (n=533) did not show the *NOS1* association with overall restless legs syndrome, risk alleles were overrepresented in patients with positive family histories of restless legs syndrome.[60] *NOS1* encodes the neuronal form of nitric oxide synthase and high expression of *NOS1* has been associated with increased risk for Parkinson's disease (figure 2, appendix). Additionally, long alleles of a repeat polymorphism in the *NOS1* promoter associate with less severe psychopathology and altered prefrontal cortex function in individuals with schizophrenia (figure 2, appendix).

A GWAS of restless legs syndrome (n=2448) observed genome-wide significant associations with variants in the *MEIS1*, *BTBD9*, *PTPRD*, *MAP2K5* or *SKOR1*, and *TOX3* regions in both discovery (n=2448) and replication (n=9689) datasets.[61] Studies have observed that variants in protein tyrosine phosphatase receptor type D (*PTPRD*) are associated and linked with restless legs syndrome (panel 1).[62,63] Notably, rare copy number variations in *PTPRD* are associated with attention deficit hyperactivity disorder, and patients with attention deficit hyperactivity disorder commonly have restless legs syndrome (figure 2, appendix). Associations of variants in meis homeobox 1 (*MEIS1*) with restless legs syndrome have also been observed in multiple studies,[20] and a sequencing study (n=7302) found that individuals with restless legs syndrome had an excess of rare, loss-of-function *MEIS1* mutations.[64] *MEIS1*, which has a similar function to *PTPRD*, is involved in neuronal development.

Multiple studies have observed associations between restless legs syndrome and BTB domain containing 9 (*BTBD9*).[20] One GWAS[65] (n=18 145) showed that effects related to *BTBD9* were exclusive to restless legs syndrome with periodic limb movements. *BTBD9* is involved in protein–protein interactions and implicated in synaptic homoeostasis. Notably, alterations in iron metabolism might have a role in the pathogenesis of restless legs syndrome, and serum ferritin concentrations decreased by 13% per *BTBD9* risk allele;[65] however, *BTBD9* effects on ferritin concentrations are inconsistent.[61,66–69] Studies in *Drosophila* observed that global loss of *BTBD9* and specific knockdown of *BTBD9* in dopaminergic neurons resulted in fragmented sleep.[69] Dopamine agonists used to treat

restless legs syndrome in human beings reversed the sleep fragmentation phenotype in *BTBD9* knockouts. Dopamine agonists can also be used to treat Tourette's syndrome and *BTBD9* variants have also been associated with risk for developing this disorder (figure 2, appendix). Finally, two mutations in *GLO1*, a gene immediately downstream of *BTBD9*, co-segregated with restless legs syndrome in four families. Conditional haplotype analyses controlling for *BTBD9* variation indicated that the relation of these mutations with restless legs syndrome was via effects in *BTBD9*. Therefore, the co-segregating variants might reside in *BTBD9* regulatory regions.[67]

Additional sequencing efforts have identified a rare variant in protocadherin alpha 3 (*PCDHA3*) co-segregating in a four-generation family with restless legs syndrome.[70] Two additional rare, missense mutations in *PCDHA3* were identified in unrelated individuals with restless legs syndrome. *PCDHA3* is predicted to be involved in the establishment and function of specific cell–cell connections in the brain.

Altogether, there is clear evidence for genetic effects in restless legs syndrome. Although developmental pathways are consistently implicated, the combined genetic effects account for only about 3% of the estimated heritability.[20] Thus, current knowledge might have little clinical utility.

