Waking up is hard to do: Scientists identify a gene important for the daily rhythms of the sleep-wake cycle

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Northwestern University scientists have discovered a new mechanism in the core gears of the circadian clock. They found the loss of a certain gene, dubbed "twenty-four," messes up the rhythm of the common fruit fly's sleep-wake cycle, making it harder for the flies to awaken.

The circadian clock drives, among other things, when an organism wakes up and when it sleeps. While the Northwestern study was done using the fly Drosophila melanogaster, the findings have implications for humans.

The research will be published Feb. 17 in the journal *Nature*.

"The function of a clock is to tell your system to be prepared, that the sun is rising, and it's time to get up," said Ravi Allada, M.D., who led the research at Northwestern. "The flies without the twenty-four gene did not become much more active before dawn. The equivalent in humans would be someone who has trouble getting out of bed in the morning."

Allada is professor of neurobiology and physiology in the Weinberg College of Arts and Sciences and associate director for the Center for Sleep and Circadian Biology.

Period (per) is a gene in fruit flies that encodes a protein, called PER, which regulates circadian rhythm. Allada and his colleagues found that twenty-four is critically important to producing this key clock protein. When twenty-four is not present very little PER protein is found in the neurons of the brain, and the fly's sleep-wake rhythm is disturbed.

It seems it was fate that the gene Allada and his team pinpointed would be important in regulating the 24-hour sleep-wake cycle. The gene's generic name is CG4857, and the numbers add up to 24, earning it the twenty-four nickname. (The fruit fly's genome was sequenced in 2000, but until now the function of this gene was unknown.)

The known core mechanisms of the circadian clock, both in flies and humans, involve the process of transcription, where RNA is produced from DNA. A portion of the control system called a transcriptional feedback loop also is important. (The word circadian comes from the Latin phrase "circa diem," meaning "about a day.")

In trying to identify new clock components, the researchers identified a new player in the system, the gene twenty-four. Instead of operating in the process of transcription, they found twenty-four operates in the process of translation: translating proteins from RNA.

Twenty-four appears to be a protein that promotes translation of period RNA to protein. "This really defines a new mechanism by which circadian clocks are functioning," Allada said. "We found that twenty-four has a really strong and critical role in translating a key clock protein. Translation really wasn't appreciated before as having such an important role in the process."

The researchers believe it is likely that a mechanism similar to that described for the fly gene twenty-four will be evolutionarily conserved and found in humans.

Allada and his Northwestern team worked with scientists at the Korea Advanced Institute of Science and Technology (KAIST). Using a Drosophila library at KAIST, the researchers first screened the behavior of 4,000 different flies looking for flies whose sleep-wake cycles were

awry. (Each fly had a different overexpressed gene and thus different behavior.) The fly with the most dramatic change was one with a longer cycle than normal, 26 hours instead of 24.

The overexpressed gene in this fly was CG4857. The researchers next removed, or knocked out, this gene in the flies. These flies had very poor sleep-wake rhythm and would sleep and wake at all times of day. The researchers found very little of the critical PER protein in the brain neurons despite the fact that per RNA is likely produced in the neurons. Without twenty-four the RNA was not translated into the PER protein, leading to dysfunction.

More information: The paper is titled "The Novel Gene Twenty-four Defines a Critical Translational Step in the Drosophila Clock."

Provided by Northwestern University