The Role of Genes in the Insomnia Phenotype

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KEYWORDS

• Insomnia • Genetics • GWAS • Animal models

KEY POINTS

- With the development of genetic model systems for sleep, it seems logical to use them to screen human insomnia genetic studies for bona fide hits and to further characterize the mechanisms behind insomnia.
- Studies on the genetics of insomnia must be an important component of future research on the disorder.
- Understanding of the role of genes in the insomnia phenotype is limited.
- There are several molecular genetic tools available that were not in existence even a few years ago.
- The time is ripe for research on the genetics of insomnia that may finally shed light on the mechanisms of this common sleep disorder.

Current conceptualizations of insomnia are largely based on the 3 Ps (Predisposing, Precipitating, and Perpetuating factors) model[1] in its original or adapted form. According to this model, the onset of acute insomnia is due to the interaction between 1 or more precipitating factors and premorbid predisposing factors. Predisposing factors can increase vulnerability to developing insomnia or, when low, may confer a degree of resiliency. There is no universally agreed-on set of predisposing factors, but virtually all presentations of the model suggest that genetic factors may play a role. Yet, there has been little research in the genetic basis of insomnia. This is beginning to change, and investigations are starting to take advantage of the powerful tools that are part of the genomics revolution currently under way. The goal of this article is to summarize current understanding of the role of genetics in the pathophysiology of insomnia.

WHAT IS THE INSOMNIA PHENOTYPE?

To study the genetics of insomnia, the phenotype of interest must be defined. Insomnia research has long been plagued by the use of a wide range of phenotypic definitions of insomnia. Efforts have been made to create a more standardized assessment approach to create greater uniformity[2,3] but substantial heterogeneity continues. At the most fundamental level, insomnia can be assessed with the single question: Do you have trouble sleeping? Although this question has face validity, it is associated with several difficulties, including interindividual variation in beliefs about what constitutes trouble. Clinical[4,5] and research[3] diagnostic systems require that the insomnia be associated with some degree of associated distress or impairment. In clinical settings, this requirement is almost always met

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because an individual is not likely to seek treatment if there are no perceived negative consequences. In community samples, there is a portion of the population who report difficulty initiating or maintaining sleep but who do not report associated consequences.[6] It is not known if those without impairment should be considered insomnia cases for genetic studies, but it seems clear that neither are they true controls. Current diagnostic systems divide insomnia into several specific subtypes, including psychophysiologic, idiopathic, and paradoxic forms that are thought to reflect subtypes in the population; however, the upcoming revisions of the *Diagnostic and Statistical Manual of Mental Disorders* and *International Classification of Sleep Disorders* have eliminated most of these distinctions due to lack of supporting evidence.[7]

Objective measures of sleep can also be used to define the insomnia phenotype and have the advantage of reduced influence by self-report biases. The gold standard for the objective measurement of sleep is polysomnography (PSG), which involves the measurement of multiple physiologic signals (electroencephalographic [EEG], electromyographic, and electrooculgraphic) over the course of the night. PSG can provide highly detailed information on sleep architecture and the time course of sleep patterns. Sleep architecture variables seem to represent individual traits that are highly heritable, suggesting that PSG may be an optimal strategy for genetics studies of insomnia.[8] Two practical limitations of PSG are that it is time consuming and expensive, hindering its applicability for the types of large-scale studies needed for many genetic approaches. More importantly, PSG studies have often failed to find objective evidence of disturbed sleep in individuals with subjective reports of insomnia.[9] This discrepancy may be due to inherent limitations in using standard visual methods for determining sleep and wake on PSG. An alternative approach is to use computer-based spectral analysis methods of the EEG signal to provide a finer-grained analysis of the microarchitecture of sleep. Compared with good sleepers, individuals with insomnia frequently demonstrate increased EEG activity in the beta frequency range during sleep.[10] Beta EEG is thought indicative of increased cortical processing, leading to the hypothesis that insomnia can be associated with a mixed state of wakefulness and sleep that an individual perceives as wakefulness. This explains the discrepancy between subjective and objective assessments of sleep found in many insomnia studies. Beta EEG power would be an ideal phenotype for genetic studies of insomnia, but spectral analysis methods can be cumbersome to implement on any large scale.

