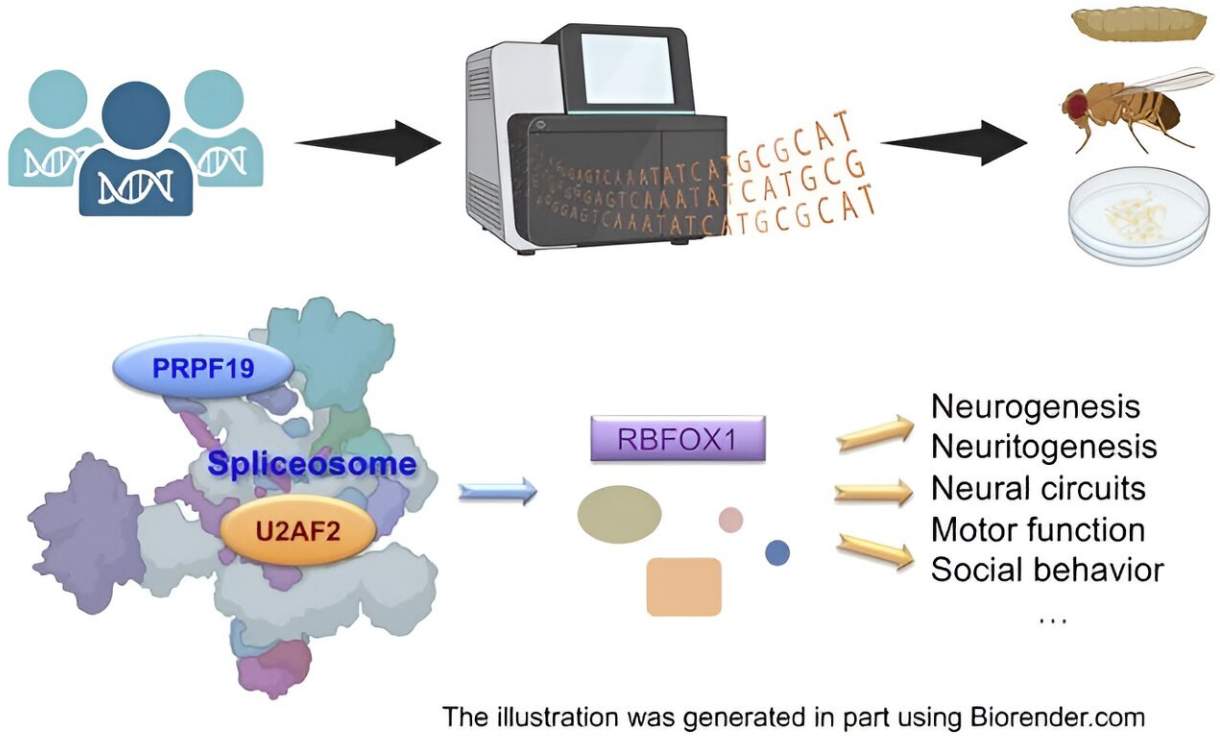
Researchers identify three genes associated with neurodevelopmental disorders

November 28 2023



Graphical abstract. Credit: *Journal of Clinical Investigation* (2023). DOI: 10.1172/JCI171235

An international study group led by researchers of Children's Hospital of Philadelphia (CHOP) have identified how three novel genes cause neurodevelopmental disorders. Researchers now have a better sense of the genes' roles in human brain development and function and their ability to serve as potential therapeutic targets in the future. The findings were recently published online by the *Journal of Clinical Investigation*.

Over the last couple of decades, researchers have identified more than 1500 genes in different signaling pathways associated with neurodevelopmental disorders. On average, about one third of patients with neurodevelopmental disorders receive a genetic diagnosis. However, little is known about how these genes are networked and how their malfunction leads to these disorders.

Prior research in other disorders has shown that issues related to gene splicing may be to blame. Before being turned into proteins, genes are transcribed into introns, or strands of RNA that do not code for proteins, and exons that code for proteins. Introns are removed in a process called splicing, which is carried out by a protein complex called the spliceosome.

Variants impacting the spliceosome have rarely been implicated in neurodevelopmental disorders. However, through a series of complex tests, researchers in this study showed that malfunctions in the spliceosome are responsible for some neurodevelopmental disorders.

"Using multiple techniques, including phenotyping, genomic sequencing, and modeling in fly and stem cells, we were able to map the genetic architecture of three genes associated with neurodevelopmental disorders, particularly developmental delay, intellectual disability, and autism," said Dong Li, Ph.D., a research faculty member in the Center for Applied Genomics and the Division of Human Genetics at CHOP and lead author on the study.

"Combining fly and human genetics helped us understand the mechanisms of how variants of these genes affect the machinery of the spliceosome and cause these disorders."

This study utilized genomic and clinical data from unrelated patients with neurodevelopmental disorders. Among the cohort, 46 patients had missense variants of the gene U2AF2, and six patients had variants of the gene PRPF19. In human stem cell and fly models, the researchers noticed issues with the formation of neurites, or protrusions on neurons that give them their shape, as well as issues with splicing and social deficits in the fly models.

Deeper profiling revealed that at third gene, RBFOX1, had missense variants that affected splicing and loss of proper neuron function. These findings were later compared with those of patients in the study, which confirmed that variants in the three genes can lead to neurodevelopmental disorders.

"We used fruit flies to study the effects of losing the function of these three genes one at a time and found that two genes independently led to brain structural and functional abnormalities, highlighting the essentiality of these genes in development," said study co-author Yuanquan Song, Ph.D., an associate professor from the Department of Pathology & Laboratory Medicine at CHOP.

"Apart from identifying patients with such variants in these genes for the first time, our extended translational modeling study efforts aimed to determine the underlying functions for these variants further elucidated their clinical relevance."

"Not only does this study identify three causative genes associated with neurodevelopmental disorders, but it helps us understand how critical pre-mRNA splicing is to the development of the central nervous system,"

said senior study author Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at CHOP.

More information: Dong Li et al, Spliceosome malfunction causes neurodevelopmental disorders with overlapping features, *Journal of Clinical Investigation* (2023). DOI: 10.1172/JCI171235

Provided by Children's Hospital of Philadelphia