Narcolepsy

Narcolepsy is a debilitating sleep disorder characterised by irresistible and excessive sleepiness typically associated with cataplexy (bilateral loss of muscle tone provoked by emotion) or other sleep phenomena (eg, paralysis, hypnagogic hallucinations; table).[71] Although narcolepsy with cataplexy is generally accepted to be caused by loss of hypocretin neurons, little evidence exists that the hypocretin neuropeptide precursor (*HCRT*) gene is involved. Instead, genetic findings have led to the hypothesis that autoimmune-mediated destruction of HCRT-containing neurons is causal.[72]

Variation in *HLA* genes, which encode major histocompatibility complex class II receptors involved in the presentation of foreign peptides to receptors on T cells, are the strongest known genetic factors influencing narcolepsy. In people of Japanese and European descent,[73] *HLA-DQB1*0602* has strong effects on the risk for narcolepsy (aggregate odds ratio=251).[74] *HLA-DQB1*0602* also increases risk for autoimmune diseases (figure 2, appendix), and along with the identification of numerous immune system genes influencing narcolepsy, this finding supports an autoimmune disorder hypothesis.

A protective haplotype, *DRB1*1301~DQB1*0603*, near *HLA-DQA2* has been identified in people of European descent with narcolepsy; they almost never carried a trans-*DRB1*1301~DQB1*0603* haplotype.[75] *HLA-DQB1* alleles are on distinct *HLA-DRB1* haplotypes in African-Americans.[20] The magnitude of these effects suggests that *HLA* profiling in suspected narcolepsy cases could have clinical utility. In view of this, an allele competition model was proposed, in which the effect of *HLA-DQB1** risk alleles are modified by *HLA-DQA1** alleles;[76] however, this concept remains open to question.[77]

Despite the strong association between narcolepsy and *HLA-DQB1*0602*, the variant occurs in many individuals without narcolepsy, suggesting that other genes are involved. Additional immune-related genes have been identified in cohorts that are positive for the *HLA-DQB1*0602* allele. Cathepsin H (*CTSH*) and tumour necrosis factor superfamily member 4 (*TNFSF4*) were implicated using this approach of studying cohorts that are positive for the HLA-DQB1*0602 allele.[78] The functions of these genes suggest that antigen presentation to specific T-cell receptors is a key part of narcolepsy aetiology. One GWAS[79] (n=3994) also identified genome-wide significant associations (panel 1) in T-cell receptor alpha (*TRA*). Examining variants exclusively in immune genes (n=12 307) further implicated *TRA*,[78] although the reported risk allele was inconsistent (appendix).

Another analysis in individuals positive for *HLA-DQB1*0602* investigated variants outside the *HLA* region.[80] A variant in the promoter of C-C motif chemokine receptor 1 (*CCR1*) was associated with narcolepsy in both discovery (n=1971; $p<0\cdot0001$) and replication (n=1109; $p=0\cdot032$). Furthermore, *CCR1* expression was associated with risk genotypes, and decreased in a subset of cases versus controls. *CCR1*-encoded receptors are abundant in early multiple sclerosis lesions, suggesting common pathogenesis between narcolepsy and multiple sclerosis (figure 2, appendix). Myelin oligodendrocyte glycoprotein (*MOG*), which has been implicated in risk for demyelinating diseases, was also implicated in familial narcolepsy (figure 2, appendix). A linkage study identified a rare variant in *MOG* co-segregating with narcolepsy in a family with 12 members with narcolepsy, all of which had the variant, but the variant was absent in 775 unrelated people without narcolepsy.[81]

Another GWAS of individuals with *HLA-DQB1*0602* (n=5689) identified a genome-wide association between a variant in purinergic receptor P2Y11 (*P2RY11*) and narcolepsy.[82] The risk allele decreased *P2RY11* expression and increased sensitivity of $CD8^+$ T cells to ATP-induced cell death. The potential role of *P2RY11* in narcolepsy is similar to the connection of *BTBD9* with restless legs syndrome. Multiple genes are encoded in the approximately 90-kb region on 19p13.2, including *P2RY11*, *PPAN*, *EIF3G*, and *DNMT1*. Sequencing of three individuals with a rare hereditary form of narcolepsy-associated deafness, cerebellar ataxia and, eventually, dementia identified a missense mutation in DNA methyltransferase 1 (*DNMT1*), suggesting that the GWAS signal for *P2RY11* might be associated with other genes in the genomic area 19p13.2. *DNMT1* encodes an enzyme required for the differentiation of $CD4^+$ cells into regulatory T cells.[83] Follow-up studies

