Found: Mouse Circadian Rhythm Gene

Never trust a mouse from Joseph S. Takahashi's laboratory to be on time. A few years ago, Takahashi and his colleagues randomly mutated genes in mice to disrupt their biological clock, the internal timepiece that creates daily cycles, or circadian rhythms, of activities such as sleeping, eating, and exploring.

Takahashi's group succeeded in creating mice whose clocks ticked in a cycle that ran significantly longer than the normal mouse's 23.7 hours. Indeed, some of these mice lost their circadian rhythms altogether (SN: 5/14/94, p. 319).

Now, the researchers have identified the gene at fault and named it *clock*. They report their finding in the May 16 CELL.

"It's the first molecular entry into the clock mechanism in mammals," says Takahashi of Northwestern University in Evanston, Ill.

While researchers had previously identified circadian rhythm genes in fruit flies and the bread mold *Neurospora crassa*, comparable mammalian genes had proved elusive. Investigators have long known that the primary mammalian pacemaker resides in brain regions called the suprachiasmatic nuclei (SCN). Last year, scientists also found that hamster retinas contain independent biological clocks (SN: 4/20/96, p. 245).

As expected, Takahashi's group observed that the *clock* gene is active in the mouse SCN and retina. More surprising, the gene is turned on elsewhere in the brain and in many tissues, including the heart, liver, and kidneys.

These findings don't challenge the SCN's dominant role in the circadian rhythms that govern sleeping and other behavioral functions, the scientists stress. In certain tissues, however, "there may be regional clocks that control specific functions," says Gene D. Block, director of the National Science Foundation Center for Biological Timing in Charlottesville, Va.

Another explanation may be that the protein encoded by *clock* can serve noncircadian roles in other tissues.

Definitive proof that Takahashi and his colleagues had found their quarry came from experiments that restored normal circadian rhythms in progeny of their genetically altered mice. By injecting snippets of DNA that included *clock* into eggs of the altered mice, the scientists produced offspring with normal rhythms, even some with shorter cycles.

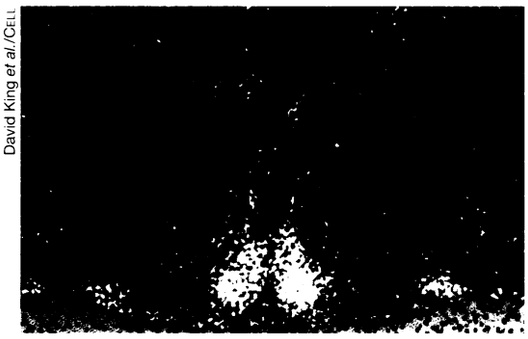
The molecule encoded by *clock* can apparently bind DNA, suggesting that it's a transcription factor, a protein that can turn genes on and off, says Takahashi.

Investigators have not yet examined whether *clock*'s protein acts directly to help establish a circadian rhythm. Instead, it could influence inputs to the mouse biological clock, such as perception of light, or disturb the signals sent out by the clock to the animal.

"We just don't know whether it's an essential gear of the clock," says Steven M. Reppert of Massachusetts General Hospital in Boston.

Another key issue centers on the presumed partner or partners of *clock*'s protein. In the fruit fly, proteins called PER and TIM and at least one unidentified protein interact to generate the circadian rhythm. Scientists are curious as to whether mouse counterparts of PER and TIM bind to *clock*'s protein and whether a fly version of that protein is the long-sought missing partner for PER and TIM.

The discovery of *clock* lends support to a proposal linking circadian rhythms and light sensitivity. In the May 2 SCIENCE, Jay C. Dunlap and his colleagues at Dartmouth Medical School in Hanover, N.H., report that proteins that help *N. crassa* respond to light also play a role in the organism's biological clock.



David King *et al.*/CELL

The suprachiasmatic nuclei, brain regions that govern most circadian rhythms in mammals, exhibit high activity (yellow) of a gene called clock.

Moreover, the bread mold proteins have a structural feature, called a PAS domain, that also exists in *clock*'s protein and in PER. Dunlap suggests that PAS is an element of many clock and photoresponse proteins, reflecting an evolutionary history in which the capacity to generate circadian rhythms arose from the ability of cells to sense the sun's daily light-dark cycles. —*J. Travis*

Computer triumphs over human champion

The end came sooner and more abruptly than anyone had expected. In the final game of a six-game match this week in New York, world chess champion Garry Kasparov resigned after just 19 moves, giving IBM chess computer Deep Blue the win. It was the first tournament that Kasparov had ever lost to any opponent, human or computer, since he became champion.

In last year's bout with Deep Blue, Kasparov won by outmaneuvering the computer and exploiting weaknesses in its play (SN: 2/24/96, p. 119; 3/30/96, p. 200). The Deep Blue team came better prepared for the rematch.

"Three things were improved this time around," says Chung-Jen Tan, manager of the Deep Blue computer chess project at the IBM Thomas J. Watson Research Center in Yorktown Heights, N.Y. "It's more powerful, we added more chess knowledge, and we developed a program to change the parameters [between games]."

Deep Blue's calculations allow it to select the best move after evaluating the consequences of different plays far more deeply into a game than a person can. This brute-force capability is particularly useful when the number of pieces left on the board is small and the computer can look even further ahead, having a smaller number of cases to consider.

"A computer is very good at solving immediate problems that have definite solutions within three or four moves for each side," says former U.S. chess champion Patrick G. Wolff of Cambridge, Mass. This time, "the programmers were able to give the computer a sensitive enough evaluation function so it was able to distinguish between certain [chess position] subtleties that before had been out of reach."

Nonetheless, the computer's capabilities remain limited. In the pivotal second game, which Deep Blue won, Kasparov overlooked a sequence of moves that would have forced a draw. Interestingly, Deep Blue also failed to detect that sequence. Chess experts later noted that the computer missed several moves earlier in the game that would have assured a quicker victory.

In the end, however, it was Kasparov's apparent loss of confidence—a decidedly human weakness—that probably decided the match. "An analysis of the games shows very clearly that cognitively Kasparov is still the better chess player," Wolff says. "What shocked me and most chess players who followed the match was how Kasparov simply fell apart at the end. He collapsed psychologically." —*I. Peterson*