Variants in synaptic scaffolding protein PPFIA3 discovered to cause new syndromic neurodevelopmental disorder

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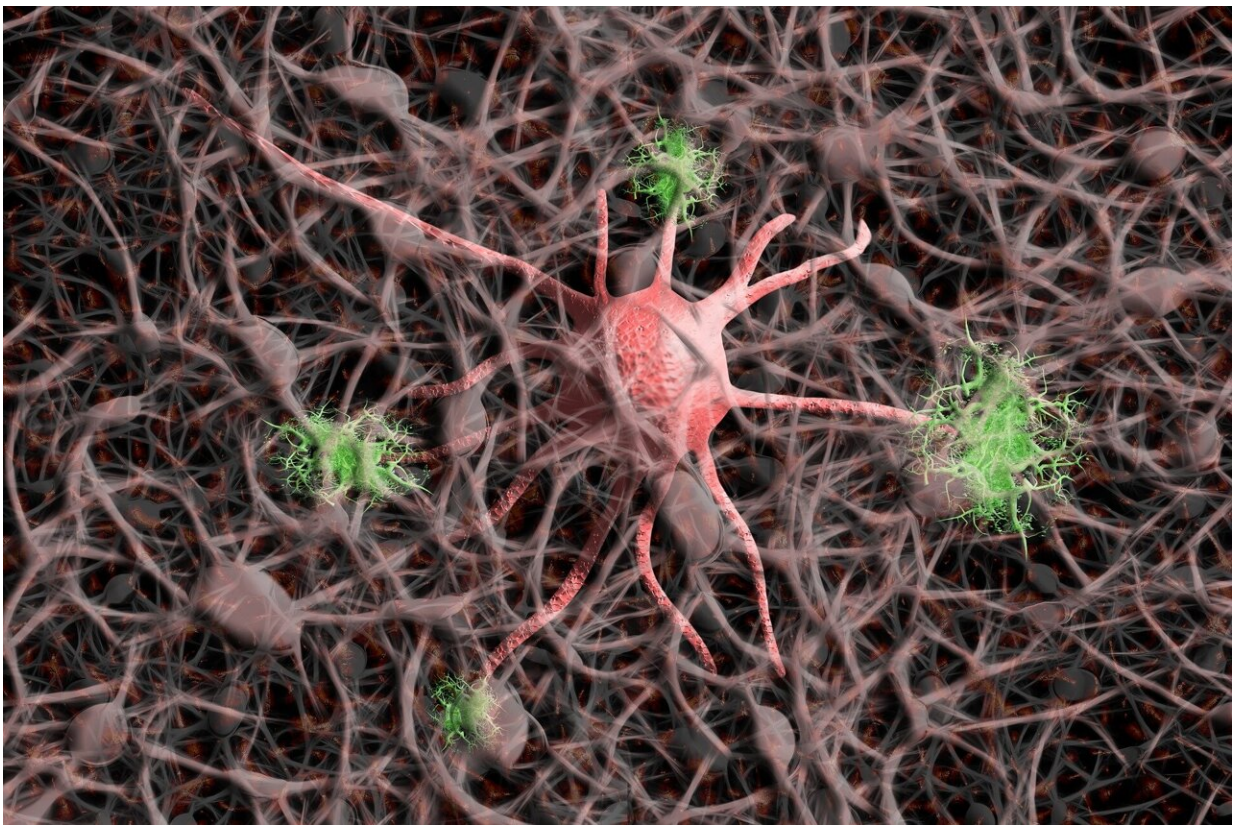

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An international collaborative study has recently discovered that variants in the PPFIA3 gene cause a previously unknown syndromic

neurodevelopmental disorder.

The study was published in the *American Journal of Human Genetics*. The research was led by postdoctoral scientist Dr. Maimuna Paul and child neurologist Dr. Hsiao-Tuan Chao, an assistant professor at Baylor College, a faculty member with the Cain Pediatric Neurology Research Foundation Laboratories at the Jan and Dan Duncan Neurological Research Institute (Duncan NRI) at Texas Children's Hospital, and an investigator at the McNair Medical Institute with The Robert and Janice McNair Foundation

The PPFIA3 gene produces the protein-tyrosine-phosphatase, receptor-type, f-polypeptide-interacting-protein-alpha-3 protein, which is a scaffolding protein present in neurons. PPFIA3 is important for the formation and function of synapses—structures that act as the junctions between neurons and are critical for proper communication between them. While the important biological role of this protein was evident, this is the first study to link a human neurological disease to PPFIA3 dysfunction.

"In 2019, we received our first referral for an individual with a rare PPFIA3 variant from the Undiagnosed Diseases Network," Dr. Chao said. "Using GeneMatcher to identify and collaborate with several researchers around the globe allowed us to discover and study 19 additional individuals with variations in this gene. So far, we identified seventeen unique PPFIA3 variants from 18 families."

The 20 individuals reported in this study exhibited delayed development, intellectual disability, hypotonia, dysmorphisms, microcephaly or macrocephaly, autistic features, and epilepsy.

PPFIA3 protein domain analysis and molecular modeling revealed that most of these variants were located in the coiled-coil domain and SAM1

domain, regions that are critical for this protein to perform its key biological functions in neuronal communication.

"To determine the disease-causing capacity of PPFIA3 variants, we turned to fruit fly models in which several powerful genetic tools exist to study disease gene variants," added lead author Dr. Maimuna Paul. "Using those, we generated transgenic fruit flies expressing either the normal version of the human PPFIA3 or five versions of the human variant protein. Flies with the altered PPFIA3 protein exhibited defects in multiple developmental processes and synapse formation."

They found that in fly embryos, the lethality due to loss of both copies of fly liprin-α could be partially reverted by the expression of the normal version of human PPFIA3, which suggests a partial functional conservation between human and fly versions of this protein. Together, several survival and behavioral assays in fruit flies suggested that the severity of the symptoms in the affected individuals and flies may correlate with the location and type of PPFIA3 variants.

"The clinical findings and functional fruit fly assays together helped us conclude that these 20 individuals have a newly recognized neurodevelopmental disorder caused by the loss of PPFIA3 function," Dr. Chao said. "This study laid a solid foundation for our future efforts to better understand the underlying disease-causing mechanisms of this disorder. This improved understanding may in the future uncover therapeutic interventions for individuals with PPFIA3-related neurodevelopmental conditions."

More information: Maimuna S. Paul et al, A syndromic neurodevelopmental disorder caused by rare variants in PPFIA3, *The American Journal of Human Genetics* (2024). DOI: 10.1016/j.ajhg.2023.12.004

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