

Mechanism identified for rare disorder of glycosylation

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Lynn Rimsky, research technologist at the Greenwood Genetic Center and coauthor on the paper, assesses zebrafish cartilage defects using confocal microscopy. Credit: Greenwood Genetic Center

Greenwood Genetic Center (GGC) researchers are reporting the

discovery of a mechanism that contributes to the tissue phenotypes seen in PMM2-CDG, the most common of the congenital disorders of glycosylation (CDGs).

CDGs are a group of over 130 [rare genetic disorders](#) caused by defects in the glycosylation of lipids and proteins. The phenotypes are variable, but often impact multiple body systems and involve neurological features. Patients with PMM2-CDG typically display hypotonia, developmental delay and intellectual disability, growth delays, movement abnormalities, and skeletal anomalies.

Using a zebrafish model of PMM2-CDG, GGC's Heather Flanagan-Steet, Ph.D., and her team of collaborators found that defects in the processing of N-cadherin, a protein that helps control cell adhesion, are responsible for the craniofacial and motility abnormalities seen in PMM2-CDG.

"Half of all proteins in the human body are glycosylated, so it is very difficult to mechanistically probe this heterogeneous group of disorders," said Flanagan-Steet, Director of Functional Studies at the Greenwood Genetic Center. "Finding the hypoglycosylated protein responsible for this CDG phenotype is like finding the needle in the haystack, but our novel approach to this disorder allowed us to not only identify this culprit, but also test therapeutic interventions."

Where most prior studies in CDGs have involved the analytical chemistry approach of identifying glycosylated proteins first followed by interrogating them for a possible connection to the disorders, Flanagan-Steet said that their 'top-down approach' of creating a zebrafish model is what accelerated the discovery.

"We studied the phenotype in the PMM2-CDG zebrafish models and let the biology tell us where to go," she said. "The biology of the phenotype

suggested possible pathways that might be disrupted which is what led us to N-cadherin."

N-cadherin processing allows for the adhesive properties of cells to fluctuate throughout normal development. When that process is disrupted, often through the altered expression of multiple proteases that control N-cadherin processing, the PMM2-CDG phenotype emerges. In the fish, that meant cartilage defects that led to craniofacial abnormalities and aberrant motility seen through altered swimming behaviors.

The researchers also found that by inhibiting furin proconvertases, one category of proteases that catalyze N-cadherin processing, multiple cellular and molecular phenotypes, including the cartilage and craniofacial defects in the zebrafish, could be rescued.

"By inhibiting the furin, we were able to improve the cartilage phenotype in over half of the fish studied suggesting that changes in the activity of these proconvertases initiate a cascade of events that leads to the skeletal disease in PMM2-CDG," said Flanagan-Steet. "This exciting outcome suggests possible nodes of therapeutic intervention for future studies, and most importantly provides hope for families around the world who have been impacted by this rare disease."

"This type of discovery represents one of the important next phases in CDG research—unraveling the elusive pathogenesis of these disorders by finding the proteins in the cell that are impacted by abnormal glycosylation," said Richard Steet, Ph.D., GGC's Director of Research. "We are also expanding our efforts to identify genetic modifiers of CDGs with our colleagues at the Clemson Center for Human Genetics (CHG). This will provide yet another promising avenue to therapies".

This work is published by *JCI Insight* with collaborators from the

University of Georgia, Sanford Children's Health Research Center, UT Southwestern Medical Center, and the Medical University of South Carolina.

More information: Elsenoor J. Klaver et al, Protease-dependent defects in N-cadherin processing drive PMM2-CDG pathogenesis, *JCI Insight* (2021). [DOI: 10.1172/jci.insight.153474](https://doi.org/10.1172/jci.insight.153474)

Provided by Greenwood Genetic Center

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