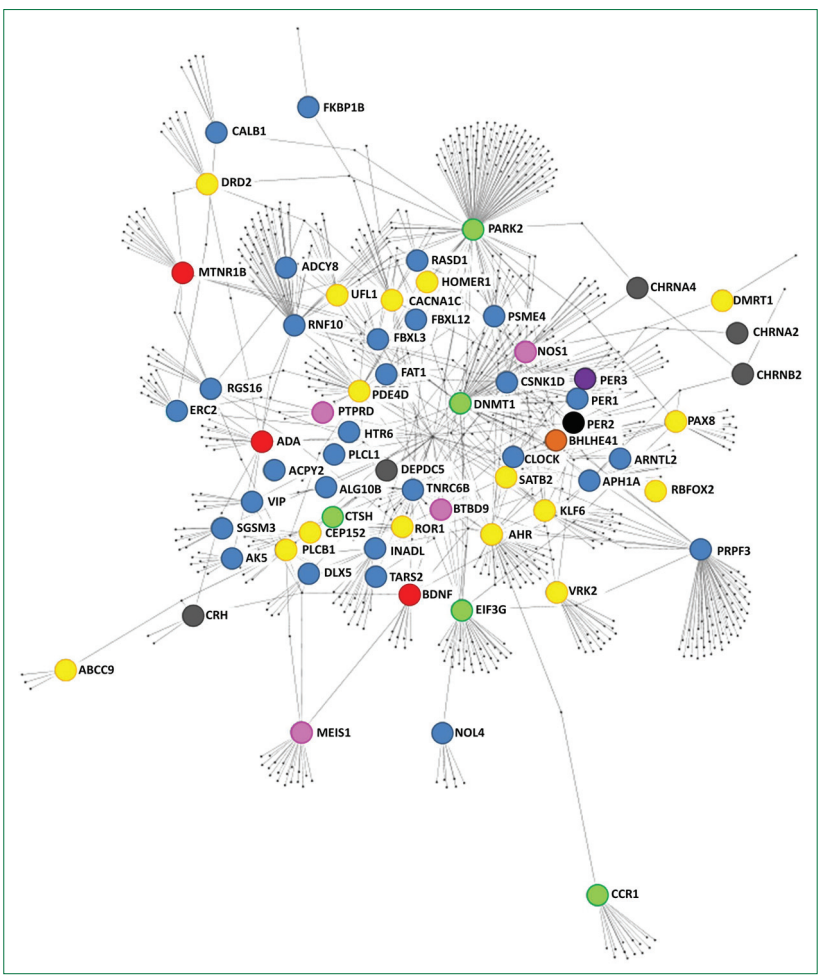

Figure 3: **Protein–protein interaction networks connecting implicated sleep genes**
A network analysis of the protein products of all genes implicated in the sleep traits included in this Review was undertaken and visualised using NetworkAnalyst. This software does integrated systems-level analyses of experimentally validated molecular interactions and 3000 pathway annotations of relevance to all mammalian cellular systems available in InnateDB. Networks were built using first-order interactions. This figure demonstrates how the majority of genes, that are implicated in the sleep traits discussed in this review, encode proteins that can be connected in an overall network system. Proteins are coloured according to implicated sleep trait: blue=circadian rhythm sleep disorder or chronotype; red=sleep EEG; yellow=sleep quantity or insomnia; pink=restless legs syndrome; green=narcolepsy; grey=other sleep disorders; purple=circadian rhythm sleep disorder or chronotype + sleep EEG; orange=sleep EEG + sleep quantity or insomnia; black=circadian rhythm sleep disorder or chronotype + sleep EEG + other sleep disorders.

