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Researchers decipher manic gene

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Flying high, or down in the dumps—individuals suffering from bipolar disorder alternate between depressive and manic episodes. Researchers from the University of Bonn and the Central Institute of Mental Health in Mannheim have now discovered, based on patient data and animal models, how the NCAN gene results in the manic symptoms of bipolar disorder. The results have been published in the current issue of "*The American Journal of Psychiatry*."

Individuals with bipolar disorder are on an emotional rollercoaster. During depressive phases, they suffer from depression, diminished drive and often, also from suicidal thoughts. The manic episodes, however, are characterized by restlessness, euphoria, and delusions of grandeur. The genesis of this disease probably has both hereditary components as well as psychosocial environmental factors.

"It has been known that the NCAN gene plays an essential part in bipolar disorder," reports Prof. Dr. Markus M. Nöthen, Director of the Institute of Human Genetics at the University of Bonn. "But until now, the functional connection has not been clear." In a large-scale study, researchers led by the University of Bonn and the Central Institute of Mental Health in Mannheim have now shown how the NCAN gene contributes to the genesis of mania. To do so, they evaluated the genetic data and the related descriptions of symptoms from 1218 patients with differing ratios between the manic and depressive components of bipolar disorder.

Using the patients' detailed clinical data, the researchers tested

statistically which of the symptoms are especially closely related to the NCAN gene. "Here it became obvious that the NCAN gene is very closely and quite specifically correlated with the manic symptoms," says Prof. Dr. Marcella Rietschel from the Central Institute of Mental Health in Mannheim. According to the data the gene is, however, not responsible for the depressive episodes in bipolar disorder.

A team working with Prof. Dr. Andreas Zimmer, Director of the Institute of Molecular Psychiatry at the University of Bonn, examined the molecular causes effected by the NCAN gene. The researchers studied mice in which the gene had been "knocked out." "It was shown that these animals had no depressive component in their behaviors, only manic ones," says Prof. Zimmer. These knockout mice were, e.g., considerably more active than the control group and showed a higher level of risk-taking behavior. In addition, they tended to exhibit increased reward-seeking behavior, which manifested itself by their unrestrained drinking from a sugar solution offered by the researchers.

Finally, the researchers gave the manic knockout mice lithium – a standard therapy for humans. "The lithium dosage completely stopped the animals' hyperactive behavior," reports Prof. Zimmer. So the results also matched for lithium; the responses of humans and mice regarding the NCAN gene were practically identical. It has been known from prior studies that knocking out the NCAN gene results in a developmental disorder in the brain due to the fact that the production of the neurocan protein is stopped. "As a consequence of this molecular defect, the individuals affected apparently develop manic symptoms later," says Prof. Zimmer.

Now the scientists want to perform further studies of the molecular connections of this disorder - also with a view towards new therapies. "We were quite surprised to see how closely the findings for mice and the patients correlated," says Prof. Nöthen. "This level of significance is

very rare." With a view towards mania, the agreement between the findings opens up the opportunity to do further molecular studies on the mouse model, whose results will very likely also be applicable to humans. "This is a great prerequisite for advancing the development of new drugs for mania therapy," believes Prof. Rietschel.

More information: Studies in humans and mice implicate neurocan in the etiology of mania, *The American Journal of Psychiatry*, DOI: 10.1176/appi.ajp.2012.11101585

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