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## The Clock Is Off

### Bipolar disorder may be linked to mutations affecting circadian rhythm

By Monica Heger

An off-kilter body clock can throw off our sleep-wake cycle, eating habits, body temperature and hormones—and mounting evidence suggests a malfunctioning clock may also underlie the mood cycles in bipolar disorder.

In a new study led by psychiatrist Alexander Niculescu of Indiana University, researchers found that children with bipolar disorder were likely to have a mutated *RORB* gene, which codes for a protein crucial to circadian clock function. The team's previous work identified alterations to this gene and other clock genes in animal models of the disorder. In the new study, the scientists compared the genomes of 152 bipolar kids with those of 140 typical kids. (Children were studied because their moods cycle more rapidly than the moods of bipolar adults, and a quicker cycle suggests a stronger connection to the circadian clock.) The team found that the bipolar children were more likely to have one of four alterations to *RORB*, and the investigators suspect the mutations prevent the body from producing the correct amount of the protein to support normal clock function.

Previous studies had shown that strictly regulating a bipolar patient's sleep schedule could improve extreme mood cycles, but experts weren't sure why—until animal studies started showing a connection to circadian clock genes.

"Every time we investigate some [abnormality] of molecular machinery linked to the clock genes, we find an association with bipolar disorder," says Francesco Benedetti, a neuroscientist at the San Raffaele Scientific Institute in Milan, Italy, who was not involved in the Indiana research. The ultimate goal, he adds, is to pinpoint the precise mechanism that links clock function with mood swings, in the hope of designing new drugs and treatments that will restore the clock to working order.

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