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Researchers Discover Heritable Sleep Disorder

Researchers studying three families with the same unusual sleep pattern have uncovered the first hereditary sleep disorder in humans caused by a single gene. Neurologist Christopher Jones and Howard Hughes Medical Institute investigator Louis Ptáček, both at the University of Utah, are now searching for the gene that causes the disorder known as familial advanced sleep phase syndrome (FASPS).

Ptáček and his colleagues concluded that a single gene was responsible for FASPS by studying how the condition was passed along from one generation to the next within the affected families. In this case, inheritance seemed to follow the same simple pattern seen with other single gene traits, such as eye color.

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"Our goal is to find the gene that is altered in FASPS and to use it to help us determine how the body's internal biological clock works," said Ptáček, whose research team published the findings in the September 1999 issue of the journal *Nature Medicine*. "Finding this gene might give us important leads not only for treating sleep disorders but also other problems related to human circadian rhythms."

All creatures—from bacteria to humans—seemingly operate on a biological clock synchronized to a 24-hour day. This internal clock controls a variety of daily biochemical and behavioral cycles—including fluctuations in sleep and wakefulness that are collectively called circadian rhythms.

People with FASPS have a "fast" biological clock—their internal clock's "day" is shorter than 24 hours. If left unconstrained by the demands of everyday life, people with a fast clock tend to go to sleep and wake up several hours earlier than normal. For example, the people examined in this study reported that while on vacation they tended to fall asleep earlier and wake up earlier than usual. In comparison, most people stay up later and wake up later while

on vacation.

Such large disruptions in circadian rhythms are rare, said Ptáček. "These aren't diseases per se, and most people just live with this sleep pattern and never see a doctor about it," he explained.

In this case, however, one woman with a severe circadian disruption did seek help from Jones, a neurologist who specializes in treating sleep disorders. "It turns out that her daughter and grandchild have a similar sleep pattern," said Ptáček.

Jones approached Ptáček, who studies genetic disorders in humans, and the two scientists led a team that interviewed the woman's extended family to determine the extent of the problem. During the course of this study, the team found two additional families with members who have FASPS. In total, the researchers found 29 people with the sleep disorder.

Biological monitoring of various hormone levels, body temperature and brain electrical activity confirmed the diagnoses and revealed some interesting changes in sleep patterns. The most notable was a consistent advance of sleep onset and the first incidence of dream sleep by more than three hours.

With the diagnoses confirmed, it was simple matter to create a family tree and map the incidence of FASPS. The results were striking—the researchers discovered that the disorder followed the simple inheritance pattern of traits caused by a single mutant gene. "This is the first Mendelian inherited sleep disorder discovered in humans," said Ptáček

Eye color is an example of a trait that follows Mendelian inheritance patterns. In the case of eye color, the gene for brown eyes (B) is dominant to the gene for blue eyes (b), which is recessive. A person with brown eyes can be BB or Bb. Only the combination of two recessive genes (bb) results in blue eyes. A brown-eyed (Bb) and a blue-eyed (bb) parent will, on average, have 50 percent brown-eyed and 50 percent blue-eyed children.

In fact, in the three families that Jones and Ptáček studied, half the children of the afflicted parents had the disorder, a classic Mendelian pattern of inheritance.

The fact that FASPS follows the simplest genetic inheritance pattern should simplify the search for the gene involved. "Mapping and cloning a gene can take five years or longer," said Ptáček. "We hope to have the FASPS gene much sooner than that."

He added that once the gene is in hand, "we will study the corresponding protein. Such studies will shed light not only on the function of the normal protein but also the altered protein leading to the FASPS trait."

That discovery, in turn, could lead to drugs that might interact with the protein. Such drugs could prove useful not only for treating FASPS, but also temporary conditions such as jet lag. But, said Ptáček, "we need to

understand the normal biology first. Then we can work on altering the clock and helping people who fly or do shift work."

Jones and Ptáček's co-authors in this study were Scott Campbell and Patricia Murphy at the Weill Medical College of Cornell University, HHMI research technicians Stephanie Zone and Alison DeSano at the University of Utah, and Fred Cooper, Bryan Jones, and Laura Czajkowski, also at the University of Utah.