ARE INSOMNIA PHENOTYPES HERITABLE?

The first step in studying the genetics of any trait is to establish that variability in its manifestation is attributable in part to genetic factors. Several approaches can be used to estimate the narrow-sense heritability of a trait (h^2) (ie, the proportion of variation in the trait that can be explained by additive genetic factors). The goal is to tease apart the relative contributions of genetic and nongenetic (environmental) factors. The 2 strategies most frequently used to establish heritability are twin studies and family studies.

In family history studies, family members of individuals affected with the condition of interest are compared with family members of unaffected individuals. If genetic factors contribute to the condition, the family members of affected individuals are more likely to also report the condition than those of unaffected individuals, given that they have shared genes. The greater the degree of genetic similarity between individuals, the more they should be alike on phenotypic measures. In an early family study of insomnia, Abe and Shimakawa[11] compared the sleep patterns of parents with their 3-year-old children. Parents who reported sleeping poorly as children tended to have children with similar patterns. Although somewhat methodologically crude, this study demonstrates that the idea that insomnia may run in families is not new.

Hauri and Olmstead[12] conducted one of the only studies of childhood-onset insomnia, which is characterized by early age of onset and a relative absence of clear precipitating factors and is thought more likely due to genetic causes. Individuals whose insomnia originated in childhood reported a positive family history of sleep complaints at a higher rate (55%) than those with adult-onset insomnia (39%). In a study of patients with insomnia presenting to a sleep disorders clinic, 35% of those with insomnia reported 1 or more family members also experiencing some form of sleep disturbance, and there was a trend toward higher rates in the families of those with an earlier age of onset.[13] In a second clinic sample from this group, there was a positive family history of insomnia in 72.7% of individuals with primary insomnia, 43.4% of those with psychiatric insomnia, and 24.1% of controls.[14]

In a larger cohort study,[15] there was almost no difference in a positive family history of insomnia in those categorized as good sleepers, as having symptoms of insomnia, and as meeting criteria

for a full insomnia syndrome (32.7%, 36.7%, and 38.1%, respectively). Significant differences were found only when the good sleepers were separated into those with and without a personal history of insomnia; those without a personal history had a significantly lower rate of family history (29.0%) than those without a past history (48.9%). This pattern of results highlights a difficulty of studying insomnia, a disorder whose clinical state can vary over time such that individuals who are good sleepers at the time of assessment may have a prior history of insomnia, making it unclear if they are truly controls.

The small body of family history studies of insomnia phenotypes suggests that there is familial aggregation. A limit of these types of studies is that family members share both genes and environment. Familial aggregation could be due to shared effects in either domain. Twin studies seek to disentangle these effects by comparing monozygotic (MZ) and dizygotic (DZ) twins raised together. The rationale for twin studies is that each twin pair is raised together and thus the family-specific environmental effects are assumed to not contribute to phenotypic differences between twins. MZ twins share 100% and DZ twins share approximately 50% of their genes, so if there are higher rates of similarity in MZ twins compared with DZ twins, it should be due to these differences in common genes. Several twin studies have investigated the genetic and environmental etiology of insomnia phenotypes (summarized in **Table 1**). The first of these was conducted in 14 MZ and 14 DZ good sleeper twin pairs who completed 1 night of PSG.[16] The participants did not have insomnia, but the study is noteworthy in

