First human gene implicated in regulating length of human sleep

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Scientists have discovered the first gene involved in regulating the optimal length of human sleep, offering a window into a key aspect of slumber, an enigmatic phenomenon that is critical to human physical and mental health.

The team, reporting in the Aug. 14, 2009 issue of *Science*, identified a mutated gene that allows two members of an extended family to thrive on six hours of sleep a day rather than the eight to eight-and-a-half hours that studies have shown humans need over time to maintain optimal health. Working from this discovery, the scientists genetically engineered mice and fruit flies to express the mutated gene and study its impact.

While most Americans obtain less than eight hours of sleep a night (the average on non-work days is 7.4 hours), and some may feel they succeed with less when engaged in exhilarating work, domestic life or recreation, scientific evidence indicates that, over time, the body suffers from this regimen, the researchers say.

"Short term and chronic disruptions in the length of optimal sleep can have serious consequences on cognition, mood and physical health, including cancer and endocrine function," says the senior author of the study, Ying-Hui Fu, PhD, UCSF professor of neurology. However, teasing out this impact can be challenging, she says, given access to such stimuli as coffee and chocolate.

The finding, she says, offers an opportunity to unravel the regulatory mechanism of sleep. While the mutation may be rare, it could offer a probe more generally into the regulatory mechanisms of sleep quality and quantity. Understanding these mechanisms could lead to interventions to alleviate pathologies associated with sleep disturbance.

Sleep remains a relatively inscrutable biological phenomenon. Scientists know that it is regulated in large part by two processes: 1) circadian rhythms -- genetic, biochemical and physiological mechanisms that wax and wane during a 24 hour period to regulate the timing of sleep, 2) and homeostasis - unknown mechanisms that ensure that the body acquires over time the necessary amount of sleep, nudging it toward sleep when it has been deprived, prompting it out of sleep when it has received enough. This regulation of sleep intensity is measured in non rapid eye movement sleep and REM sleep. Interactions between the circadian rhythms and homeostatic mechanisms influence the timing, duration and quality of sleep and wakefulness.

But "the details in the process are really completely unknown," says Fu.

In 2001, the team discovered a mutated gene that caused some members of several families to be "morning larks," awaking around 3:30 a.m. and going to bed around 7:30 p.m. The condition, which the researchers named "familial advanced sleep phase syndrome," is believed to be primarily a variant, or mutated, form of a gene involved in regulating circadian rhythms. The total daily sleep time in people with this condition is normal.

In the current study, the team identified a small extended family in which a mother and her adult daughter had life-long shorter daily sleep requirements than most individuals. Fu's lab then studied blood samples from these women and their extended family. They identified a mutation in a gene known as hDEC2, which is a transcription factor that represses

expression of certain other genes and is implicated in the regulation of circadian rhythms.

Next, the team genetically engineered mice and fruit flies to express the mutated human gene, and Ying He, PhD, a postdoctoral fellow in the Fu lab, studied its impact on their behavior and sleep patterns. Mice slept less, as seen in the extent of their scampering about in the dark (mouse preference) over the course of 24 hours and in electroencephalography (EEG) and electromyography (EMG) measurements indicating reduced nonREM and REM sleep. While lacking a Lilliputian size EEG to monitor the fruit flies, He studied the miniscule creatures' activity and sleep patterns by tracking the frequency of their movements through infrared light.

Next, the team compared the response of the genetically engineered mice and normal mice to the consequence of six hours of sleep deprivation. The engineered mice needed to compensate for their lost sleep to a much lesser extent - as seen in nonREM and REM measures - than their normal counterparts.

"These changes in sleep homeostasis in the mutant mice could provide an explanation for why human subjects with the mutation are able to live unaffected by shorter amounts of sleep throughout their lives," says Fu.

The next step, she says, is determining the DEC2's precise role. "We know the gene encodes a protein that is a transcriptional repressor and we know it makes the repressor's activity weaker. But we don't know if the weaker repressor is directly related to the shorter amount of sleep, because proteins can have many functions. It could be the protein functions as part of a larger transcriptional machinery, not necessarily as a repressor."

DEC2 could be involved in modulating "sleep quantity" alone, or it could

be mediating both "sleep quantity" and "wakefulness-behavioral drive," according to Fu. The latter drive, she says, is critical for the procurement of food, shelter, and mates and could be more potent in individuals with this mutation.

"The mouse model also provides an opportunity to investigate whether there are other behaviors or physiological conditions associated with a short sleep syndrome," says Fu. She suspects there will be.

Source: University of California - San Francisco