MedicalXpress

Researchers identify new circadian clock component

May 16 2013

Northwestern University scientists have shown a gene involved in neurodegenerative disease also plays a critical role in the proper function of the circadian clock.

In a study of the common fruit fly, the researchers found the gene, called Ataxin-2, keeps the clock responsible for sleeping and waking on a 24-hour rhythm. Without the gene, the rhythm of the fruit fly's sleep-wake cycle is disturbed, making waking up on a regular schedule difficult for the fly.

The discovery is particularly interesting because mutations in the human Ataxin-2 gene are known to cause a rare disorder called spinocerebellar ataxia (SCA) and also contribute to amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. People with SCA suffer from sleep abnormalities before other symptoms of the disease appear.

This study linking the Ataxin-2 gene with abnormalities in the sleep-wake cycle could help pinpoint what is causing these neurodegenerative diseases as well as provide a deeper understanding of the human sleep-wake cycle.

The findings will be published May 17 in the journal *Science*. Ravi Allada, M.D., professor of neurobiology in the Weinberg College of Arts and Sciences, and Chunghun Lim, a postdoctoral fellow in his lab, are authors of the paper.

Period (per) is a well-studied gene in fruit flies that encodes a protein, called PER, which regulates circadian rhythm. Allada and Lim discovered that Ataxin-2 helps activate translation of PER RNA into PER protein, a key step in making the circadian clock run properly.

"It's possible that Ataxin-2's function as an activator of protein translation may be central to understanding how, when you mutate the gene and disrupt its function, it may be causing or contributing to diseases such as ALS or spinocerebellar ataxia," Allada said.

The fruit fly *Drosophila melanogaster* is a model organism for scientists studying the sleep-wake cycle because the fly's genes are highly conserved with the genes of humans.

"I like to say that flies sleep similarly to humans, except flies don't use pillows," said Allada, who also is associate director for Northwestern's Center for Sleep and Circadian Biology. The biological timing mechanism for all animals comes from a common ancestor hundreds of millions of years ago.

Ataxin-2 is the second gene in a little more than two years that Northwestern researchers have identified as a core gear of the circadian clock, and the two genes play similar roles.

Allada, Lim and colleagues in 2011 reported their discovery of a gene, which they dubbed "twenty-four," that plays a role in translating the PER protein, keeping the sleep-wake cycle on a 24-hour rhythm.

Allada and Lim wanted to better understand how twenty-four works, so they looked at proteins that associate with twenty-four. They found the twenty-four protein sticking to ATAXIN-2 and decided to investigate further. In their experiments, reported in *Science*, Allada and Lim discovered the Ataxin-2 and twenty-four genes appear to be partners in

PER protein translation.

"We've really started to define a pathway that regulates the circadian clock and seems to be especially important in a specific group of neurons that governs the fly's morning wake-up," Allada said. "We saw that the molecular and behavioral consequences of losing Ataxin-2 are nearly the same as losing twenty-four."

As is the case in a mutation of the twenty-four gene, when the Ataxin-2 gene is not present, very little PER protein is found in the circadian pacemaker neurons of the brain, and the fly's sleep-wake rhythm is disturbed.

More information: "ATAXIN-2 Activates PERIOD Translation to Sustain Circadian Rhythms in Drosophila," by C. Lim et al *Science*, 2013.

Provided by Northwestern University