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Gene-environment interactions could influence several psychiatric disorders

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(PhysOrg.com) -- Male mice born with a genetic mutation that's believed to make humans more susceptible to schizophrenia develop behaviors that mimic other major psychiatric illnesses when their mothers are exposed to an assault to the immune system while pregnant, according to new Johns Hopkins research.

What was most surprising to researchers was that the mental illnesses the mice developed didn't look like schizophrenia, which they were genetically predisposed to, but more like mood and anxiety disorders, suggesting that one gene mutation can lead to different mental illnesses when influenced by the same environmental factor.

"Psychiatric diseases have genetic roots, but genes alone do not explain the entire disease," says Mikhail V. Pletnikov, M.D., Ph.D., an associate professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine and the study's leader. "When we study genes in conjunction with environmental challenges, we can better understand how diseases develop."

Pletnikov hopes his research, which appears in the December issue of the journal *Biological Psychiatry*, may be a small step toward eventually finding ways to prevent mental illnesses in humans. "The main goal here is to understand how gene-environment interactions take place on the molecular level so that you can find suitable drug targets, ultimately stopping these diseases before they happen," he says. "It all can start before birth."

Pletnikov and his team studied a mutant human form of the Disrupted-in-Schizophrenia 1 gene (mhDISC1), breeding mice in the laboratory with this mutation. This genetic variation is believed to be associated with vulnerability to major mental illnesses in humans. The mhDISC1 mice were impregnated, and at the ninth day of gestation (the equivalent to the middle or end of the first trimester in a human pregnancy), one group was given a drug to stimulate the immune system, forcing it to react as if it had been exposed to a virus like influenza or a parasite like toxoplasma. The rest of the pregnant mice — whose fetuses also had the mutated gene— were kept as a control group and their immune systems were left unchallenged.

The study found that prenatal immune stimulation in mhDISC1 mice produced behavioral abnormalities that were not present in the unchallenged mice: elevated anxiety, depression-like responses, an altered pattern of sociability and a weakened response to stress. The unchallenged mice did not show those behaviors, even though they also had the mutant gene. Pletnikov says the findings suggest that the same mutation, in this case mhDISC1, can lead to different illnesses, depending on interactions with environmental factors.

This may provide an explanation, he says, for why the extended Scottish family in which scientists first discovered this genetic mutation had members who suffered not solely from schizophrenia but also from major depression and bipolar disorder. “This one gene mutation can lead to very different clinical manifestations,” Pletnikov says.

Along with the behavior differences, Pletnikov and his team also found that parts of the brain, including the amygdala and the hypothalamus, were smaller in the mice that had been prenatally challenged. A similar abnormality can be found in those same areas of the brain in humans with major depression and bipolar disorder.

Previous studies have suggested that the prenatal immune response to a microbe — be it a major illness or just transient flu-like symptoms barely noticed by the pregnant woman — may be responsible for the increased incidence of adult psychopathology in humans. But this hypothesis, Pletnikov says, has been difficult to prove. Using this mouse model, he suggests, is a valuable way to study the relationship between gene-environment interactions and mental illness, and should be replicated to find more of these interactions to gain a better understanding of these relationships.

Future studies, he says, will try to sort out whether different timing or stimulating different parts of the immune system might lead to specific types of mental illness, as well as explore the consequences of other environmental adverse events such as stress or drug abuse.

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