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After 10-year search, scientists find second 'short sleep' gene

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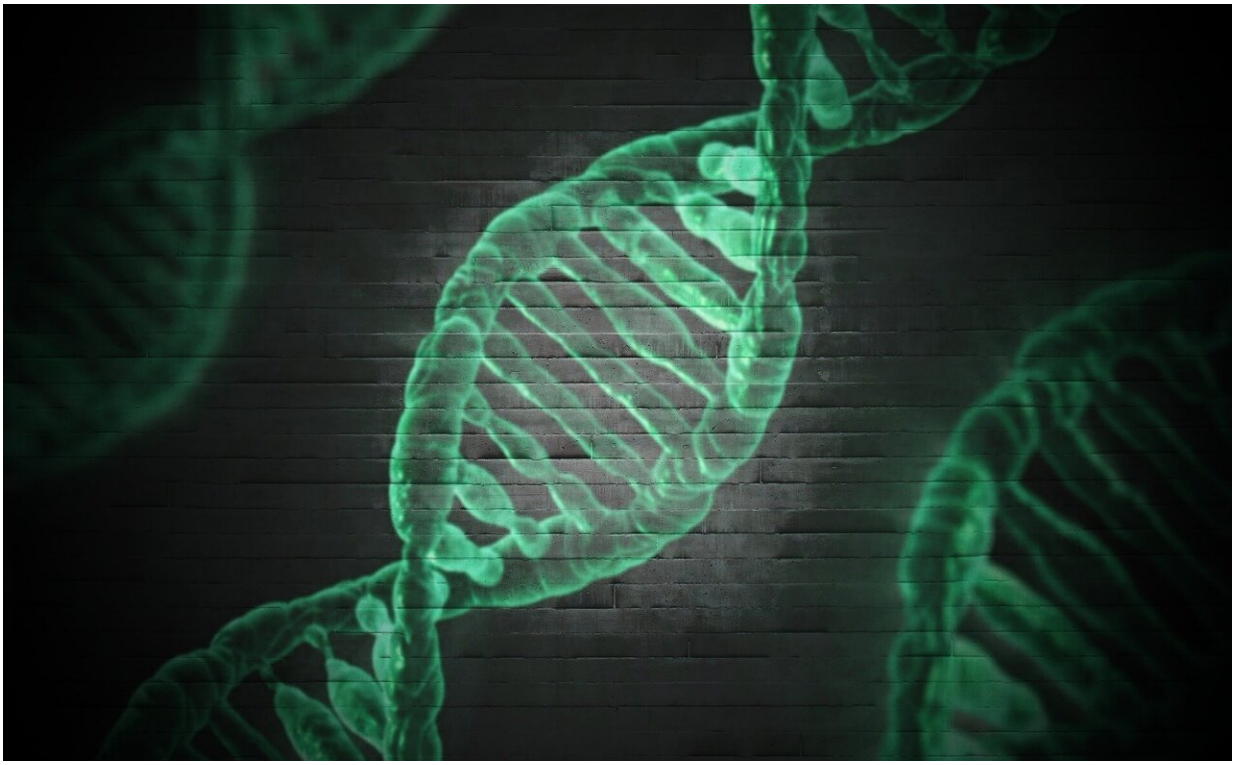

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After a decade of searching, the UC San Francisco scientists who identified the only human gene known to promote "natural short sleep"—lifelong, nightly sleep that lasts just four to six hours yet leaves individuals feeling fully rested—have discovered a second.

"Before we identified the first short-sleep gene, people really weren't thinking about sleep duration in genetic terms," said Ying-Hui Fu, Ph.D., professor of neurology and a member of the UCSF Weill Institute for Neurosciences. Fu led the research teams that discovered both short sleep genes, the newest of which is described in a paper published August 28, 2019 in the journal *Neuron*.