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investigated variants in this region across two cohorts. The most significant associations were located in a *PPAN-P2RY11-EIF3G* haplotype block, not in *DNMT1*.[84] The most consistent association was for a eukaryotic translation initiation factor 3 subunit G (*EIF3G*) variant that increased *EIF3G* expression, which correlated with *P2RY11* expression.[84] Thus, variants in *EIF3G* might regulate expression of *P2RY11*, and effects of regional variation on narcolepsy might relate to dysregulation of multiple genes.

Additional evidence for immune system dysfunction in narcolepsy includes a genome-wide copy number variation analysis (n=988) in cases with *HLA-DQB1*0602*.[85] People with narcolepsy had a larger global burden of copy number variations than did controls, and pathway analysis revealed enrichment of rare, large copy number variations in immune response genes. Specifically, duplications in parkin RBR E3 ubiquitin protein ligase (*PARK2*) were suggestively associated with narcolepsy (p=0·031). *PARK2* is associated with early-onset and autosomal recessive juvenile Parkinson's disease and potentially functions in class I major histocompatibility complex-mediated antigen processing and presentation (figure 2, appendix).

Another study supports the hypothesis that common variants with small effects contribute cumulatively to narcolepsy risk.[86] A total of 476 446 variants were assessed for cumulative effects in 393 cases with the *HLA-DQB1*0602* allele. Polygenic risk for narcolepsy was strongest (58·1%) when assessing all variants marginally associated with narcolepsy (p≤0·05) and one variant tagging the *HLA* region. Polygenic risk was reduced to 1·3% when excluding the *HLA* region and 0·8% when exclusively studying implicated variants in the *TRA*,[79] *CPT1B* or *CHKB*,[86] and *P2RY11* regions.[82] Thus, although most of the polygenic risk is explained by *HLA*, other genes might have small roles.

Altogether, the associated genes suggest that dysfunction in neuronal development influences restless legs syndrome and the immune system influences narcolepsy. Although genetic studies have furthered understanding of disease causes, available data do not seem helpful in identifying therapeutic targets; damage could be irreversible once a patient presents with symptoms. However, genetic studies might provide useful information for disease screening before symptom onset.

Other sleep disorders

In addition to the disorders discussed throughout this Review, a number of less well studied sleep disorders show evidence for heritability and familial aggregation. Examples include nocturnal frontal lobe epilepsy (sleep-related hypermotor epilepsy),[87,88] parasomnias,[55,89–91] and sleep paralysis.[55,90,92]

Evidence for genes influencing risk for these disorders is scarce and this is an important subject for future research; results might offer insight into additional risk factors for more common or well-studied sleep phenotypes. For example, nocturnal frontal lobe epilepsy is inherited in an autosomal dominant pattern.[88] Acetylcholine receptor genes are strongly implicated in about 12% of cases. Other implicated genes include potassium sodium-activated channel subfamily T member 1 (*KCNT1*), DEP domain containing 5 (*DEPDC5*), and corticotropin releasing hormone (*CRH*) (figure 2, appendix).[87,88] Since specific syndromes of epilepsy are associated with differences in EEG patterns,[87] future research assessing the effects of these genes on EEG-based sleep characteristics might be useful. Furthermore, alleles in *HLA* distinct from those associated with narcolepsy are implicated in sleepwalking and different non-REM parasomnias (figure 2,

appendix).[55,91] Notably, automatic behaviour, which is a form of sleepwalking, affects over 40% of individuals with narcolepsy. Future studies that are focused on individuals with narcolepsy and comorbid sleepwalking could identify a patient subgroup that is useful for identifying underlying genes. Similarly, recurrent isolated sleep paralysis is common in narcolepsy; one study of recurrent isolated sleep paralysis observed nominal effects related to variants in *PER2*,[92] which merit further investigation (figure 2, appendix).

