Gene distinguishes early birds from night owls and helps predict time of death

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Many of the body's processes follow a natural daily rhythm or so-called circadian clock. There are certain times of the day when a person is most alert, when blood pressure is highest, and when the heart is most efficient. Several rare gene mutations have been found that can adjust this clock in humans, responsible for entire families in which people wake up at 3 a.m. or 4 a.m. and cannot stay up much after 8 at night. Now new research has, for the first time, identified a common gene variant that affects virtually the entire population, and which is responsible for up to an hour a day of your tendency to be an early riser or night owl.

Furthermore, this new discovery not only demonstrates this common polymorphism influences the rhythms of people's day-to-day lives—it also finds this genetic variant helps determine the time of day a person is most likely to die.

The surprising findings, which appear in the November 2012 issue of the *Annals of Neurology*, could help with scheduling shift work and planning medical treatments, as well as in monitoring the conditions of vulnerable patients.

"The internal 'biological clock' regulates many aspects of human biology and behavior, such as preferred sleep times, times of peak cognitive performance, and the timing of many physiological processes. It also influences the timing of acute medical events like stroke and heart attack," says first author Andrew Lim, MD, who conducted the work as

a postdoctoral fellow in the Department of Neurology at Beth Israel Deaconess Medical Center (BIDMC).

"Previous work in twins and families had suggested that the lateness or earliness of one's clock may be inherited and animal experiments had suggested that the lateness or earliness of the biological clock may be influenced by specific genes," adds Lim, who is currently an Assistant Professor in the Division of Neurology at the University of Toronto.

The work originated several years ago while Lim was working in the laboratory of BIDMC Chief of Neurology Clifford Saper, MD, PhD. Lim and the other lab members were studying why older people have trouble sleeping and had joined a research project based at Rush University in Chicago involving 1,200 people who signed on as healthy 65-year-olds and would receive annual neurological and psychiatric examinations.

The cohort's original intent was to determine if there were identifiable precursors to the development of Parkinson's disease or Alzheimer's disease. As part of the research the subjects were undergoing various sleep-wake analyses using a wristband called an actigraph, which provides a reliable record of an individual's pattern of activity. Additionally, in order to provide the scientists with information on sleep-wake patterns within a year of death, the participants had agreed to donate their brains after they died.

But the investigation took a new turn when Lim learned that the same group of subjects had also had their DNA genotyped. Teaming up with investigators from Brigham and Women's Hospital (BWH), Lim and his colleagues compared the wake-sleep behavior of these individuals with their genotypes. These findings were later verified in a group of young volunteers.

They soon discovered a single nucleotide near a gene called "Period 1" that varied between two groups that differed in their wake-sleep behavior. At this particular site in the genome, 60 percent of individuals have the nucleotide base termed adenine (A) and 40 percent have the nucleotide base termed guanine (G). Because we have two sets of chromosomes, in any given individual, there's about a 36 percent chance of having two As, a 16 percent chance of having two Gs, and a 48 percent chance of having a mixture of A and G at this site.

"This particular genotype affects the sleep-wake pattern of virtually everyone walking around, and it is a fairly profound effect so that the people who have the A-A genotype wake up about an hour earlier than the people who have the G-G genotype, and the A-Gs wake up almost exactly in the middle," explains Saper, who is also the James Jackson Putnam Professor of Neurology and Neuroscience at Harvard Medical School. Also, expression of the Period 1 gene was lower in the brains and white blood cells of people with the G-G genotype than in people with the A-A genotype, but only in the daytime, which is when the gene is normally expressed.

This discovery marks the biggest contribution of a single genotype in a large population to determine the time of day when people wake up or go to sleep. But could the variant also affect other aspects of the body's circadian rhythm?

"Virtually all physiological processes have a circadian rhythm, meaning that they occur predominantly at certain parts of the day. There's even a circadian rhythm of death, so that in the general population people tend on average to be most likely to die in the morning hours. Sometime around 11 am is the average time," says Saper.

When the investigators went back and looked at the people in the study (many of whom had enrolled more than 15 years ago at age 65) who had

died, they found that this same genotype predicted six hours of the variation in the time of death: those with the AA or AG genotype died just before 11 a.m., like most of the population, but those with the GG genotype on average died at just before 6 p.m.

"So there is really a gene that predicts the time of day that you'll die. Not the date, fortunately, but the time of day," says Saper.

Lim says that additional work is needed to determine the mechanisms by which this and other gene variants influence the body's biological clock. In addition to helping people optimize their schedules, the research could eventually lead to novel therapies to treat disturbances of this clock as seen in jet lag or shift work.

"Also, working out which causes of death are influenced by gene variants like the one we identified may eventually lead to rational timed interventions—such as taking heart medications at particular times depending on which version of the gene variant one carries—to provide protection during an individuals' period of greatest risk," says Lim. The potential clinical applications may be as diverse as the many processes that the circadian clock controls.

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