Table 1
Twin studies of insomnia phenotypes

Authors	Sample	Phenotypes	Heritability
Webb & Campbell,[16] 1983	14 MZ, 14 DZ Young adults	Sleep latency Wake time	N/A
Partinen et al,[17] 1983	2238 MZ, 4545 DZ Adults	Sleep length Sleep quality	$h^2 = 0.44$ $h^2 = 0.44$
Heath et al,[18] 1990	1792 MZ, 2101 DZ Adults	Sleep quality Initial insomnia Sleep latency Anxious insomnia Depressed insomnia	$h^2 = 0.32$ $h^2 = 0.32$ $h^2 = 0.44$ ♂, 0.32 ♀ $h^2 = 0.36$ $h^2 = 0.33$
Heath et al,[19] 1998	1792 MZ, 2101 DZ Adults	Composite score	12.1% of Variance in ♀, 8.3% in ♂
McCarren et al,[20] 1994	1605 MZ, 1200 DZ Male veterans	Trouble falling asleep Trouble staying asleep Waking up several times Waking up tired Composite score	$h^2 = 0.28$ $h^2 = 0.42$ $h^2 = 0.26$ $h^2 = 0.21$ $h^2 = 0.28$
de Castro,[50] 2002	86 MZ, 129 DZ Adult good sleepers	Sleep duration Number of wake-ups	$h^2 = 0.30$ $h^2 = 0.21$
Watson et al,[21] 2006	1042 MZ, 828 DZ Young adults	Insomnia	$h^2 = 0.64$
Boomsma et al,[22] 2008	548 Twins, 265 siblings Adults	Insomnia factor	$h^2 = 0.20$
Gregory et al,[23] 2004	2162 MZ, 4229 DZ Age 3–7 y	Sleep problems scale	$h^2 = 0.18$ ♂, 0.20 ♀
Gregory et al,[24] 2006	100 MZ, 200 DZ Age 8	Sleep onset delay Night wakings	$h^2 = 0.17$ for Child report, 0.79 for parental report $h^2 = 0.27$ for Child report, 0.32 for parental report
Gregory,[25] 2008	100 MZ, 200 DZ Age 8	Dyssomnia scale	$h^2 = 0.71$
Gregory et al,[24] 2006	192 MZ, 384 DZ Age 8	Sleep problems score	$h^2 = 0.61$

that there were significant dominant genetic effects for both sleep-onset latency and several measures of time spent awake during the night. Partinen and colleagues[17] collected self-reported sleep data from a much larger sample of 2238 MZ and 4545 DZ adult twin pairs and found significant heritability for sleep length ($h^2 = 0.44$) and sleep quality ($h^2 = 0.44$). It may be that individuals with insomnia are simply those at one end of the distribution of these traits in the population, in which case studying the genetics of sleep-wake traits in general may provide insight into the pathophysiology of insomnia.

The twin study with the broadest assessment of sleep and insomnia phenotypes was conducted with the Australian Twin Registry.[18] Their survey of 1792 MZ and 2101 DZ twin pairs included several questions related to sleep quality, disturbance, and overall patterns. Of most relevance for insomnia, additive genetic influences were found for sleep quality ($h^2 = 0.32$), initial insomnia ($h^2 = 0.32$), sleep latency ($h^2 = 0.44$ for men and 0.32 for women), anxious insomnia ($h^2 = 0.36$), and depressed insomnia ($h^2 = 0.33$). In a subsequent report based on this twin registry,[19] genetic influences accounted for 12.1% of the variance in a composite sleep disturbance factor for women and 8.3% for men. In a study of twin pairs from the Vietnam Era Twin Registry,[20] heritability estimates were trouble falling asleep ($h^2 = 0.28$), trouble staying asleep ($h^2 = 0.42$), waking up several times per night ($h^2 = 0.26$), waking up feeling tired and worn out ($h^2 = 0.21$), and a composite sleep score ($h^2 = 0.28$). A questionnaire item, "How often do you have trouble falling asleep of staying asleep?" from the University of Washington Twin Registry yielded a heritability of 0.64.[21] Lastly, a survey of twins and siblings found that the insomnia-related questions clustered on a single factor, which had a heritability of 0.20.[22]

