Risk gene for bipolar disorder decoded

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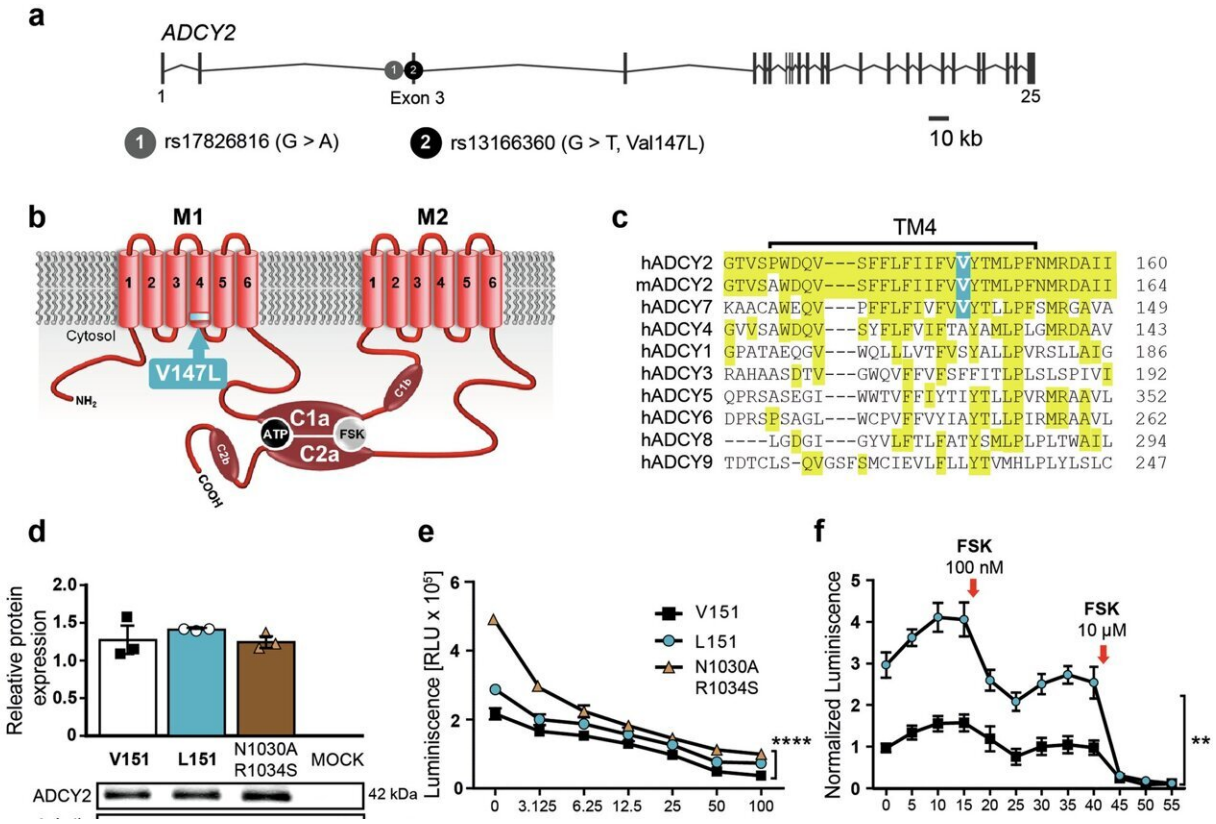

Consequences of Val147Leu substitution on ADCY2 activity and subcellular localization. Credit: *Molecular Psychiatry* (2024). DOI: 10.1038/s41380-024-02663-w

The risk gene adenylyl cyclase 2 is associated with bipolar disorder, as has been repeatedly confirmed in genome-wide association studies. However, until now there has not been any proof of a causal relationship.

Researchers from the Max Planck Institute of Psychiatry (MPI) have now provided this: For the first time, they experimentally demonstrated that mice with a risk variant of the gene showed behavioral changes reminiscent of manic symptoms in patients with bipolar disorder. Patients, or at least some of them, are also likely to carry this mutation. In the long term, this could provide an entry point for new, more effective and more individualized therapies.

The findings are published in the journal *Molecular Psychiatry*.

The probability of developing bipolar disorder in the course of an individual's life is around 1%. This means that it affects about 2.5 million people in Germany. The affective disorder is usually debilitating and difficult to treat. There are likely various genes that make people more susceptible to bipolar disorder.

MPI scientists, led by research group leader Jan Deussing, wanted to know what function the risk gene adenylyl cyclase 2 has in this context. They used cell cultures and mouse models to understand the underlying molecular processes.

In cell culture experiments, they were first able to show that the risk variant of adenylyl cyclase 2 leads to a reduced ability to produce the signaling molecule cAMP, which is important for the transmission of information within the cell. Based on this, they artificially induced the corresponding adenylyl cyclase 2 mutation in mice.

As a result, the rodents showed mania-like behavior in the form of increased activity, stronger exploratory behavior and a more active approach to a novel environment. At the same time, their cognitive abilities were impaired; a side effect of bipolar disorder that is also observed in patients.

Further evidence of the connection with the psychiatric illness was found in the rodents' hyperresponsiveness to amphetamine. Just as in humans, administering amphetamine led to increased hyperactivity in the animals. In addition, the release of dopamine in the brains of the mice was increased—another effect that experts have observed similarly in people suffering from bipolar disorder.

One theory to explain mania in humans is based on the increased release of dopamine. Experts also assume that the balance between activating and inhibiting neuronal networks is disturbed.

In the mouse model, the MPI scientists also observed a strengthening of the activating networks. One of the most effective drugs for the treatment of bipolar disorders is lithium, which also showed its effectiveness in reducing mania-like symptoms in the mouse model.

Genes play an important role in the development of bipolar disorders, but environmental factors such as stress are also involved. This was confirmed in the mouse model: the rodents with the disease-associated gene variant reacted differently under stress, switching from a manic to a depressive phase earlier. This allows the researchers to draw conclusions regarding the corresponding signaling pathways that are affected.

Signaling molecule as a new therapeutic approach

The findings on the significance of adenylyl cyclase 2 could provide entry points for new, more effective and more individualized therapeutic approaches. "The mutation has a direct effect on the activity of the protein. The so-called second messenger signaling molecule cAMP, which triggers various signaling pathways, is involved here.

"It is found in many signaling pathways in the human body and therefore probably represents a favorable starting point for future therapies," says

Deussing.

The MPI scientist and his team selected the risk gene adenylyl cyclase 2 for their analyses because the disease-associated gene variant directly alters the activity of the protein. Most of the other gene variants identified for bipolar disorders have no direct effect on the activity of a protein, as they are not located in regions of the genome that directly code for proteins.

This makes them less suitable for the analysis of molecular processes in the mouse model, as the differences between humans and animals are much greater here. The properties of the proteins themselves are, however, almost identical in humans and mice.

More information: Paromita Sen et al, A bipolar disorder-associated missense variant alters adenylyl cyclase 2 activity and promotes mania-like behavior, *Molecular Psychiatry* (2024). DOI: 10.1038/s41380-024-02663-w

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