Gene that makes people 'early to bed and early to rise' demystified

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The recent discovery that a mutant "clock" gene made some people "early to bed and early to rise," a condition known as familial advanced sleep phase syndrome (FASPS), offered one of the first glimpses into the genetic basis of sleep in humans. Now, researchers report in the Jan. 12, 2007 issue of the journal *Cell* new evidence that helps to explain just how their bodies' natural alarm clocks get set to such an early wake-up time.

In studies of mice carrying the human FASPS gene, the researchers found that the mutant version of the Period 2 (Per2) clock gene--which is crucial for resetting the body's central clock in response to light--cannot be chemically modified by another enzyme that controls it. That failure leads to a reduction in the number of copies of the Per2 "message," and the characteristic shifted sleep pattern.

Eventually, such insight into the factors influencing people's so-called circadian, or daily, rhythm might lead to therapies that could adjust the body's clock in those suffering from conditions including jet lag or shift work sleep disorder, according to the researchers.

"This study highlights the power of natural human mutations to uncover things [about the circadian clock] that we might not otherwise have learned, or that we might have misunderstood before," said Howard Hughes Investigator Louis Ptácek, of the University of California, San Francisco.

"Most of the information we've had about these clock genes has been based on the Drosophila model and Per2 knockout mice," which lack the Per2 clock gene altogether, added study author Ying-Hui Fu, who is also at UCSF.

Based on those studies, "everybody had thought a short or long period depended on a change in protein stability," she said. "That's how we thought the system should work. But this paper shows that is not the case. It comes back instead to the transcription level as the most important step."

FASPS is a relatively rare, inherited condition in which people are "morning larks," with early morning awakening and early sleep times. People with the condition generally show changes in core body temperatures and other characteristics governed by the circadian clock that are shifted up by three to four hours. The syndrome is passed on in a dominant fashion, meaning that it takes just one copy of the abnormal gene to exhibit symptoms.

The UCSF group had earlier discovered a variant of the human Per2 gene that causes FASPS. They also showed that the so-called "S662G" variant, in which the serine building block normally present at position 662 is replaced by glycine, prevented a regulatory enzyme from tacking a phosphate onto the encoded protein.

Now, the researchers report additional evidence that the lost "phosphorylation" prevents a cascade of chemical modifications that are normally primed by the initial event.

Moreover, they show that the human gene inserted into otherwise normal mice causes them to rise early, symptoms that mirror those in people with FASPS. In contrast, a mutation that mimicked an increase in phosphorylation at amino acid 662 increased the transcription of PER2

and pushed the animals' sleep pattern later.

Their studies in mice revealed that the amino acid change associated with FASPS, which alters the charge of the residue, alters the ability of PER2 to regulate its own transcription. PER2 presumably manages such regulation through interaction with other proteins since it doesn't bind DNA itself, they said.

The findings led the researchers to suggest a model of clock function in which cells sense changing PER2 levels over time, beginning a new daily cycle when a certain threshold is crossed.

"In S662G individuals or mice, the alteration in transcription leads to production of less PER2, while the clock protein's degradation remains unaffected," they explained. Thus, the researchers added, "PER2 levels are lower at all time points and, in the latter half of a cycle, fall below the threshold earlier than normal, leading to activation of transcription earlier and resulting in a shorter period."

The advance in understanding of PER2's role may ultimately lead to methods for people, such as nurses who must care for patients in the middle of the night, to synchronize their internal clocks with their regular or changing daily routines, the researchers said.

Someday "people with jet lag or shift work--some of the most common of sleep disorders--might take a pill and be back to normal again," Fu said.

"When we fly to Europe, we set our watch ahead several time zones and our watch is back on track," Ptácek added. "We don't understand the [internal] human clock well enough to advance or delay it that way. But with all that we've learned from the fruit fly, mouse and now human about the gears and how they are working, we're getting closer to a

'button' that might be able to do that."

Source: Cell Press