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Scientists uncover 95 regions of the genome linked to PTSD

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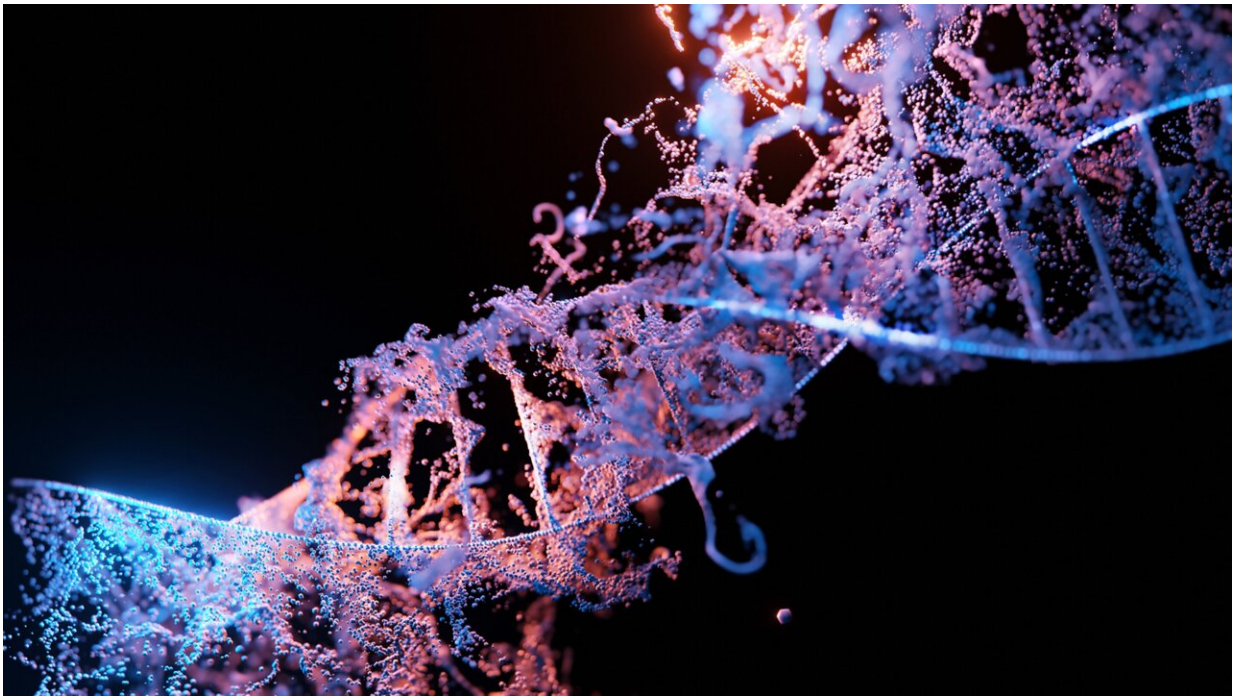

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In post-traumatic stress disorder (PTSD), intrusive thoughts, changes in mood, and other symptoms after exposure to trauma can greatly impact a person's quality of life. About 6% of people who experience trauma develop the disorder, but scientists don't yet understand the neurobiology underlying PTSD.

Now, a new genetic study of more than 1.2 million people has pinpointed 95 loci, or locations in the genome, that are associated with risk of developing PTSD, including 80 that had not been previously identified. The study, from the PTSD working group within the Psychiatric Genomics Consortium (PGC—PTSD) together with Cohen Veterans Bioscience, is the largest and most diverse of its kind, and also identified 43 genes that appear to have a role in causing PTSD. The work appears in *Nature Genetics*.

"This discovery firmly validates that heritability is a central feature of PTSD based on the largest PTSD genetics study conducted to date and reinforces there is a genetic component that contributes to the complexity of PTSD," said Caroline Nievergelt, co-first and corresponding author on the study and a professor in the Department of Psychiatry at the University of California, San Diego. Adam Maihofer, a genetic epidemiologist in Nievergelt's lab, was a co-first author as well.