Synaptic homoeostasis in sleep and other disorders of the brain

Genetic factors influence the risk for disorders of the brain, and most studies have focused on the effects of individual genes for each disorder uniquely. However, biological functions of recurrently implicated genes suggest convergent mechanisms (figure 3). Although evidence for pleiotropic genetic effects is discussed throughout this Review, identification of the overarching mechanisms of gene effects (ie, genes that interact in a network or have similar biological function) might represent a more useful approach to understanding the genetics connecting sleep and neurological disorders. Understanding of genetic mechanisms could inform more effective treatment by providing knowledge of how convergent mechanisms influence risk for multiple disorders in the same individual, and establishing biological connections across seemingly distinct conditions. One such overlapping mechanism is synaptic homoeostasis.

The function of sleep is still debated;[93] however, researchers agree that sleep has strong, neuron-specific effects on the function of molecular, cellular, and network mechanisms of plasticity. Studies show that synapses are strengthened during wakefulness and downscaled during sleep,[94] that neuronal firing in visual cortical neurons returns to baseline during periods of sleep deprivation, and that sleep suppresses firing-rate homoeostasis.[95] Because sleep is important to synaptic homoeostasis, and synaptic gene dysfunction is implicated in numerous disorders of the brain with common sleep problems,[96–99] sleep disruption could lead to more severe neurological symptoms by exacerbating atypical synaptic pruning. Synaptic gene dysfunction might also increase the likelihood of negative sleep-related outcomes.

This complex connection can be illustrated via evidence for pleiotropic effects of synaptic homoeostasis genes on sleep and autism spectrum disorder, a neurodevelopmental condition with strong evidence for synaptic imbalance[100] and high insomnia prevalence.[101] Numerous autism spectrum disorder-related genes encode proteins important to synaptic function, including *BDNF*, SH3 and multiple ankyrin repeat domains 3 (*SHANK3*),[102] and homer scaffolding protein 1a (*HOMER1a*).[103,104] Evidence for pleiotropy exists for all these genes (figure 2, appendix). However, whether they influence sleep and neurodevelopmental disorders independently or jointly remains unclear.

BDNF is implicated in autism spectrum disorders without specific evidence for sleep disruption, and in sleep without influence on neurodevelopmental disorders (figure 2, appendix). Conversely, there is a strong body of evidence indicating that *SHANK3*, which encodes a post-synaptic scaffolding protein, influences the combined phenotype of autism spectrum disorder symptoms with sleep disturbances and intellectual disability (figure 2, appendix). *SHANK3* contains a binding site for another post-synaptic protein-encoding gene, *HOMER1a*. SHANK3 and HOMER1b are observed to co-immunoprecipitate from brain and colocalise at postsynaptic densities,[105] indicating a functional connection between the proteins. Effects of *HOMER1a* in mice include increases in expression with sleep deprivation,[106] *HOMER1a*-related differences in accumulation of delta power after sleep deprivation,[103,104] and more non-REM sleep and an inability to sustain long bouts of wakefulness in mice without *HOMER1a*.[107] Although some rare, potentially deleterious variants in *HOMER1a* have been identified in people with autism spectrum disorders (figure 2), sleep disturbances were not reported in these individuals (appendix).

The pleiotropic effects connecting many genes implicated in sleep and brain disorders are still not well defined. However, the connection of multiple genes involved in synapse function indicates a promising shared mechanism. Studies of such mechanisms could establish the more functionally relevant genes from a large genetic network (eg, those encoding rate-limiting enzymes, activators, or repressors) that disrupt systems related to sleep problems in neurological disorders, and point to novel therapeutic strategies for sleep disturbances within these populations.

