Newly discovered form of childhood ALS caused by single gene

By Zack Fishman
May 31, 2021

A DNA analysis of several patients with four particular variants of a metabolic gene found that the patients have a newly identified form of early-onset amyotrophic lateral sclerosis, or ALS, a rare neurodegenerative disease usually diagnosed in older adults.

The study, published Monday in *Nature Medicine*, found that the disease-causing gene variants lead to an uncontrolled creation of a category of fats that can impact motor neurons, which control voluntary movement. The gene, SPTLC1, is the first single-gene cause of ALS related to metabolism.

The findings give scientists the insight to begin devising treatments for this form of ALS, and the authors of the study successfully tested a treatment that turned off the variants in skin cells in petri dishes.

Carsten Bönnemann, a senior author of the paper, said the findings add metabolic disease to the list of possible causes of ALS, and he believes that other forms of the disease should be investigated for similar causes.

"Our results show for the first time that ALS can be caused by changes in the way the body metabolizes lipids," said Bönnemann, a senior investigator at the National Institute of Neurological Disorders and Stroke, a part of the U.S. National Institutes of Health. "We hope these results will help doctors recognize this new form of ALS and lead to the development of treatments that will improve the lives of these children and young adults."

Amyotrophic lateral sclerosis, also known as Lou Gehrig's disease, is a disease of the nervous system, in which muscle control is progressively lost as the condition affects the brain's motor neurons, which control voluntary movement. ALS is a fatal disease with no cure, and there are as many as 30,000 ALS cases in the U.S. and about 223,000 in the world.

ALS does not have a known cause, beyond the 5% to 10% of cases that are genetically inherited, and it most frequently occurs in people between the late 40s and early 60s — very rarely at early ages.

According to Bönnemann, a pediatric neurologist, the investigation began when he examined Claudia Digregorio, an Italian patient who as a teenager traveled from Italy to the NIH, in Maryland, after developing an unknown, debilitating disease. Digregorio — who was blessed by Pope Francis and is now 20 — first showed ALS-like symptoms that began in early childhood, and a progressive weakening of her muscles required her to get

a surgically implanted tracheostomy to help her breathe, as well as a wheelchair to move.

Genetic sequencing of her and her family's DNA showed that she alone possessed a variant of the SPTLC1 gene, which encodes a protein that helps make compounds known as sphingolipids. The gene variant was previously associated only with a sensory disorder that did not match what was seen in Digregorio or, eventually, any of the other patients in the study, Bönnemann said.

He and his colleagues reached out to international collaborators and soon found other people with early-onset ALS and one of four SPTLC1 variants. In the study, the authors sequenced part of the DNA of 11 patients to understand the effects of these variants.

The variants in six patients were found to be absent in their parents and must have arisen as a mutation. These patients developed problems with walking and muscle stiffness at an early age, and their conditions worsened to the point of having varying degrees of challenge with walking and breathing, similar to Digregorio's. Showing symptoms in their motor neurons, all the patients met the definition of ALS.

The other five subjects were from a family in which all the children carried an SPTLC1 variant, inherited from the father, and they had experienced different degrees of the disease.

The researchers found that the variants caused the SPTLC1 protein to become misshapen, altering the function of the protein complex it is a part of: serine palmitoyltransferase, or SPT. The group of proteins create sphingolipids, which form structural components of cells and are necessary for cell function but are toxic in excess amounts.

But in cells with the ALS-causing gene variants, SPT is left unregulated, making it go into "constant overdrive" and overproduce ceramides and other sphingolipids in motor neurons, according to Bönnemann.

The study's authors concluded that the four variants in the SPTLC1 gene cause this unusual form of ALS. Bönnemann expressed interest in investigating similar effects in other ALS patients, particularly those whose condition is not caused by genetics.

"We have a clean single-gene cause for this; we know exactly what's happening," Bönnemann said. "It's now worthwhile to look for ceramides in sporadic ALS and see whether they're partly driving the disease as well."

Bönnemann and his team also created an experimental treatment that silenced the ALS-causing gene variants and tested it on skin-cell lines taken from the patients. All people have two copies of each gene, one from each parent, and all four SPTLC1 variants are dominant, meaning they provide the blueprint of the protein even if only one of a person's two SPTLC1s is a harmful variant.

The treatment turned off the harmful variants in the skin cells, allowing the remaining healthy copy to dictate the creation of properly functional proteins.

"It's precision medicine in a dish at this point in time, but it's proof of principle that inactivation of the mutation will be therapeutically beneficial," Bönnemann said.

Another possible kind of treatment, according to the neurologist, is a down-regulating drug that limits the production of sphingolipids within healthy boundaries. Screening drug libraries with cell lines from these patients could identify a future therapeutic, a process Bönnemann said could be "relatively quickly gratifying."

The study, "Childhood amyotrophic lateral sclerosis caused by excess sphingolipid synthesis," published May 31 in Nature Medicine, was authored by Payam Mohassel, Sandra Donkervoort, Matthew Nalls, A. Reghan Foley, Ying Hu, Alec R. Nickolls, Sarah B. Neuhaus, Dimah Saade, Carsten G. Bönnemann, Christopher Grunseich and Naemeh Pourshafie, National Institute of Neurological Disorders and Stroke (National Institutes of Health); Museer A. Lone and Thorsten Hornemann, University of Zurich; Kenneth Gable, Sita D. Gupta and Teresa M. Dunn, Uniformed Services University of Health Sciences; Jonas Alex Morales Saute, Hospital de Clínicas de Porto Alegre; Ana Lucila Moreira, Universidade de São Paulo; Fernando Kok, Hospital das Clínicas da Universidade de São Paulo; Alessandro Introna, University of Bari Aldo Moro; Giancarlo

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