Several studies have been conducted by Gregory and colleagues[23] examining sleep problems in youth. Total scores on a 4-item sleep problem scale showed modest evidence of additive genetic influence ($h^2 = 0.18$ for boys and 0.20 for girls). A second study of 8-year old twin pairs involved both the childrens' self-ratings of their sleep and their parents' ratings of how well they perceived that their children slept.[24] Parental ratings are commonly used to account for children not having developed good skills for observing their own sleep patterns, but a drawback of this approach is that the parents are not observing all aspects of their childrem's sleep. Estimates of additive genetic influences on the sleep-onset delay subscale were different for parental ($h^2 = 0.79$) compared with child ($h^2 = 0.17$) ratings. Estimates for the night wakings subscale were more comparable, with estimates of 0.32 and 0.27 for parental and child reports, respectively. A dyssomnia scale was computed based on 10 items from the parental rating scale that showed evidence of substantial heritability ($h^2 = 0.71$).[25]

In summary, family and twin studies demonstrate that insomnia phenotypes tend to aggregate in families, with a greater degree of genetic similarity correlating with greater phenotypic similarity. With few exceptions, heritability estimates in adults were consistently in the range of 0.25 to 0.45, regardless of the exact question or phenotype used. In children, parental estimates of sleep problems demonstrate substantially greater heritability, with estimates across studies ranging from 0.60 to 0.80. Mild sleep problems may be more likely to go unnoticed by parents, so their ratings capture mostly the more severe cases that likely have stronger genetic underpinnings than when the full spectrum of severity is considered. Thus, insomnia, broadly defined, is moderately heritable when rated by individuals, with approximately one-third of the variance in symptoms attributable to genetic factors.

GENES RELATED TO INSOMNIA

Now that it is established that insomnia phenotypes are partially due to genetic factors, the next question is, Which genes are involved? One approach to identifying specific genes related to insomnia is to select candidate genes based on a priori knowledge about the mechanisms underlying regulation of sleep and wake. A reasonable starting point is genes involved in the generation of circadian rhythms because there is strong interplay between circadian and sleep mechanisms. These so-called clock genes have been well characterized, as have the transcriptional-translational feedback loops through which these genes produce circadian rhythms.[26] Several studies have examined the relationships among sleep-wake characteristics and clock genes, which may be of relevance for insomnia.

In one study, Laposky and colleagues[27] created mice carrying a null allele for a core circadian clock gene: BMAL1/Mop3. These mice demonstrated alterations in sleep-wake characteristics, including greater sleep fragmentation, reduced duration of sleep bouts, and altered total sleep time. In a human study, Viola and colleagues[28] focused on the *PER3* gene and compared individuals homozygous for either the short ($PER3^{4/4}$) or long ($PER3^{5/5}$) alleles. The group with the long allele, compared with those with the short allele, had shorter sleep latency and spent a greater proportion of the night

in slow-wave sleep. Several studies have examined the relationships between clock genes and sleep-wake characteristics in patients with mood disorders. For example, Serretti and colleagues[29] found an association between the 3111T/C *CLOCK* gene polymorphisms and insomnia symptoms in patients with major depression. In a larger cohort study in Finland, Utge and colleagues[30] examined the associations between 113 single nucleotide polymorphisms (SNPs) across 18 clock genes and sleep disturbance in individuals with depression and controls. They found that the *TIMELESS* gene was associated with early morning awakenings in the depressed group, but that this effect was different for men and women.

In addition to the clock genes, several studies have examined genes related to the various neurotransmitter systems involved in sleep-wake regulation.

