

Childhood abuse and biological sex linked to epigenetic changes in functional neurological disorder

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Functional movement/conversion disorder (FMD), part of the spectrum of Functional Neurological Disorder (FND), is a neuropsychiatric condition marked by a range of neurological symptoms, including tremors, muscular spasms and cognitive difficulties. Despite being the

second-most common cause of referrals to neurology outpatient clinics after headache, scientists have struggled to pin down the disorder's root cause. Female sex and a history of childhood trauma are factors associated with higher risk of developing FMD, but it's been unclear why.

A new study from investigators of the Brigham and Women's Hospital, in collaboration with researchers at the National Institute of Neurological Disorders and Stroke, demonstrated that FMD is characterized by epigenetic changes, and that women and childhood abuse survivors with FMD have different epigenetic profiles linked to this condition. Their study, which examined the genomes of over 100 individuals and was recently published in *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, is the first to demonstrate the occurrence of epigenetic changes in FMD.

"This study finally takes FMD out of a cloud of confusion and provides a neuroscientifically grounded explanation for why childhood trauma and female sex are associated with this disorder," said lead author Primavera A. Spagnolo, MD, Ph.D., scientific director of the Mary Horrigan Connors Center for Women's Health and Gender Biology and assistant professor of psychiatry at HMS.

FMD has been mired by a long history of stigma and misconceptions surrounding this condition and its causes. For centuries, FMD and other FND have been mislabeled as "hysteria," based on the idea that the symptoms originated from abnormal movement of the uterus. In the late 19th century, Freud proposed that FND was caused by psychological stressors induced by traumatic events, which were "converted" into neurologic symptoms. The influence of this theory left little room for alternative hypothesis for many years.

It wasn't until the early 2000s that scientists began to ask whether a

patient's genetics could contribute, together with exposure to [environmental factors](#), to FMD's development. More recently, they've begun investigating whether epigenetic changes—genome alterations caused by environmental factors—could be a mechanism underlying this disorder and its manifestations.

Researchers at Brigham and NINDS analyzed DNA from a cohort of 57 FMD patients and 47 controls, matched by childhood trauma exposure and biological sex. Using principal component analysis and enrichment analysis, they identified a core of epigenetic changes at the level of biological pathways implicated in chronic stress and [chronic pain](#), including immune-related pathways. However, at the transcriptional level—the process of copying out the DNA sequence of a gene into messenger RNA—female patients and those with an history of childhood trauma showed distinct profiles.

"We were astonished by the fact that there was almost no overlap," Spagnolo said. "FMD subjects that are female or have a history of [childhood trauma](#) present unique epigenetic changes that may explain why those subtypes of patients have different disease characteristics."

The group hopes that other researchers can use their findings to further understand the role of genetic and environmental interactions in FMD and other poorly understood functional disorders. Also, they hope that their approach of focusing on the biological sex most associated to the disease may be applied to the investigation of many other medical conditions characterized by sex-disparities.

"One next step is to replicate these findings in other patient populations," Spagnolo said. "The other is to do a deep dive into the [epigenetic changes](#) that we have observed in pathways related to [chronic stress](#) and pain and understand how those changes relate to what is happening at the clinical level."

More information: Primavera A. Spagnolo et al, Methylome changes associated with functional movement/conversion disorder: Influence of biological sex and childhood abuse exposure, *Progress in Neuro-Psychopharmacology and Biological Psychiatry* (2023). [DOI: 10.1016/j.pnpbp.2023.110756](https://doi.org/10.1016/j.pnpbp.2023.110756)

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