

Rare diseases: On the verge of diagnosis

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Drs. Saunders, Thiffault collaborate internationally to discover gene-disease associations

Rare diseases are individually very rare, but collectively they're not rare at all, with one in 10 children diagnosed with a rare disease. New disease-gene assertions are being made at a stunning rate, with around 40 new genes discovered each month. This work is possible through genomic sequencing, where the DNA code is read for each patient and checked for variants, which are akin to spelling mistakes.

Many of these new disease-gene assertions are through the identification of de novo variants, which means the variant is not present in either parent. Such variants are interesting because they rarely occur and often tend to be pathogenic. However, if they are found in a new gene not yet associated with human disease, additional patients and other evidence is needed to assert a gene-disease relationship.

Researchers at Children's Mercy studied 21 new de novo variants in genes of unknown significance. In the following Q&A, Carol Saunders, PhD, Clinical Director, and Isabelle Thiffault, PhD, Director of Translational Genetics at the Center for Pediatric Genomic Medicine, talk about how this research could lead to better understanding of rare diseases.



Dr. Isabelle Thiffault (left) and Dr. Carol Saunders of the Center for Pediatric Genomic Medicine conduct research to link genes to rare diseases and eventually lead to treatments or cures.

What prompted you to conduct the study?

Dr. Saunders: We had a growing list of patients with interesting variants in new genes that had insufficient evidence linking them to disease in humans. This means we didn't have enough data to classify the variant as pathogenic and we couldn't just call it benign. Without further evidence, these patients and families are left without a diagnosis.

In hopes of finding answers, we shared information on patients with de novo variants in 21 new genes with researchers around the world to find more such cases. It takes more than one patient to establish a gene-disease relationship—more evidence and more replicates are needed to make genetic diagnosis.

Why are these genes significant?

Dr. Thiffault: The problem is trying to prove that they are significant—we don't always know. Many of these conditions are so rare that only a couple of people worldwide have the same particular disease—the aim is to find them!

Why is it important to collaborate with your peers around the world?

Dr. Saunders: One way we find additional patients with variants in our gene of interest is through an online matchmaking service that connects us to other researchers with similar patients. Sometimes it takes a while to get a match with a patient that a variant in the same gene, but it's these collaborations that lead to publishing new gene-disease associations and will ultimately give us the confidence to say this is diagnostic for a particular patient. We have ongoing research collaborations with colleagues in Italy, Netherlands, Canada, Australia, France, Belgium and the U.K.

Knowing that a gene is associated with a certain condition helps us understand the biology of humans, which may eventually lead to treatment or a cure.

How do you decide if a gene is linked to a disease?

Dr. Thiffault: As part of our study, we used a new scoring tool to assess the level of evidence for each gene-disease association. This incorporates case-level genetic data, functional studies, animal models which all together helps us determine if there's strong enough evidence for a gene-disease association. Having enough well-phenotyped patients with variants in a gene of interest is a necessary part of this—you can't just rely on animal modeling.

We're the first to publish this exercise for curating new genes with de novo variants identified through clinical testing, which we hope becomes the new model. We really view it as a community service and if everybody would share their case level data and variant curation, researchers and clinical labs would have so much more information and be able to provide accurate reporting for patients with rare disease.

We intend to repeat this exercise with a whole new list of ~100 genes. These findings not only provide patients with answers, but allows families to network with others affected by the same new genes.

Do other organizations share their data?

Dr. Saunders: Some do and some don't. We are one of a handful of clinical laboratories that share the interpretation of every clinically curated variant from our laboratory with a database called ClinVar, which other laboratories can freely access to see our interpretation. We get questions every week from people around the world trying to interpret variants in their own patients, and this exchange of information is extremely useful. If our interpretation disagrees with another lab, we work to resolve the issue. We find out what data we each have and how we came to the conclusion, so we can get the right data out there.

What is bench-to-bedside research and why is it important?

Dr. Saunders: Bench-to-bedside research is when results from our lab are directly used to develop new ways to treat patients in our hospital.

We've identified numerous treatable conditions in the lab. In some cases it's identifying a vitamin a child may be missing which can be absolutely life-saving. This would not be possible if we didn't have the kind of tools we have in our lab. These capabilities will continue to grow as we adopt new tools that can look at different types of variants in the genome. Translating that into clinical testing and what that means for patients is really important. We're helping change the course of people's lives for the better.

What is your hope for the next 10 years?

Dr. Thiffault: We have a limited understanding of the genome right now. Even though we can sequence the whole genome for the most part, we're only looking at 2 percent of gene sequences. There are about 8,000 genetic diseases, yet we don't know what genes go with half of these cases and within each gene there are thousands of potential variances.

I hope we really have a good understanding of the rest of the genome we don't understand to be able to provide answers to more patients and families.

What is the biggest takeaway for parents?

Dr. Saunders: I want parents to know the rate of new disease gene discovery is astonishing and just because they don't have an answer now, doesn't mean it's the end of the road. New genes and new information will lead to better understanding of rare diseases.

Over the course of our year-long study, at least half of the genes moved from limited evidence to strong or moderate evidence, which led to a diagnosis. So, it's important to re-evaluate things every year if you don't have any answers yet. We're always working on new research and new testing that will be meaningful for our patients and their families.



Dr. Thiffault (left) and Dr. Saunders shared information with researchers from around the world to collect evidence for establishing gene-disease relationships.

Read the full study: *On the verge of diagnosis: Detection, reporting, and investigation of de novo variants in novel genes identified by clinical sequencing.*

[<https://onlinelibrary.wiley.com/doi/full/10.1002/humu.23646>]

Learn more about [The Center for Pediatric Genomic Medicine at Children's Mercy.](https://www.childrensmercy.org/research/pediatric-genomic-medicine/)

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