

FRYL gene variants linked to a new neurological disorder

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A recent study from the lab of Dr. Hugo J. Bellen, distinguished service professor at Baylor College of Medicine and investigator at the Jan and Dan Duncan Neurological Research Institute (Duncan NRI) links the FRYL gene to a new neurodevelopmental disorder in humans. The researchers used fruit flies to establish that the loss of a functional copy of the FRY-like transcription coactivator (FRYL) gene is the underlying

cause of this new disorder in fourteen individuals.

The study was [published](#) in the *American Journal of Human Genetics*.

FRYL belongs to the Furry protein family, which is evolutionarily conserved from yeast to humans. The functions of FRYL in mammals are largely unknown, and variants in FRYL have not previously been associated with a [genetic disorder](#).

"This foundational study paves the way for not only a better understanding of the biological role of this gene but also opens avenues to study this new disorder," Dr. Bellen said.

Finding a cohort of 14 patients with FRYL variants

In collaboration with Dr. Wendy Chung, who was initially at Columbia and later at Boston Children's Hospital, the team recruited fourteen unrelated individuals through the Pediatric Cardiac Genomics Consortium, the SPARK consortium, and the GeneMatcher website. The individuals presented with [developmental delay](#), [intellectual disability](#), dysmorphic features, and other congenital anomalies in multiple systems including heart and gastrointestinal issues. A few also had autism, seizures, and low muscle tone.

To find the genetic cause for their symptoms, the team analyzed the DNA of these individuals. Upon examining their exome (i.e. the protein-coding part of the genome), they found that a majority of individuals were missing portions of the FRYL gene and the remaining individuals had missense mutations that are akin to misspellings in the gene, all of which result in a FRYL protein that is either non-functional or has a reduced function. Further, they found that FRYL variants were not genetically inherited but arose spontaneously in all individuals except one.

Using fruit flies to identify the cellular location and function of FRYL

"To understand in which cells and how this protein functions, we turned to the fruit fly model," said lead author Dr. Xueyang Pan, who is a postdoctoral fellow in the Bellen lab. Humans have two Furry [genes](#), FRY and FRY-like, whereas flies have one furry (fry) gene which bears close sequence resemblance to its human counterparts.

First, they found that this gene is expressed in multiple tissues in flies, including the central nervous system where it is present in neurons but not in glia, a cell type that provides physical and chemical support to the neurons.

Next, they found that the loss of both copies of this gene was lethal at the embryonic or [larval stage](#), which gave a clue that it plays a critical role during development. Dr. Pan and others then created mutant clones lacking fry in the wings and eyes of flies with a normal genetic background outside the clones. The loss of fry causes developmental defects such as multiple wing hairs in the mutant wing clones as well as small, rough eyes caused by cell death in the mutant eye clones.

Modeling human FRYL variants in fruit flies

The team then created transgenic flies with the four missense variants found in affected individuals using two different genetic methods. One of the variants exhibited traits characteristic of severe functional loss of the protein, whereas two others behave as partial loss-of-function variants.

In summary, these findings support the idea that fry is critical for the proper development of various organs in [fruit flies](#), and insufficient

functional levels of its human counterpart FRYL cause a previously unknown neurodevelopmental disorder. This study sets the stage for future explorations to discover gene mechanisms and explore potential therapies for this condition.

More information: Xueyang Pan et al, De novo variants in FRYL are associated with developmental delay, intellectual disability, and dysmorphic features, *The American Journal of Human Genetics* (2024). [DOI: 10.1016/j.ajhg.2024.02.007](https://doi.org/10.1016/j.ajhg.2024.02.007)

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