

MARCH 31, 2005

Researchers Identify Cause of "Early Bird" Sleep Disorder

A few rare people who consistently nod off early, then wake up wide-eyed much before dawn, can blame a newly-found mutant gene for their sleep troubles, Howard Hughes Medical Institute researchers announced today.

This odd "time-shift" trait—called familial advanced sleep phase syndrome (FASPS)—was studied in one affected family by neurologist Louis J. Ptacek, a Howard Hughes Medical Institute researcher, and Ying-Hui Fu, at the University of California, San Francisco. Their report appears in the March 31, 2005, issue of the journal *Nature*.

"Some of them would never come to a doctor to find out what's going on with their sleep pattern, because they aren't troubled by it. But others are bothered by being out of phase with the rest of the world."

— Louis J. Ptáček

The sleep-shifting mutation they found is in "a gene that was not previously shown in mammals to be a circadian rhythm gene," Ptacek explained. It's not yet clear how the mutant gene works to shift people's sleep time, their circadian rhythm, he added. But follow-on experiments in fruit flies and mice yielded results that are intriguing.

When the mutant gene was inserted into the flies, for example, it did the opposite of what was seen in the human family: it lengthened circadian rhythm. Yet in genetically engineered mice, the same gene change made the mice early risers—mimicking what was seen in humans with FASPS.

So, studies of all three organisms—flies, mice and humans—"will help us understand the similarities and differences" in how the gene works in different settings, in different genetic backgrounds, he said. Experiments can be done in mice and flies, with results applying to humans, while the studies of humans can inform what's being seen in the flies and mice.

In addition, "these results show that the gene is a central component of the mammalian circadian clock, and suggest that mammalian and fly clocks may have different regulatory mechanisms, despite the highly conserved nature of their individual components," the research team wrote in *Nature*. Such studies may help unravel some of the fundamental mysteries of how circadian rhythms are established and maintained in creatures that have evolved along very different paths.

As for the affected individuals, Ptacek said most are able to live normal lives, and some are proud of being able to arise before dawn and get a lot done while everything is quiet. A few, however, are constantly bothered by living out of sync with everyone else's daily schedule.

"Some of them would never come to a doctor" to find out what's going on with their sleep pattern, Ptacek said, "because they aren't troubled by it. Often, they have adjusted and accommodated their jobs to match their ability. But others are bothered by being out of phase with the rest of the world."

He said the FASPS subjects don't seem to sleep any more or less than other people; they just sleep at different times. And there is apparently no connection to the better-known problem called narcolepsy.

Ptacek said it was also found—in the family's six affected individuals—that "they all have asthma, and they all have migraine headaches, with aura. Now, that could be purely coincidental, but a more important possibility is that these are part of the same syndrome." So far, however, "we haven't even looked at that yet."

He estimated that a very small number (about .3 percent) of the human population seems to have this "circadian clock" shift. And in earlier research, Ptacek and his colleagues had discovered an entirely different gene that causes a similar clock-shift. Both arise because of so-called point mutations in the genes. This means that altering a single base-pair in the gene's long DNA chain is enough to change a person's sleep behavior. Evidence from tissue culture experiments with the second gene suggests the change causes a protein—an enzyme called a kinase that is made by the gene - to be less active than normal.

The lead author of the paper in *Nature* is Ying Xu, a member of the team in San Francisco. Other team members are at the University of Vermont and the University of Utah.