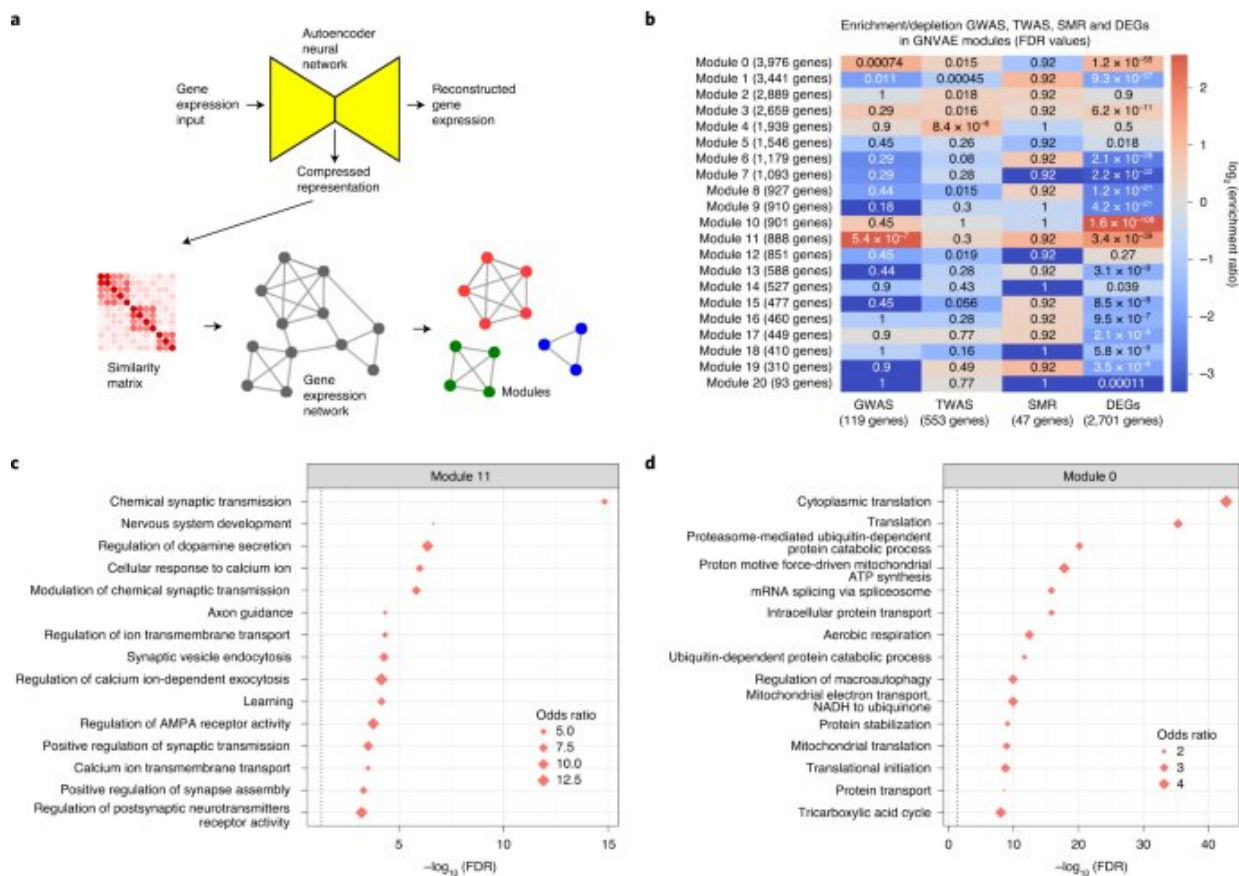


New study finds the placenta, not just the brain, plays a central role in genetic risk of schizophrenia

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Inferring a caudate nucleus gene coexpression network with deep neural networks. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-38140-1

More than 100 genes linked to the risk of schizophrenia seem to cause illness because of their role in the placenta rather than in the developing brain, according to a new study led by the Lieber Institute for Brain Development.

Scientists had generally assumed for over a century that genes for schizophrenia risk were principally, if not exclusively, about the brain. But the latest research, just published in *Nature Communications*, found that the [placenta](#) plays a much more significant role in developing illness than previously known.

"The secret of the genetics of schizophrenia has been hiding in plain sight—the placenta, the critical organ in supporting prenatal development, launches the developmental trajectory of risk," says Daniel Weinberger, M.D., senior author of the paper and Director and CEO of the Lieber Institute for Brain Development, located on the Johns Hopkins medical campus in Baltimore.

"The commonly shared view on the causes of schizophrenia is that genetic and environmental risk factors play a role directly and only in the brain, but these latest results show that placenta health is also critical."

The researchers found that schizophrenia genes influence a critical function of the placenta to sense nutrients in the mother's bloodstream, including oxygen, and exchange nutrients based on what it finds. The schizophrenia risk genes are more lowly expressed in the cells of the placenta that form the core of this maternal-fetal nutrient exchange, called trophoblasts, negatively affecting the placenta's role in nurturing the developing fetus.

The paper also identifies several genes in the placenta that are causative factors for diabetes, [bipolar disorder](#), depression, autism and [attention deficit hyperactivity disorder](#), or ADHD. The scientists, however, found

far more [genetic associations](#) with genes for schizophrenia than for any of these other disorders.

The researchers also discovered that the risk genes for schizophrenia found in the placenta may have a relatively greater effect on heritability, the likelihood of illness inherited from ancestors, than risk genes found in the brain.

"Targeting placenta biology is a crucial new potential approach to prevention, which is the holy grail of public health," says Gianluca Ursini, M.D., Ph.D., the lead author on the paper and an investigator at the Lieber Institute. "Scientists could detect changes in placental risk genes decades before the possible onset of a disorder, possibly even in the mother's bloodstream during pregnancy. If doctors knew which children were most at risk of developmental disorders, they could implement early interventions to keep them healthy."

The scientists also found interesting sex-based differences in the placenta risk genes. Different genes were associated with schizophrenia risk based on whether the placenta came from a male or female child. In pregnancies with male children, inflammatory processes in the placenta seem to play a central role. Previous research has shown males are more vulnerable than females to prenatal stress. Generally speaking, developmental disorders such as schizophrenia occur more frequently in men and boys.

The researchers also uncovered concerning results about COVID-19 pregnancies. The scientists studied a small sample of placentas from mothers who had COVID-19 during pregnancy and found the schizophrenia genes for placenta risk were dramatically activated in these placentas. The finding indicates that COVID-19 infection during pregnancy may be a risk factor for [schizophrenia](#) because of how infection affects the placenta. Lieber Institute scientists are pursuing this

possibility with research examining COVID-19 placentas to learn more.

The Lieber Institute researchers hope their ongoing study of the genes of the placenta will one day lead to new treatment and diagnostic tools, perhaps revolutionizing the field of prenatal medicine.

"In the modern era of molecular and genetic medicine, the standard treatment for a complicated pregnancy is still primarily bedrest," says Dr. Weinberger. "These new molecular insights into how [genes](#) related to disorders of the brain and other organs play out in the placenta offer new opportunities for improving prenatal health and preventing complications later in life."

More information: Prioritization of potential causative genes for schizophrenia in placenta, *Nature Communications* (2023). [DOI: 10.1038/s41467-023-38140-1](https://doi.org/10.1038/s41467-023-38140-1)

Provided by Lieber Institute for Brain Development

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