Moms can transmit psychiatric trouble to kids, according to study

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Individual symptoms, such as anxiety, avoidance and a heightened response to stress, can be transmitted from mother to child and even grandchildren by multiple nongenetic mechanisms, a new study by

investigators at Weill Cornell Medicine and other institutions shows. The pre-clinical findings, published May 13 in *Nature Communications*, may lead to tools to predict if a child is at risk of developing behavioral problems later in life after exposure to stress signals in the womb.

"Genetic and nongenetic inheritance are different but complementary mechanisms to pass information from one generation to the next," said senior author Dr. Miklos Toth, a professor of pharmacology at Weill Cornell Medicine. "It will be necessary to develop tools to determine if the familial occurrence of a disease is based on a nongenetic, as opposed to genetic, mechanism. On a positive note, nongenetic, in contrast to genetic, inheritance of disease is not inevitable and, if recognized in time, may be prevented."

Studies in humans have previously suggested mothers can pass down behavioral traits to their children and grandchildren in a nongenetic manner. Grandchildren may be affected because fetuses produce early precursors to sperm and oocytes as they develop in the womb. A well-documented example of this transmission is the increased vulnerability of adult children and grandchildren of Holocaust survivors to psychological stress.

Because it would be unethical to perform controlled experiments on interactions between women and their developing or newborn children, the mechanisms by which these behavioral symptoms are passed on have been difficult to determine. So Toth and colleagues turned to mice, where they could separate the genetic effects of maternal influence on new generations from those that occur in the womb and after birth. Their strategy was to transfer offspring at various stages of development; for example, when the embryo was 1 day old or immediately after birth, to a surrogate mother.

The group began with female mice missing one copy of a serotonin

receptor, one of a family of proteins found on the surface of nerve cells that transmit the message carried by the neurochemical serotonin to the cell's interior. Reduced activity of serotonin or its receptors is associated with anxiety, depression and stress disorders in humans and similar behavioral traits in mice.

The scientists found that mutant females, in addition to their behavioral symptoms, showed signs of inflammation and immune activation during gestation that were transmitted to their fetuses. Newborn mice that didn't inherit the serotonin receptor mutation nevertheless showed similar signs of immune activation, and the males later developed anxiety-like behavior. Studies by others have shown that when high levels of inflammatory cells are present in an individual, some of these cells can enter the brain and lead to psychiatric problems. These studies raise the possibility that one mechanism for the nongenetic transfer of a behavioral trait is through the immune system, Toth said.

Although some of the grandchildren displayed immune system aberrations and behavioral symptoms, embryo-transfer experiments demonstrated the transmission was not direct from the grandmother. Instead, the whole process appeared to start anew, passing from the affected mother to her child.

Another set of embryo-transfer experiments showed that a different behavioral trait in the mutant mice, a heightened response to stress, was directly transmitted to the grandchildren through nongenetic changes in the fetuses' developing oocytes.

"Our study helps explain why individuals, even within the same family, can display various combinations of anxiety, depression, bipolar disease and schizophrenia symptoms," Toth said. "We found that, at least in mice, each symptom can be passed on by a distinct mechanism."

The group then asked how an indicator of stress or infection makes its mark on an offspring's brain and persists to adulthood once it has been transferred from the mother. They turned to epigenetics, the study of how a series of chemical modifications to DNA, called methylation, can change how a gene is expressed but not the nature of its informational content. In the affected offspring, the scientists found these modifications on genes that are involved in nerve signaling and linked to behavioral traits.

"This paper begins to reveal what lies beneath the enigmatic and complex pathology of psychiatric disease, which is remarkably prevalent in today's society," said lead author Dr. Emma Mitchell, a former graduate student in Toth's lab and a clinical trial associate at Shionogi Inc.

With clues from the mouse studies, the team is investigating a bacterial infection that inflames human fetal membranes, called chorioamnionitis. They hope to identify small proteins produced in this condition that lead to immune system effects on the fetal brain. They are also trying to develop a blood test for signs of prenatal exposure to stress in newborns, who may then be periodically assessed and given extra support for cognitive and behavioral issues that develop as they grow up.

Toth emphasized many children are resilient and may never show signs of behavioral problems despite early exposure to adverse conditions. But early intervention can help ameliorate any problems a child may have before he or she grows more difficult to treat, he said.

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