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Tinkering with Our Clock

Inserting a gene that controls human sleep habits into mice can transform the rodents into “early birds.” This result provides insight into the molecular mechanisms that drive biological clocks.

Most organisms have an internal clock that synchronizes their activities to the 24-hour day—the so-called circadian rhythm.

PER2 is one of the genes that controls this rhythm in humans. But in 0.3 percent of the population, the gene goes awry, causing familial advanced sleep phase syndrome (FASPS), which drives people early to bed and very early to rise.

Despite causing such a striking effect, the change in the protein encoded by the mutant *PER2* gene is quite subtle: a single protein building block, or amino acid, is changed from a serine to a glycine.

To better understand how *PER2* works, Louis J. Ptáček and Ying-Hui Fu of the University of

California, San Francisco, genetically engineered mice with the human gene. Sure enough, when the animals received the FASPS *PER2* mutation, their natural rhythm shortened from an average of 23.7 hours to less than 22. When the researchers made another simple amino acid switch in the protein, turning the same serine into an aspartate, the period lengthened to 24.8 hours. Resetting of the mice’s clock seemed linked to the activity of the gene. The first mutation lowered gene expression, and the second boosted it.

According to Fu, the results have implications far beyond sleep disorders. Night-shift nurses are more prone to breast cancer, she notes, and chemotherapy is more effective at certain

times. Strokes, aneurysms, asthma and depression tend to occur at particular times of day. “Sleep is at the center of all body functions, so understanding circadian rhythm will help us understand related problems,” Fu says.

—Karen A. Frenkel

