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Sleepless in *Drosophila*

By Brian Moy, Staff Writer

Researchers at the **University of Pennsylvania** reported in *Science* the identification of a gene whose influence on potassium channel activity could have implications for treating insomnia and other sleep disorders. Although sleep is an essential process conserved from flies to humans,[1] finding a human homolog of the gene may prove to be difficult. However, regulation of sleep remains a poorly understood phenomenon, and knowing the homolog would aid in the design of better insomnia drugs.

The gene, which the researchers called *sleepless* (*sss*), was identified using a genetic screen of *Drosophila melanogaster* mutants that experienced less daily sleep than is normal. The *sleepless* gene encodes a glycosylphosphatidylinositol-anchored protein that was enriched in the brains of mutant flies. Lack of sleepless protein in *D. melanogaster* led to a greater than 80% reduction in amount of sleep compared with that for wild-type flies.[2]

> **"The finding is important because we don't truly understand sleep regulation."**
> ***—Ying-Hui Fu, University of California, San Francisco***

Although moderate decreases in the level of sleepless protein in *D. melanogaster* caused a minimal decline in baseline sleep, it led to severe reductions in sleep rebound, which is recovery sleep after sleep deprivation. Only a few genes have been shown to be important for sleep rebound.[3]

"The finding is important because we don't truly understand sleep regulation," said Ying-Hui Fu, a professor of neurology at the **University of California, San Francisco**. "The identification of *sleepless* in the *Drosophila* model provides a foundation for identifying gene mutations in mammalian systems, perhaps even in humans, which are related to sleep."

A previous genetic screen in *D. melanogaster* identified the *shaker* (*sh*) gene as required for homeostatic regulation of sleep.[4] A mutation in *shaker* causes one of the shortest-sleeping phenotypes known.

In the *Science* paper, genetic and molecular analyses revealed that *quiver* (*qvr*), a mutation that impairs *shaker*-dependent potassium current, is an allele of *sleepless*. Shaker protein levels were lower in *sleepless* mutant flies than in wild-type flies.

Shaker encodes a voltage-dependent potassium channel that controls membrane repolarization and transmitter release.[4] Defective shaker potassium channels lead to increased neuronal excitability.

Based on the relationship between *shaker* and *quiver*, the UPenn researchers proposed that the sleepless protein "signals homeostatic sleep drive by enhancing potassium channel activity and thus reducing neuronal excitability."

Amita Sehgal and colleagues are now using bioinformatics to identify a human homolog of *sleepless*. Sehgal, principal investigator and corresponding author on the *Science* paper, is a professor of neuroscience at UPenn Medical School.

She noted that "the process of identifying a human homolog of the *sleepless* gene is rather difficult because sleepless is a really small protein. When looking for homologs using bioinformatics, you usually use larger proteins."

If a human homolog is identified, Sehgal said it could be useful to look for a compound that mimics the effects of the sleepless protein to restore potassium channel activity and lower neuronal excitability.

She added that her team also plans to investigate exactly how sleepless regulates the activity of potassium channels. "Perhaps by tinkering with the channels encoded by *sleepless*, we can restore the phenotype of *sleepless* and improve homeostatic sleep drive."

Chiara Cirelli, an associate professor of psychiatry at the **University of Wisconsin–Madison**, told *SciBX* that "if we can characterize how the sleepless mechanism works, we might be able to go after downstream targets of the protein to reduce neuronal excitability."

However, Cirelli added that manipulating neuronal excitability is tricky and could lead to epileptic seizures. To avoid side effects, "we would have to find a drug that specifically acts on neurons regulated by the potassium channels encoded by *sleepless*."

In the absence of a human homolog of *sleepless*, Cirelli thinks a therapeutic to minimize neuronal excitability and improve sleep quality will have to act on *shaker*. However, she noted that targeting *shaker* could be difficult because there are at least 16 *shaker*-like genes in mammals, whereas *Drosophila* only has one version of the gene.

Cirelli and colleagues have previously shown that mice carrying a null mutation in one of the many *shaker*-like genes spent 21% more time awake than did wild-type mice. Additionally, Cirelli's study identified Kv1.2 as a mammalian homolog of the shaker protein. Kv1.2 is the α-subunit of a *shaker*-like voltage-dependent potassium channel that is highly expressed in the mammalian thalamocortical system.[5]

Cirelli's research is aimed at knocking out all of the genes in the fly genome to screen for other mutants implicated in sleep regulation.

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COMPANIES AND INSTITUTIONS MENTIONED

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