Serotonin

The serotonin transporter-linked polymorphic region (5HTTLPR) gene has been extensively studied in psychiatric genetics. The short allele is associated with reduced efficiency of transcription and has been shown to confer risk for several psychiatric disorders. One pharmacogenetic study of patients with major depression found that the short allele was associated with an increased likelihood of developing new or worsening insomnia in response to fluoxetine treatment.[31] Brummett and colleagues[32] examined the relationship between sleep quality and the serotonin transporter gene in caregivers of individuals with dementia. They found a significant gene $\times$ environment interaction with caregiving, such that caregivers with the short allele were more likely to report poor sleep quality than those with the long allele, but there was no relationship for noncaregivers. The availability of serotonin in the brain is influenced by monoamine oxidase A, and 2 studies have found relationships between monoamine oxidase A polymorphisms and insomnia phenotypes.[33,34]

GABA

Sedative hypnotic medications almost universally act through the inhibitory γ-aminobutyric acid (GABA) system. Buhr and colleagues[35] reported a case study of a patient with a missense mutation of the β_3 subunit of the $GABA_A$ receptor. The patient had insomnia, as did several members of his family, suggesting that this mutation may have affected sleep. *Drosophila* with the mutant $GABA_A$ receptor Rdl^{A302S}, which is associated with increased channel current, exhibited decreased sleep latency.[36]

Adenosine

Adenosine is thought to play a role in the regulation of sleep homeostasis, so genes affecting adenosine activity could influence sleep-wake dynamics and hence insomnia. Individuals with the G/A allele of the adenosine deaminase gene had fewer awakenings at night, spent more time in slow wave sleep, and had higher delta power than those with the G/G allele.[37] Gass and colleagues[38] focused on 117 SNPs from 13 genes related to adenosine transporters, receptors, and metabolism enzymes in cases with depression and controls. Polymorphisms in the *SLC29A3* gene, which is related to adenosine metabolism, were associated with early morning awakenings only in women.

Hypocretin/Orexin

There has been an increased interest in the role that hypocretins/orexins play in sleep regulation. Prober and colleagues[39] created zebrafish that overexpressed hypocretin that led to a phenotype characterized by hyperarousal and reduced ability to initiate and maintain sleep.

Taken together, these candidate gene studies provide preliminary evidence that genes affecting both circadian mechanisms and neurotransmitters known to be involved in sleep-wake regulation may have some bearing on insomnia phenotypes; however, more work needs to be done in this area.

A limitation of the candidate genes approach is knowing which genes to examine, but the mechanisms underlying insomnia and sleep-wake regulation are not fully known. An alternate strategy is to perform a hypothesis-free search through the use of gene discovery strategies, such as linkage and genome-wide association studies (GWAS). The first gene discovery study of sleep-related phenotypes examined a subset of the Framingham Heart Study Offspring Cohort.[40] The phenotypes of interest were usual bedtime and sleep duration. Linkage analysis failed to find any associations with log odds greater than 3 (a standard criterion for significance), but 5 peaks with log odds greater than 2 were found, including a linkage between usual bedtime and *CSNK2A2*, a gene known to be a component of the circadian clock. In a population-based test, usual bedtime was associated with the SNP rs324981, located in the gene *NPSR1*, which encodes the neuropeptide S receptor.

Allebrandt and colleagues[41] pooled data from several cohorts to conduct a GWAS of

self-reported sleep duration. With a discovery sample of 4251 individuals and replication sample of 5949, they identified an associated intronic variant in the *ABCC9* gene, which is related to K_{ATP} channels. What is interesting about this study is that rather than stopping after the GWAS, the investigators took this finding into a model system by interfering with this gene in *Drosophila* neurons using RNA interference, which resulted in flies that did not sleep for the first 3 hours of the night, validating the importance of this gene for sleep regulation.

The only other GWAS of insomnia phenotypes conducted to date included 10,038 individuals in Korea.[42] Cases with insomnia and controls were defined based on responses to a series of questions about their sleep patterns. A GWAS found associations between case-control status on the ROR1 gene, which modulates synapse formation, although this association did not reach genome-wide significance.

