Transmembrane protein variants found to cause a new developmental disorder

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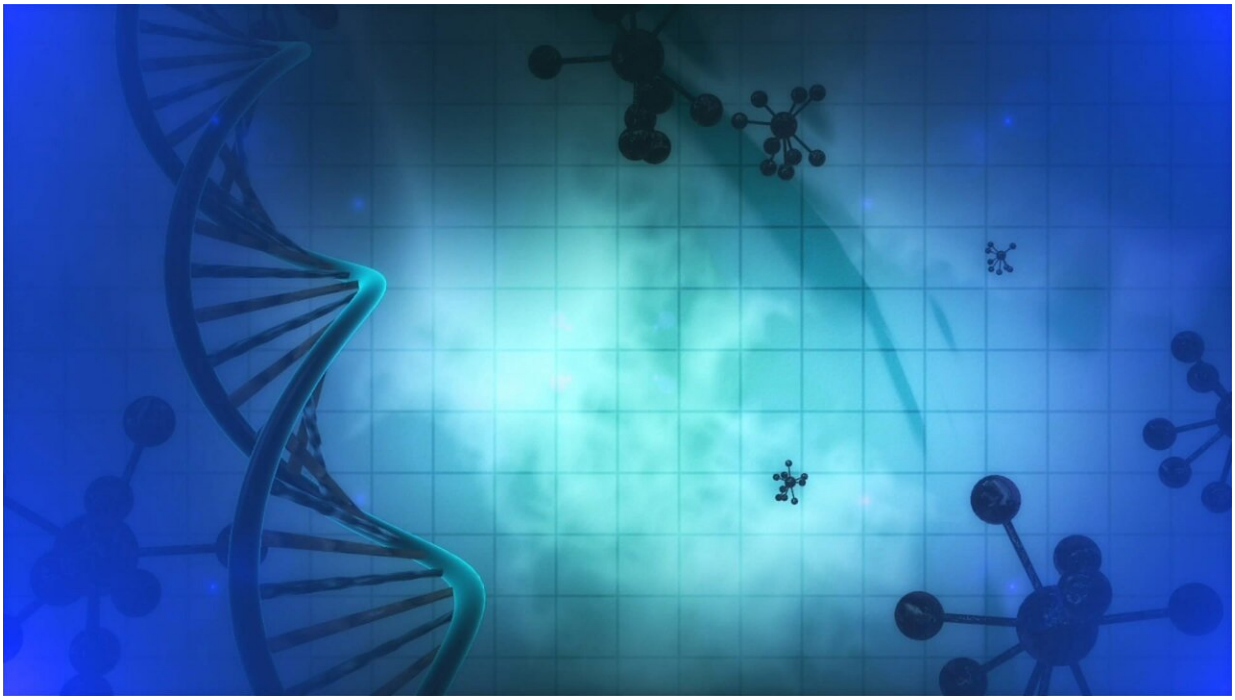

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A recent study has discovered a biological role of a specific transmembrane protein called TMEM208. The research, published in the Proceedings of the National Academy of Sciences, showed that a majority of fruit flies lacking this gene do not survive, and the few that do survive have many developmental defects.

Similarly, a child with variants in both copies of this gene presented with global developmental delays, seizures, and a multisystem disorder. The overlapping symptoms in flies and the affected individual suggested a defect in a fundamental developmental pathway as the cause of this condition.

Fly TMEM208 mutants show cell polarity defects and ER stress

Transmembrane proteins are a large family of proteins that span the entire width of the lipid bilayer that surrounds many types of cells and organelles in multicellular organisms, including animals and plants. Gene variants in the human TMEM family are associated with cancer, neurodegeneration, and several genetic disorders. Despite their abundance in most cells and functional importance, little is known about the biological role of each of these proteins.

The authors conducted a literature survey of ~300 human TMEM proteins which revealed that many of them were localized in the endoplasmic reticulum, an organelle of the cell that is important for proper folding, quality control, processing, and eventual sorting, and trafficking of proteins to their respective destinations.

The research was conducted in the lab of Dr. Hugo J. Bellen, distinguished service professor at Baylor College of Medicine and principal investigator at the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital

To study their individual roles, the Bellen team knocked down the expression of 38 of these genes in flies. One of the candidate genes identified from this screen was an uncharacterized fly version of human TMEM208.

To examine the role of the fly TMEM208 gene in greater detail, the Bellen team used CRISPR technology to generate flies that lack this gene. They found this gene is expressed broadly in many tissue types; its loss results in lethality in ~90% of progeny, and the few that do survive had malformed eyes and wings and died earlier.

"Interestingly, the symptoms in these flies hinted toward defects in the way cells are oriented and arranged in these tissues," lead author Dr. Debdeep Dutta said. "We conducted further experiments to test its role in planar cell polarity (PCP) and found that Tmem208 interacts with and regulates the levels of Frizzled, a key player in PCP. In addition, we found these escapers showed modest levels of endoplasmic reticulum stress—a cellular stress response triggered by improper folding and trafficking of proteins."

Human TMEM208 variants cause developmental defects and seizures

Through the Undiagnosed Diseases Network, the Bellen team identified a child who presented with global developmental delay, seizures, respiratory distress, and structural defects in the gut, bones, and heart.

Genome sequencing of this child's DNA revealed two variants in this gene—the first was a 'point mutation' analogous to misspelling in a word, and the second was a 'frameshift mutation,' which produces a truncated version of TMEM208 protein.

Next, Dr. Dutta and the Bellen team generated 'humanized' flies that mimicked these mutations which revealed that both human variants did not have sufficient functional TMEM208 protein. Moreover, skin cells derived from the patient had a decreased capacity to respond to ER stress.

"Finding a definitive diagnosis for the first documented patient with a rare disorder is always challenging," Dr. Bellen said. Our approach of using fruit flies not only helps us in a diagnosis but also points us to the precise molecular cause of this rare condition, which opens pathways and molecular targets that can be further leveraged to develop a targeted therapy.

More information: Debdeep Dutta et al, Loss of the endoplasmic reticulum protein Tmem208 affects cell polarity, development, and viability, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2322582121

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