

JANUARY 12, 2001

## First Human Circadian Rhythm Gene Identified

Researchers exploring the genetic basis of a rare syndrome that causes people to fall asleep and awaken earlier than normal have pinpointed the first human gene that controls circadian rhythm. The finding establishes a link between the human circadian system and that of animal models such as *Drosophila*, mice and hamsters, say the researchers. It also raises the possibility of treating jet lag, as well as sleep problems in adolescents, the elderly and shift workers.

A research team that included Howard Hughes Medical Institute investigator Louis J. Ptacek reported that a mutation in a gene called *hPer2* is responsible for familial advanced sleep-phase syndrome (FASPS) in members of a Utah family. This syndrome typically causes sleep onset around 7 p.m., and spontaneous awakening around 2 a.m., in affected family members. The research was published online by the journal *Science* on January 12, 2001. The article will also appear in print in a future issue of *Science*.

---

"While advanced sleep-phase syndrome is common among the elderly — who tend to fall asleep and wake earlier as they age — a familial syndrome was not identified until 1999."

— Louis J. Ptáček

---

"While advanced sleep-phase syndrome is common among the elderly who tend to fall asleep and wake earlier as they age a familial syndrome was not even identified until 1999," said Ptacek, who is at the University of Utah. The first FASPS family was identified by Christopher Jones, who is co-first-author of the *Science* paper with Kong Toh, both of whom are at the University of Utah.

"This was a seminal observation, and nobody else had ever recognized the syndrome," said Ptacek. "One problem with distinguishing a familial circadian disorder is that there are wide normal variations in sleep patterns, with some of us being 'morning larks,' some of us 'night owls,' and many of us somewhere between. These variations are presumably complex, involve

contributions from multiple genes, and are also influenced by environmental factors."

According to Ptacek, individual members of the Utah family identified by Jones showed strong symptoms of a distinctive ASPS-type sleep pattern—as revealed by their answers to a questionnaire that covered sleep habits and time-preferences for activities such as test-taking and exercise.

Once the researchers identified the affected family members, they used linkage analysis to attempt to find the mutant gene underlying the syndrome. In these studies they attempted to locate the chromosome region, or locus, that held the genetic mutation unique to the affected family members, based on its location relative to known genetic markers. In their initial analysis, the only significant linkage they found proved to be a false positive result that yielded no relevant genes near the marker that seemed to be inherited most often with the mutation. Then, however, they decided to concentrate on linkages to markers near the tips of the chromosomes, called telomeres.

"The telomeres of chromosomes are places where there's a high rate of recombination between chromosomes," said Ptacek. "So, a marker could be pretty close to the locus that contains the gene and still have recombinations between the marker and the locus."

The hunch paid off, said Ptacek, and the analysis revealed that affected family members shared a common locus near the telomere of chromosome 2q. Further studies revealed that the candidate gene was homologous to *Drosophila* and mouse genes that when mutated were known to speed up circadian rhythm.

Detailed sequence studies of the candidate human gene, *hPer2*, in the affected family members, revealed a key change in a single amino acid—from serine to glycine—at position 662 in the *hPer2* protein. This single alteration, the scientists found, occurred in the portion of the *hPer2* protein that governed binding to an enzyme called casein kinase one-epsilon (CK1 $\epsilon$ ). In animal models, this enzyme was shown to regulate proteins involved in controlling the length of circadian rhythms.

Their experiments also showed that the mutation disrupted phosphorylation of the *hPer2* protein by CK1 $\epsilon$ . "We're quite excited about the finding that this serine 662 is absolutely critical for phosphorylation by casein kinase one epsilon," said Ptacek. "How that phosphorylation ultimately controls circadian rhythms we don't know for sure, but we hope to find the answer through more detailed studies of phosphorylation in this part of the protein," he said. According to Ptacek, the disruption in phosphorylation of the *hPer2* protein may prevent the protein from acting as a sort of rheostat that helps adjust the length of the circadian rhythm according to the amount of phosphorylation.

"Circadian rhythm is probably governed by a balance of phosphorylation of different proteins," said Ptacek. "And in a normal, healthy twenty-four-hour clock, many proteins are being phosphorylated by casein kinase one epsilon,

and it's the balance of one protein versus another that produces the normal rhythm."

The discovery of the mutant *hPer2* gene's role in altering human circadian rhythm represents only the first such finding, and there will likely be many others to come, said Ptacek. As an indication, he notes that many other families have now been identified with FASPS that do not show the same mutation. Further studies of such rare syndromes will likely yield important insights into the human circadian machinery, he said, with potentially practical clinical benefits.

"A great many elderly people show these kinds of problems," he said. "And many adolescents have the opposite problem—delayed sleep phase syndrome—in which insomnia prevents them from getting to sleep at a reasonable time." Also, he said, a thorough understanding of the human circadian system could lead to drugs to allow travelers and nightshift workers to avoid potentially hazardous fatigue.

"If we could shift our internal clock as easily as we could switch our wristwatches, we would adjust a lot better when we fly to Paris or London from Salt Lake City, for example," he said. "And, it is well known that sleepiness is a contributor in many traffic fatalities and on-the-job accidents."