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Q&A: Advanced genetic tools help researchers ID new neurodevelopmental syndrome

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In a recent study, a Yale-led research team described for the first time a rare neurodevelopmental syndrome that begins affecting patients during infancy and typically causes developmental delays, severe seizures, cardiac dysrhythmia, and recurring infection.

After conducting a genetic analysis on 18 individuals with similar symptoms—but for whom there was no established diagnosis—and comparing the results with other findings, the research team, led by Yale's Saquib Lakhani and Lauren Jeffries, was able to discern the genetic roots of what they determined was a syndrome shared by all of the patients.

According to their findings, published in the journal *Genetics in Medicine*, the newly defined syndrome—now known as Jeffries-Lakhani Neurodevelopment Syndrome, or JELANS—arises when patients have variants in a gene called CRELD1, which has known roles in the cardiac and immune systems but had never before been characterized in patients with neurodevelopmental symptoms.

The discovery would not have been possible, researchers say, without next-generation DNA sequencing, a tool refined within the past decade that can rapidly sequence thousands of genes or even entire genomes.

"The advancements in DNA sequencing have completely transformed how we approach patients," said Lakhani, clinical director of Yale School of Medicine's Pediatric Genomics Discovery Program and senior author of the study.

With next-generation sequencing, researchers can uncover alterations in genes—also known as variants—shared by people around the world with similar symptoms. That allows them to draw connections that may have been missed when relying on symptoms alone.

In this case, and in a growing number of others, it means a disorder that had gone undiscovered is now named and defined, giving those affected by it much-needed answers and researchers a clearer route to treatment development.

Lakhani and Jeffries, an associate research scientist and medical geneticist with the Pediatric Genomics Discovery Program and lead author of the study, recently sat down with Yale News to discuss JELANS and the process of identifying a new syndrome, how the program's "gene-centric" approach to care yielded this discovery, and how it benefits families facing these rare disorders.

This interview has been edited and condensed.

This study included numerous individuals experiencing similar symptoms. Why did you suspect that this group of symptoms might in fact be a previously unknown syndrome?

Jeffries: It may be surprising to know that, even in 2024, while over 7,000 rare genetic disorders are already defined, the majority of our 20,000 genes are still not well understood. So, while comparing clinical notes across patients is still critical to our work, in the Pediatric Genomics Discovery Program we utilize a "gene-centric" approach, meaning that instead of comparing symptoms, we look for genetic differences as our first step.

In this particular case, GeneDx—a commercial lab headquartered in Connecticut that we collaborate with—had genetically screened 10 patients who had compound heterozygous variants for the CRELD1 gene. That means that the patients had two variants in this gene, one coming from their mom and one from their dad. GeneDx then asked if we wanted to look into this further. Most of the patients in our full cohort ended up sharing the exact same change, which was remarkably suspicious.

What is needed to identify a novel syndrome?

Lakhani: In general, you need a certain number of patients and consistency in the characteristics of those patients. You also typically need basic science evidence—which could be biochemical, cell system, or animal model testing—that corroborates that the variation in the gene in question is associated with the condition in the patients you've identified, and that it causes some changes or abnormalities in the scientific testing. And ultimately you need to be able to get a paper describing the syndrome published, indicating that your peers have accepted the evidence defining the syndrome.

How were you able to determine the characteristics of JELANS?

Jeffries: We worked with an incredible team of researchers to find 18 patients from 14 families in the U.S., Canada, and the U.K., including one who we cared for in our pediatric ICU here at Yale. When no established diagnoses were identified for them, their genetic data was analyzed under the research lens. From this deeper analysis of genetic data, the CRELD1 gene emerged as the candidate to study.

We also looked through their clinical data to see what patterns might exist. All of the patients had low muscle tone at birth. In the majority of cases, epilepsy developed by around five months of age, and all patients had seizures at some point in time. Cardiac dysrhythmias and recurrent infections were also common, and we noticed that several patients had shared facial features such as large-appearing eyes.

Lakhani: We then studied the gene in frogs. We first wanted to see what happened when we removed the gene, because that can give us a clue as to what the gene is important for. When we fully knocked out the gene, the frog embryos did not survive. But when the gene was partially knocked out, we found that there were a lot of developmental defects in

these frogs.

Interestingly, surviving tadpoles with the gene significantly knocked out were more susceptible to developing seizures. That showed us that CRELD1 is important for the development of the embryo overall and that if it's limited in function, it can also increase the susceptibility to seizures.

However, these patients aren't missing CRELD1, they have variations in it: letter changes in the gene that result in changes to the CRELD1 protein but do not cause the protein to completely disappear.

When we tested the patient forms of the protein in tadpoles, we found that they did not function the same way as the normal form of CRELD1. Taken together, the clinical and basic science data provides solid evidence that JELANS is a new syndrome caused by variants in the CRELD1 gene.

Is there additional research needed on this syndrome?

Jeffries: As more patients are identified to have JELANS, I think we'll further refine the clinical syndrome and begin to uncover the molecular mechanisms underlying the symptoms. For instance, we'll get a better sense of whether the immune system is affected, leading to the increased risk of infection, and how common cardiac dysrhythmias are and what's the underlying cause.

Why is it important to describe and name a syndrome beyond simply treating the symptoms?

Lakhani: The families of children with undiagnosed diseases frequently go through wandering medical diagnostic odysseys—doctor after doctor,

test after test—without ever reaching an answer.

Parents can go their entire lives wondering what happened to their child, whether their other children can get the disease, whether they did something to cause it. Knowing a syndrome name and the underlying genetic cause can be so powerful by bringing a sense of closure and relief to families.

Jeffries: It's validating. It's clarifying. With a syndrome name, families can find a community and move forward. Especially for rare disorders, in syndrome support groups families can share their stories, discuss what treatments have worked and what treatments haven't, and just talk to other parents who understand.

Lakhani: And in some countries, it can be hard to get resources without a specific diagnosis. With a diagnosis, families may qualify for support services, so it can have practical implications even beyond the knowledge.

In this case, how will the discovery inform treatment?

Jeffries: Understanding this syndrome at the molecular level is essential for the ultimate goal of finding treatment that's targeted and specific to this disorder and that is meaningful in helping patients thrive.

Is this an approach others can use?

Lakhani: Everyone who cares for patients should be thinking about this. For many years, as physicians we would look at certain patients and say, "They've got something underlying." But we could never put our finger on it because we didn't have a robust way to test broadly for genetic conditions; we had to just do the best we could.

But we now have a tool that allows us to see if there's a genetic explanation for a child's condition. We no longer have to just do the best we can with limited information. We can actually try to find answers. It's something that has had an incredible impact and it's something we regularly encourage others to pursue.

Jeffries: And while the discovery of JELANS was through a research endeavor, we want to be clear that DNA sequencing is not just for uncovering new syndromes. Genetic testing can be ordered by a doctor and is available for patients with all sorts of descriptive diagnoses, such as autism, intellectual disability, epilepsy, and cerebral palsy, where symptoms determine the diagnosis.

A patient's genes may reveal a more specific diagnosis than any constellation of symptoms can define; understanding the molecular cause can ultimately give patients clearer answers and, hopefully, more targeted treatments.

More information: Lauren Jeffries et al, Biallelic CRELD1 variants cause a multisystem syndrome, including neurodevelopmental phenotypes, cardiac dysrhythmias, and frequent infections, *Genetics in Medicine* (2023). DOI: 10.1016/j.gim.2023.101023

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