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For **GeneCards** see http://www.genecards.org

For **Gene Ontology** see http://geneontology.org

For **KEGG** see http://www.genome.jp/kegg

Search strategy and selection criteria

We searched PubMed for original research papers and reviews published up to Oct 31, 2016. For each section of this Review, search criteria were modified according to subject. For example, in the EEG section we used the following terms: "heritability AND EEG", "genetics AND EEG", and "genes AND EEG". We additionally searched Google Scholar using similar terms for any articles that might not be available in PubMed. We included data from studies of adults and children reflecting all genetic ancestries. We also identified articles through searches of the authors' own collections. Literature for each gene of interest included in the Review was also searched for any relation with other neurological disorders. Search criteria for Google Scholar were as follows: "neurological disorders AND sleep", "neurological disorders AND sleep disorders", and "[each gene] AND neurological disorders". All genes of interest were also searched in the Online Mendelian Inheritance in Man (OMIM), RefGene, and autworks databases. The reported biological functions of genes discussed in this Review are based on detailed assessment of data available in The Human Gene Database (GeneCards), Gene Ontology, and the Kyoto Encyclopedia of Gene and Genomes (KEGG). For the section on synaptic homoeostasis in sleep and other disorders of the brain, we focused on synaptic pruning genes on the basis of the authors' research in the related fields. Search criteria were as follows: "sleep AND *SHANK3*" and "autism AND *HOMER1A*".

Conclusions and future directions

Considerable progress has been made towards understanding the genetics of sleep and sleep disorders. However, as discussed throughout this Review, much remains to be done to robustly establish genetic effects. Reliance on multiple self-reported phenotypes is a primary hurdle. Although numerous genes have been implicated with respect to chronotype, effects are generally small, so large samples are necessary to detect signals. Similarly, genome-wide studies of insomnia have found potential candidates that need validation. Large samples are also needed to show an effect for EEG-based characteristics (in which studies so far have been limited to small-sample candidate gene approaches), and potential candidate genes still require validation. In general, functional evidence and evidence of clinical relevance is also lacking. For instance, although genetic studies of restless legs syndrome have identified reproducible effects, the clinical utility of these associations has yet to be determined.

Despite the challenges of previous and ongoing studies, underlying genetic architecture clearly influences sleep. Thus, sleep and sleep disorders represent a promising and exciting area of complex-disease genetics research. The existing foundation of evidence could support a wide range of future studies, from the development of accurate, high-throughput phenotypes to functional genetic studies. Given the clear public health implications of sleep disturbances, research advances are clearly needed to understand fully the insights that these genetic discoveries provide about the pathogenesis of sleep disturbances and how genetic information could help to identify new drug targets. Sleep has been shown to have similar mechanisms to humans in some powerful model systems, including mice,[108] *Caenorhabditis elegans*,[109] *Drosophila melanogaster*,[110] and zebrafish,[111] allowing important functional genomics studies. Furthermore, rapidly developing mobile technology could be used to assess human sleep,[112] and substantial resources are available for studies of genetic factors underlying sleep traits, including the Precision Medicine Initiative in the USA[113] and the UK Biobank.[114]

For more on the **Precision Medicine Initiative** see https://ghr.nlm.nih.gov/primer/precisionmedicine/initiative

In addition to sleep-related effects, pleiotropic effects in neurological disorders have been described for many genes. However, evidence is poor in some cases, including potentially biased candidate gene approaches, analyses done in small samples, and results that have yet to be replicated in more than one dataset (appendix). We hope that the evidence presented here will facilitate further investigation into the substantial overlap between genetic mechanisms regulating sleep and the risk for neurological disorders. Ultimately, these pleiotropic effects might provide mechanistic insights to inform the treatment of sleep problems in general and, more specifically, in individuals with neurological disorders.

Altogether, assessment of sleep and sleep disorders is ideally suited to the vision of precision medicine. Translating genetic discovery, evidence for pleiotropy, pharmacogenomics, and implicated therapies into practice will greatly improve patient care and reduce the large burden of sleep disorders on public health.

Contributors

OJV and BTK did the article searches and made the tables. OJV generated the figures and was responsible for researching and incorporating evidence related to pleiotropic effects. All authors contributed equally to final writing and editing of the manuscript.

Declaration of interests

PRG reports grants from Merck, and consultancy fees from General Sleep, outside the submitted work. OJV, BTK, BAM, and AIP declare no competing interests.

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