According to Fu, many scientists once thought that certain sleep behaviors couldn't be studied genetically. "Sleep can be difficult to study using the tools of human genetics because people use alarms, coffee and pills to alter their natural sleep cycles," she said. These sleep disruptors, the thinking went, made it difficult for researchers to distinguish between people who naturally sleep for less than six hours and those who do so only with the aid of an artificial stimulant.

Natural short sleepers remained a mystery until 2009, when a study conducted by Fu's team discovered that people who had inherited a particular mutation in a gene called DEC2 averaged only 6.25 hours of sleep per night; study participants lacking the mutation averaged 8.06 hours. This finding provided the first conclusive evidence that natural short sleep is, at least in some cases, genetic. But this mutation is rare, so while it helped explain some natural short sleepers, it couldn't account for all of them.

"Sleep is complicated," said UCSF's Louis Ptáček, MD, the John C. Coleman Distinguished Professor in Neurodegenerative Diseases and co-senior author of the new study. "We didn't think there was just one gene or one region of the brain telling our bodies to sleep or wake." Ptáček and Fu reasoned that there had to be other, as yet undiscovered, causes of short sleep.

As the new study describes, a breakthrough came when the researchers identified a family that included three successive generations of natural

short sleepers, none of whom harbored the DEC2 mutation. The researchers used gene sequencing and a technique known as linkage analysis, which helps scientists pinpoint the exact chromosomal location of mutations associated with a particular trait, to comb through the family's genome. Their efforts uncovered a single-letter mutation in a gene known as ADRB1 that, like the mutation in DEC2, was associated with natural short sleep.

Eager to understand how the newly discovered mutation might lead to short sleep, the researchers performed a series of experiments in lab-grown cells and in mice that had been genetically engineered to harbor an identical mutation in the mouse version of ADRB1.

The cell-based experiments revealed that the mutant form of the beta-1 adrenergic receptor—the protein encoded by the ADRB1 gene, which plays a role in a variety of essential biological processes—degrades more rapidly than the non-mutant version, suggesting that it might also function differently.

This hunch was confirmed in mouse experiments. The researchers discovered that the ADRB1 gene was highly expressed in the dorsal pons, a region of the brainstem involved in regulating sleep. Using a technique known as optogenetics, in which cells are modified so they can be activated by light, the researchers focused light on neurons in the pons to stimulate those in which ADRB1 was expressed. Triggering these neurons immediately roused sleeping mice—specifically, those that were experiencing non-REM sleep, the sleep phase during which these neurons are not normally active—demonstrating that these neurons promote wakefulness.

Additional experiments showed that wakefulness-promoting neurons in the pons with the mutated version of ADRB1 were more easily activated. Furthermore, the ratio of wakefulness-promoting to sleep-promoting

neurons skewed heavily towards the former in mice with the ADRB1 mutation. These experiments suggest that the mutant form of ADRB1 promotes natural short sleep because it helps build brains that are easier to rouse and that stay awake longer.

Though they sleep less, natural short sleepers don't suffer any of the adverse health effects associated with sleep deprivation. "Today, most people are chronically sleep deprived. If you need eight to nine hours, but only sleep seven, you're sleep deprived," Fu said. "This has well-known, long-term health consequences. You're more likely to suffer from cardiovascular disease, cancer, dementia, metabolic problems and a weakened immune system."

But natural short sleepers actually seem to benefit from this quirk of their biology. Fu says researchers have found that short sleepers tend to be more optimistic, more energetic and better multitaskers. They also have a higher pain threshold, don't suffer from jet lag and some researchers believe they may even live longer. Though the exact reasons for these benefits remain unknown, Fu and Ptáček think their work represents an important step towards understanding the connection between good sleep and overall health.

"Natural short sleepers experience better sleep quality and sleep efficiency," Fu said. "By studying them, we hope to learn what makes for a good night's sleep, so that all of us can be better sleepers leading happier, healthier lives."

More information: *Neuron*, Shi et al. "A rare mutation of β1-adrenergic receptor affects sleep/wake behaviors." www.cell.com/neuron/fulltext/S0896-6273(19)30652-X , DOI: 10.1016/j.neuron.2019.07.026