Animal models provide opportunities for methodological approaches not possible in humans, such as experimental breeding. Wu and colleagues[43] conducted a forward genetic screen in *Drosophila* of approximately 3000 lines to identify short-sleeping mutants. Short-sleeping flies tended to sleep in shorter bouts compared with longer-sleeping flies, suggesting that they may have had difficulty with sleep maintenance, a possible insomnia phenotype. The short-sleeping flies also exhibited reduced arousal thresholds and were more easily awoken. It is not known whether these flies were short sleepers because of impaired sleep ability (ie, insomnia) or reduced sleep need, but the reduced arousal threshold of these mutants suggests some degree of overlap with insomnia. The sleep changes were associated with a novel allele of the dopamine transporter gene.

Seugnet and colleagues[44] selectively bred flies with shorter sleep durations and were able to produce flies they referred to as insomnia-like whose total sleep time was only 60 minutes per day. The flies had difficulties with initiating and maintaining sleep, increased waking activity levels, and impairments in learning on an avoidance task and in motor coordination. The investigators propose that this animal model captures both the nighttime and daytime characteristics of insomnia. Gene profiling identified 1350 genes that were differentially expressed in the insomnia-like flies compared with wild-type flies, many of which fell into categories related to metabolism, neuronal activity, behavior, and sensory perception.

This collection of studies is noteworthy in the degree to which they represent some of the various research strategies that can be used for discovery of genes that may relate to insomnia. Few studies have been conducted, several of which involved phenotypes of only marginal significance for insomnia. A great deal of work needs to be done.

FUTURE DIRECTIONS

The research described in this article indicates that insomnia phenotypes are heritable, with approximately 30% to 40% of the variability in insomnia related to genetic factors. In terms of the search for specific genes that relate to the pathophysiology of insomnia, the sleep field is 10 to 20 years behind the work that has been accomplished for mood disorders and schizophrenia. Furthermore, compared with the attention received by mood disorders and schizophrenia, there are few investigators pursuing the genetics of insomnia, so progress is likely to be slow for the foreseeable future. Nevertheless, a research agenda for some of the next steps that are needed is laid out:

1. There is a need for more consistent phenotyping of insomnia in genetic studies of humans. As described previously in this review, the existing studies have primarily used a wide range of homemade sleep questions rather than validated measures. Most of these questions did not include assessments of daytime impairment due to poor sleep, which is necessary for determining whether some may meet diagnostic criteria for an insomnia disorder.[4,5] Thus, much of the literature to date is more related to insomnia symptoms rather than to insomnia itself. It may be that the genetic architecture of insomnia disorder is such that it is not merely one end of the distribution of scores on these symptom-related traits and requires validated case and control definitions to determine underlying genes. Efforts to create a more standardized assessment of insomnia[2] should facilitate greater homogeneity across studies in the future.
2. Additional GWAS are needed to identify genetic variants that contribute to insomnia phenotypes. The advantage of this approach is that it requires no prior hypothesis about which genes are likely to influence the trait and is instead considered hypothesis generating. GWAS studies may lead to the discovery of novel pathways and mechanisms involved not only in insomnia phenotypes but also in sleep-wake regulation in general. GWAS is predicated on the common-variant hypothesis, which states that disease is related to genetic variants (alleles) that are common in the population,

each of which explains a small proportion of the variance. Although this approach has been fruitful in identifying risk genes for a wide range of conditions,[45] the past decade of GWAS research has highlighted the critical need for replication because many significant findings from one study are not confirmed in subsequent investigations.

