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Mutation in NFKB2 gene causes hard-to-diagnose immunodeficiency disorder CVID

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A 30-year-old woman with a history of upper respiratory infections had no idea she carried an immunodeficiency disorder – until her 6-year-old son was diagnosed with the same illness.

After learning she has common variable immunodeficiency (CVID), a disorder characterized by recurrent infections, such as pneumonia, and decreased antibodies, the woman, her husband, their three children and parents joined a multidisciplinary University of Utah study and researchers identified a novel gene mutation that caused the disease in the mom and two of her children. The researchers discovered that a mutation in the NFKB2 gene impairs a protein from functioning properly, which interferes with the body's ability to make antibodies and fight infection. The children's father did not have the mutation, nor did a third sibling or the woman's parents.

Another 35 people with CVID were tested for the gene mutation, and one other unrelated person was found to have it. His father wasn't tested, but no one else in his family immediate family had the mutation, so the researchers don't know whether he could have inherited the disorder from his father or developed the gene mutation sporadically.

CVID typically doesn't present with symptoms until adulthood and it's not uncommon for someone to reach their 20s, 30s or beyond before being diagnosed, according to Karin Chen, M.D., co-first author of the study published Thursday, Oct. 17, 2013, in the *American Journal of Human Genetics* online. Identifying the NFKB2 mutation will make it

easier to recognize and treat the disorder, particularly after a test developed in conjunction with the study by ARUP Laboratories becomes available as early as next May.

"If we can screen patients for genetic mutations, we can identify disease complications associated with that gene, start looking for them and treating them sooner," says Chen, instructor of pediatric immunology at the University's School of Medicine.

There's no cure for CVID, but it can be treated with monthly infusions of antibodies at a cost of $5,000 to $10,000 per treatment.

Identifying the gene mutation and developing the test for it took approximately two years, a fast turnaround made possible because of the multidisciplinary research that the University of Utah Health Sciences encourages and is known for doing. The study involved researchers from the U School of Medicine's Departments of Pediatrics, Pathology, Human Genetics and Program in Molecular Medicine and ARUP, which is a University-owned, nationwide testing laboratory.

Emily M. Coonrod, Ph.D., a research scientist with the ARUP Institute for Clinical and Experimental Pathology, is co-first author with Chen. Karl V. Voelkerding, M.D., also of the Institute for Clinical and Experimental Pathology and a U professor of pathology, is the senior author.

CVID probably is underdiagnosed, making it hard to know how common it is. But the disorder is estimated to occur in one in 10,000 people to one in 50,000 people, meaning it is one of more common types of immunodeficiency disorders, according to Chen. University physicians currently treat about 150 CVID patients in the Intermountain Region. Historically, CVID has been diagnosed clinically by doctors who are aware of the symptoms and then have individuals tested for low levels of

antibodies.

No mutation had been identified in NFKB2 before this study. But Attila Kumánovics, M.D., assistant professor of pathology and co-author on the study, had perused the medical literature and found that a mouse model had been developed that carried a similar mutation in the NFKB2 gene and also had immunodeficiency. That was a key development, according to Voelkerding. "This meant that the finding in our patients could be correlated to literature."

To identify the gene mutation, the researchers drew on the clinical experience of two U of U physicians who have studied and treated CVID patients: Harry R. Hill, M.D., professor of pathology and pediatrics, and John F. Bohnsack, M.D., professor of pediatrics, who also are co-authors of the study. Hill donated DNA samples he'd collected from 34 CVID patients over many years and Bohnsack, a pediatric immunologist, recommended for the study two families he'd worked with, including the mom and her three children and a family whose son he'd diagnosed with the disorder.

The researchers performed exome sequencing in the two families and used bioinformatics approaches, including the VAAST algorithm developed at the University, to rapidly identify gene mutations that can cause disease. VAAST identified the NFKB2 mutation in the mom and her two affected children and in the patient in the second family. Sequencing of the NFKB2 gene in the 34 other CVID patients did not reveal any other NFKB2 mutations.

"We know the NFKB2 mutations caused the disease in the four patients in this study, but it's difficult to predict how common NFKB2 mutations will ultimately be in other CVID cases," says Voelkerding.

But the discovery suggests that the NFKB2 genetic pathway is an entirely

new mechanism for immune deficiency, according to Lynn B. Jorde, Ph.D., professor and chair of the U Department of Human Genetics and co-author on the study. "Finding the cause of a rare disease often teaches us a lot about other diseases," he says. "It's like this little window, but it opens up a big room."

Provided by University of Utah Health Sciences