

# Loss Of Circadian Genes Results In Epilepsy 6/7/2004

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**From:** JWissmille ([jwissmille\\_at\\_aol.com](mailto:jwissmille_at_aol.com))

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Loss Of Circadian Genes Results In Epilepsy  
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Source: Cold Spring Harbor Laboratory

A meticulous series of experiments and the fortuitous use of a vacuum cleaner lead to breakthrough new insight on the genetic basis of epilepsy.

Circadian rhythms -- the normal ups and downs of body rhythms help organize physiological processes into a 24 hour cycle, affecting everything from body temperature, hormone levels and heart rate, to pain thresholds.

Scientists have now discovered that the combined deletion of three circadian genes, encoding the PAR bZip transcription factor protein family, results in accelerated aging and severe epilepsy in mice. Owing to the roughly 95% identity of PAR bZip proteins between mice and humans, it is anticipated that PAR bZip mutations may also underlie some forms of human epilepsy.

A copy of this important new study is being released in advance of its June 15th publication date by the journal *Genes & Development* (<http://www.genesdev.org>).

"The objective of the study was to assign physiological functions to the small family of PAR bZip transcription factors," explains Dr. Ueli Schibler, principal investigator of the study and in whose lab the first PAR bZip transcription factor was found nearly 15 years ago. The PAR bZip transcription factor family is composed of three proteins (DBP, HLF and TEF), all of which display distinct patterns of circadian accumulation: In tissues with high amplitudes of circadian clock gene expression (like the liver), PAR bZip protein levels change up to 50-fold throughout the day. However, in the brain, where clock gene expression varies little, PAR bZip protein levels barely change.

To explore the functional significance of the PAR bZip protein family, Dr.

Schibler and colleagues disrupted one, two, or all three of the PAR bZip genes in mice. The single, double, and triple knock-out mice (as they are known) appear normal, but it quickly became apparent that the triple knock-out mice (i.e. those missing all three PAR bZip genes) have markedly short life spans: 50% died within two months, and less than 20% survived to one year. The cause of early death, though, was not immediately apparent.

As Dr. Schibler recounts, "It was by serendipity that my two collaborators Fred Gachon and Pascal Gos identified the cause of mortality. Both of them took very meticulous notes, and in looking at their files noticed that more mice died on Mondays and Thursdays, when the animal keepers clean the room hosting these mice with the vacuum cleaner. Placing a cage with triple knockout mice and, as a control, a cage with double knockout mice, close to a vacuum cleaner revealed a tragedy when the vacuum cleaner was turned on: About half of the triple knockout mice immediately started "wild-running" and then displayed terrible spasms." Many of these animals died as a consequence of the sound-induced epileptic attacks. In contrast, none of the DBP/HLF double knockout mice were affected by the noisy vacuum cleaner.

The researchers monitored brain electrical activity in the mice to confirm their observation that those mice lacking all three PAR bZip genes are prone to epileptic seizures. The recording of electroencephalograms (EEGs) during several days revealed that all of the triple knockout mice also suffered from generalized spontaneous seizures (in addition to the sound-induced epilepsies). Interestingly, though, DBP and HLF single knockout mice and DBP/HLF double knockout mice are no more seizure-prone than wild-type (genetically normal) mice. All examined mice lacking the TEF gene – even TEF single knockout mice – show some abnormal EEG activities, but these only develop into generalized (and frequently lethal) seizures when the other two PAR bZip transcription factors are also lacking.

Further work by Dr. Schibler and colleagues revealed that the cause of these epileptic attacks may lie in yet another gene, called Pdxk. The Pdxk gene encodes an enzyme that converts vitamin B6 into its physiologically active form, pyridoxal phosphate (PLP), and PLP is crucial for the metabolism of several neurotransmitters. Dr. Schibler is quick to point out that "Although vitamin B6 deficiency has been known to provoke epilepsies in humans and laboratory rodents, PDXK misregulation has never been discovered thus far."

Indeed, the researchers found that Pdxk expression is regulated by the PAR bZip transcription factors in both the liver and the brain. Furthermore, Pdxk expression is abnormally low in the brains of PAR bZip triple knockout mice, suggesting that the downregulation of Pdxk in these mice may be at least partly responsible for their epilepsy.

The potential role for Pdxk misregulation in human epilepsy is even more intriguing, given the close proximity of Pdxk to the CSTB gene, which is thought to be responsible for the hereditary form of human epilepsy known as "Unverricht-Lundborg Disease."

As Dr. Schibler explains, "It now becomes important to examine whether promoter mutations in CSTB (expansion of a GC-rich dodecamer) can also influence the expression of the gene next door, namely PDXK. Clearly, with the limited resolution obtained in human haplotype mapping, it cannot be excluded that underexpression of PDXK contributes to the Unverricht-Lundborg disease."

While the scientific community considers this novel role for PAR bZip transcription factors and Pdxk in epilepsy, Dr. Schibler's group is already at work on the premature aging phenotype displayed by the triple knockout mice. "We already have some ideas on what these circadian transcription factors do in the liver, and we also have some clues (speculations) on why their elimination might provoke premature aging. But we would like to finish our experiments before spilling the beans."

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Contact: Heather Cosel  
coselpie@cshl.edu  
Cold Spring Harbor Laboratory