3. An alternative to the common-variant view is the rare-variant hypothesis, which states that genetic variants that are rare in the population (<1% minor allele frequency) are more likely to have large effects and explain the majority of variation in risk to disease in the population. The extreme of the rare-variant hypothesis is mendelian mutations, in which a single variant is sufficient to produce disease, as in Huntington disease. Several tools have emerged in the past few years to facilitate the search for rare variants. Efforts, such as the 1000 Genomes project (www.1000genomes.org), have created databases of normative genetic variation against which the results of individual studies can be compared. Next-generation sequencing technologies, such as exome and even whole-genome sequencing, are more practical due to the rapid decline in costs for these methods. To the authors' knowledge, there have been no studies using these approaches in the search for insomnia-related genes.
4. Although studies have begun to identify genes that are associated with insomnia, the molecular underpinnings of this disease remain unclear for 3 primary reasons. First, insomnia is a broad disease composed of both primary (direct) and secondary (ie, stress, diet, and so forth) causes, ranging from environmental factors to single-gene polymorphisms to combinatorial resultd of 10s if not 100s of genetic polymorphisms. Second, human studies are messy, often relying on subjective rather than objective data, making it difficult to correlate phenotype with genotype. Third, human studies are limited to single-gene polymorphisms that cause insomnia but no other behavioral or developmental disorders. Finally, the best studies in humans often localize a disease to a chromosomal region that includes 100s of genes—How best to shave this number down to 1 or at most a handful of genes?

A simple answer to these problems is one that has been successfully offered to unravel many of medicine's seemingly intractable questions, such as, How do we develop from a single cell into a complex organism? How do our bodies maintain a 24-hour rhythm even in the absence of external cues? and How do our cells regulate gene expression? The solution time and again has been to use functional genetics in powerful model systems.

For a model system to be useful, it must meet several criteria that make it superior to direct genetic studies in humans. Practically, it must be cheap and have a short lifespan, a short generation time, and moderate to high fecundity. It must also be useful as a genetic system, with a fully sequenced genome and tools available to target disruption of specific genes. Finally, it must be capable of reproducing the human behavior or disease state, in this case an inability to initiate or maintain quality sleep. To this end, several model systems have been developed to study the genetics of sleep that can easily be used to better understanding of the mechanisms underlying insomnia.

Mice are the most obvious choice for an insomnia model system. They are mammals with a nervous system that resembles humans—approximately 90% genome conservation and rapid eye movement and non–rapid eye movement sleep states as determined by EEG. They also have a powerful genetic tool kit that allows researchers to target disruption or overexpression of specific genes and to do so in defined subsets of the brain during discrete temporal windows, such as in adultd or only after sleep deprivation. These tools have been used in the study of narcolepsy by creating mice with altered orexin signaling[46] as well as by identifying a novel narcolepsy-like gene, the glutamate receptor-binding protein, *homer1*.[47] Insomnia studies have lagged, but recent work by De Boer and colleagues[48] has demonstrated that disinhibition of the calcium channel, *CACNA1A*, results in reduced sleep, likely by disrupting adenosine signaling.

Although mice offer a powerful genetic system, they do have drawbacks, in particular, a long generation time that can translate into a gap of years between an experimental idea and meaningful data. To streamline the process, 2 models with high fecundity and short generation times have been developed to study the genetics of sleep: the fruit fly *Drosophila melanogaster* and the nematode *Caenorhabditis elegans*. Like mice, both systems offer powerful genetic tool kits that permit researchers to disrupt or overexpress genes in subsets of the nervous system in defined temporal windows. These tools have been used most successfully in *Drosophila* in which Hendricks and colleagues[49] first demonstrated that altering cyclic adenosine monophosphate signaling could lead to insomnia-like reductions in sleep. Since that time, 10s of genes have been identified and

characterized with similar phenotypes, with more genes likely to be identified in the future.

With the development of these powerful and fast genetic model systems for sleep in general, it seems only logical to use them to screen human insomnia genetic studies for bona fide hits and to further characterize the mechanism behind insomnia. Inclusion of these models must be an important component of future research on the genetics of insomnia. As this summary of the extant research demonstrates, understanding of the role of genes in the insomnia phenotype is limited. On a more positive side, there are several molecular genetic tools available that were not in existence even a few years ago. The time is ripe for research on the genetics of insomnia that may finally shed light on the mechanisms of this common sleep disorder.

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