Gene explains why some are sleepy and sad

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SAN FRANCISCO -- University of California researchers have found a genetic explanation for why some chipper early birds turn glum in the wintertime.

Scientists at UC San Francisco made the discovery by studying DNA, the body's genetic blueprint. They've uncovered a gene mutation linked to extreme early risers -- people waking as early as 2:30 a.m. and hitting the sack before 8 p.m. The mutation seems to affect how people react to changing light patterns, and also how likely they are to develop seasonal depression.

Researchers have long believed sleep, light and mood to be related, but this study is the first to show exactly how that relationship works at the genetic level.

"I think it's a very important study" because it shows that internal clocks are "very largely within our genes," said Emmanuel Mignot, a professor at the Stanford Center for Sleep Sciences and Medicine, who was not involved in the study.

Mignot explained that people's sleep schedules depend on those internal clocks, also called "circadian rhythms."

"Circadian rhythms regulate everything we do," Mignot said. The clock guides the body in a number of ways: cuing dreams, lowering body temperatures to help people snooze longer, and producing the stress-regulating chemical cortisol as a person is about to wake up.

To figure out what biological gears set these internal clocks, scientists often study people with unusual sleep patterns.

"What we're trying to get down to is: What is the biology that makes you be a morning lark and me be a night owl?" said Dr. Louis Ptacek, a neurology professor at UC San Francisco who co-authored the recent UCSF study.

Ptacek's team has studied hundreds of families with unusual sleeping habits, like going to bed unusually early in the evening and waking early as well. They found three early risers had the same rare mutation in the PER3 gene, which is associated with our internal clocks. These three people also suffered from seasonal affective disorder -- depression that typically grows during the winter, when light exposure decreases.

Ptacek wondered if the mutation explained the irregular sleep pattern and also wondered, "Is seasonal

affective disorder actually caused by the same mutation?"

The scientists inserted the gene mutation in mice to see how it affected their sleep. In normal light cycles -- 12 hours of light and 12 hours of dark -- the mutant mice behaved -- and slept -- normally. But under conditions with four hours of light and 20 hours of darkness, the mice's clocks went haywire and caused them to wake and sleep four hours apart from non-mutant mice.

What's more, the mice exhibited behaviors associated with depression. In a test commonly used to assess depression-like behaviors, the group suspended the mice by their tails for a short period of time to watch how the mice tried to free themselves and how quickly they gave up. After exposure to shorter light conditions, mice without normal PER3 gave up more easily. When treated with antidepressants, the mice regained their pluck.

The researchers found that the PER3 mutation causes the body's number of clock-regulating proteins to break down more easily, lowering their overall number. With fewer regulatory proteins, mice (and people) seem to respond differently to altered light exposure, changing their sleep patterns and potentially growing depressed.

Stanford's Mignot said the study helps explain why the internal clock is so powerful.

"If you try to sleep against your circadian tendency, it's not good," Mignot said, explaining that those who work night shifts have increased health risks for cancer, psychiatric problems and obesity.

It also suggests that some cases of seasonal affective disorder may have a genetic cause.

"There clearly is a family history element to depression," said Dr. Carl Olden, a member of the board of directors of the American Academy of Family Physicians, who practices in Yakima, Washington. Olden frequently treats patients with seasonal depression; the academy estimates that about 5 percent of the U.S. population each year suffers from the disorder.

But psychologist Steven LoBello of Auburn University at Montgomery warned against drawing links to seasonal depression. In a recent study reviewing the scientific literature, LoBello found that little scientific proof supports the existence of seasonal affective disorder. He discovered that studies often called upon subjects to remember their state of depression in the distant past and even prompted them to think about particular times of year when they were more depressed, biasing them toward reporting seasonal differences that might not actually exist.

When he analyzed data collected without these biases, LoBello found no relationship between depression and the season or sunlight.

Still, Ptacek said most psychiatrists think seasonal affective disorder is real. His team is continuing to search for more mutations associated with early birds, as well as continuing to investigate the PER3 mutation's relation to seasonal depression.

That will help Ptacek understand the power genes have over sleep as well as their limitations. "We have electric light," he said. "We also set alarms, we drink coffee and we drink alcohol."

In other words, genes may help dictate sleep schedules, but people are constantly rebelling.

"We as humans," he said, "are not always good at listening to our biology."

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