The findings both confirm previously discovered genetic underpinnings of PTSD and provide many novel targets for future investigation that could lead to new prevention and treatment strategies.

"It's exciting that we see the exponential increase in loci with increases in sample size we see for other disorders," said Karestan Koenen, senior author on the study, an institute member of the Broad Institute of MIT and Harvard, and an investigator with the Stanley Center for Psychiatric Research at Broad. Koenen leads the Stanley Center's Biology of Trauma Initiative and the Global Neuropsychiatric Genomics Initiative, and is a professor of psychiatric epidemiology at the Harvard T. H. Chan School of Public Health. "This is a milestone for PTSD genetics."

Genetic roots

Previous twin and genetic studies, including an investigation by the same

team in 2017 and an expanded study in 2019, showed that PTSD has a genetic component, and that many genes contribute to the condition.

But these analyses pointed to different genetic loci across datasets, and many studies struggled to distinguish loci that were specific to PTSD risk from those that were also linked to conditions such as depression and cardiovascular disease. Genetic datasets have also historically focused on people of European ancestry, even though there is a disproportionately high burden of trauma and PTSD among people of African, Native American, and Latin American ancestry in the United States and globally.

In the new study, Nievergelt, Koenen, and other researchers from the PGC compiled data from 88 different genome-wide association studies, which use genetic data from large groups of people to look for associations between regions of the genome and the chance of developing a condition or trait.

In all, the dataset contained information about the risk of developing PTSD from more than 1.2 million individuals of European ancestry (including about 140,000 with PTSD), about 50,000 with African ancestry (including about 12,000 with PTSD), and about 7,000 with Native American ancestry (about 2,000 with PTSD).

Meta-analysis of the data revealed 95 loci strongly associated with PTSD, including 80 that had not been identified previously. Forty three genes appeared to play a role in causing PTSD, including some that affect brain cells called neurons, brain chemicals called neurotransmitters, ion channels (which allow ions to pass in and out of cells), connections between neurons called synapses, and the endocrine and immune systems. The researchers found that PTSD shared many genetic features with depression, as well as several PTSD-specific loci.

Although previous studies found a higher prevalence of PTSD in females than males, the researchers did not find evidence for this in their data. They examined the X chromosome, which earlier studies did not do, and found five loci linked with PTSD. But they add that these changes on the X chromosome would have similar effects in males and females.

To more deeply probe how PTSD genetics affect the brain, the team studied gene expression data and found that the cerebellum, the brain region that controls movement and balance, may be involved in the disorder in addition to regions scientists have previously connected with PTSD, such as the cortex and amygdala.

In particular, the research team found that interneurons, which connect motor and sensory neurons, were involved in PTSD risk. Future studies could help determine how key genes in these tissues and cells affect PTSD symptoms and behaviors.

"For the first time, we are approaching a genetic architecture for PTSD, which both validates prior understanding of some of the critical biology underlying trauma-related disorders, while also pointing towards exciting and novel new targets and mechanisms," said Kerry Ressler, a co-leader of the PGC—PTSD working group, chief scientific officer at McLean Hospital, and Professor of Psychiatry at Harvard Medical School. "These data are an important first step in next generation approaches to novel interventions for PTSD."

In line with previous findings, Nievergelt, Koenen, and their colleagues also found that polygenic scores—a calculation of a person's genetic chance of developing a certain condition based on millions of single-letter changes in their DNA—for PTSD risk are not readily translatable across populations. The researchers say this disparity highlights the importance of continuing to expand the depth and diversity of

populations included in future studies of PTSD.

"We know that trauma and PTSD disproportionately affects under-resourced populations globally, particularly African ancestry populations," said Koenen. "Our next steps will focus on addressing that inequity through partnerships with African scientists to make sure research in PTSD genetics benefits everyone equally."

More information: Genome-wide association analyses identify 95 risk loci and provide insights into the neurobiology of post-traumatic stress disorder, *Nature Genetics* (2024). DOI: 10.1038/s41588-024-01707-9

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