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# A cautionary tale on genome-sequencing diagnostics for rare diseases

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Children born with rare, inherited conditions known as Congenital Disorders of Glycosylation, or CDG, have mutations in one of the many enzymes the body uses to decorate its proteins and cells with sugars. Properly diagnosing a child with CDG and pinpointing the exact sugar gene that's mutated can be a huge relief for parents—they better understand what they're dealing with and doctors can sometimes use that information to develop a therapeutic approach. Whole-exome sequencing, an abbreviated form of whole-genome sequencing, is increasingly used as a diagnostic for CDG.

But researchers at Sanford-Burnham Medical Research Institute (Sanford-Burnham) recently discovered three children with CDG who are mosaics—only some cells in some tissues have the mutation. For that reason, standard exome sequencing initially missed their mutations, highlighting the technique's diagnostic limitations in some rare cases. These findings were published April 4 in the *American Journal of Human Genetics*.

"This study was one surprise after another," said Hudson Freeze, Ph.D., director of Sanford-Burnham's Genetic Disease Program and senior author of the study. "What we learned is that you have to be careful—you can't simply trust that you'll get all the answers from gene sequencing alone."

## Searching for a rare disease mutation

Complicated arrangements of sugar molecules decorate almost every protein and cell in the body. These sugars are crucial for cellular growth, communication, and many other processes. As a result of a mutation in an enzyme that assembles these sugars, children with CDG experience a wide variety of symptoms, including intellectual disability, digestive problems, seizures, and low blood sugar.

To diagnose CDG, researchers will test the sugar arrangements on a common protein called transferrin. Increasingly, they'll also look for known CDG-related mutations by whole-exome sequencing, a technique that sequences only the small portion of the genome that encodes proteins. The patients are typically three to five years old.

## A cautionary tale for genomic diagnostics

In this study, the researchers observed different proportions and representations of sugar arrangements depending on which tissues were examined. In other words, these children have the first demonstrated cases of CDG "mosaicism"—their mutations only appear in some cell types throughout the body, not all. As a result, the usual diagnostic tests, like whole-exome sequencing, missed the mutations. It was only when Freeze's team took a closer look, examining proteins by hand using biochemical methods, did they identify the CDG mutations in these three children.

The team then went back to the three original children and examined their transferrin again. Surprisingly, these readings, which had previously shown abnormalities, had become normal. Freeze and his team believe this is because mutated cells in the children's livers died and were replaced by normal cells over time.

"If the transferrin test hadn't been performed early on for these children, we never would've picked up these cases of CDG. We got lucky in this

case, but it just shows that we can't rely on any one test by itself in isolation," Freeze said.

Provided by Sanford-Burnham Medical Research Institute