Researchers confirm postpartum depression heritability, home in on treatment mechanism

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Postpartum depression (PPD), a common subtype of major depressive disorder, is more heritable than other psychiatric conditions, yet the

genetics of PPD are understudied compared to these other psychiatric conditions., such as anxiety and bipolar disorder.

To remedy that, UNC School of Medicine researchers led an international team of researchers to conduct the largest-ever meta-analyses of genome-wide association studies (GWAS) to investigate the genetic architecture of PPD.

Published in the *American Journal of Psychiatry*, their research shows that approximately 14 percent of the variation seen in PPD cases can be attributed to common genetic factors. A patient's PPD is often not merely the result of environmental factors, such as past trauma. Instead PPD susceptibility carries a significant genetic component.

The researchers, led by first author Jerry Guintivano, Ph.D., assistant professor of psychiatry at the UNC School of Medicine, also revealed the genetic architecture of PPD, which they report significantly correlates with the genetic architecture of major depression, bipolar disorder, anxiety disorders, posttraumatic stress disorder, insomnia, and polycystic ovary syndrome. This means PPD symptoms likely occur as a result of the interplay between the same genes involved in these other psychiatric and hormone-related conditions.

"We studied about 1.1 million regions of the human genome," Guintivano said, "and we can see that PPD has a similar genetic signature to these other psychiatric conditions. The genetic risk factors for PPD appear to be shared by other disorders, such as major depression, bipolar disorder, and anxiety."

The researchers also discovered that genetic regions involving GABAergic neurons is associated with PPD, particularly in the thalamus and hypothalamus. GABAergic neurons control the release of the neurotransmitter GABA.

Brexanolone, the only FDA-approved PPD treatment, is known to circulate throughout the body and brain. UNC researchers had discovered earlier this year that the drug worked through GABAergic neurons to treat PPD symptoms so effectively. But now, this new research suggests brexanolone likely acts on GABAergic neurons in two particular brain regions.

"We view our finding as a refinement of the mechanism by which brexanolone works," Guintivano said. "We now have preliminary evidence suggesting we should target GABAergic neurons in the thalamus and hypothalamus for future research."

Although the researchers revealed much about the genetics of PPD, more than ever before, they still had a limited data set. The best genome-wide association studies pull data from hundreds of thousands of individuals with a particular condition, such as major depression or schizophrenia.

For their study, Guintivano and colleagues used 18 cohorts of European ancestry (17,339 PPD cases and 53,426 controls), one cohort of East Asian ancestry (975 cases and 3,780 controls), and one cohort of African ancestry (456 cases and 1,255 controls), totaling 18,770 PPD cases and 58,461 controls.

Although this was the largest PPD GWAS to date, Guintivano said there were still too few PPD cases to pinpoint specific locations within the genome that are associated with PPD risk.

More information: Jerry Guintivano et al, Meta-Analyses of Genome-Wide Association Studies for Postpartum Depression, *American Journal of Psychiatry* (2023). DOI: 10.1176/appi.ajp.20230053

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