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Study finds genetic variant among people who experience a rare recovery from ALS

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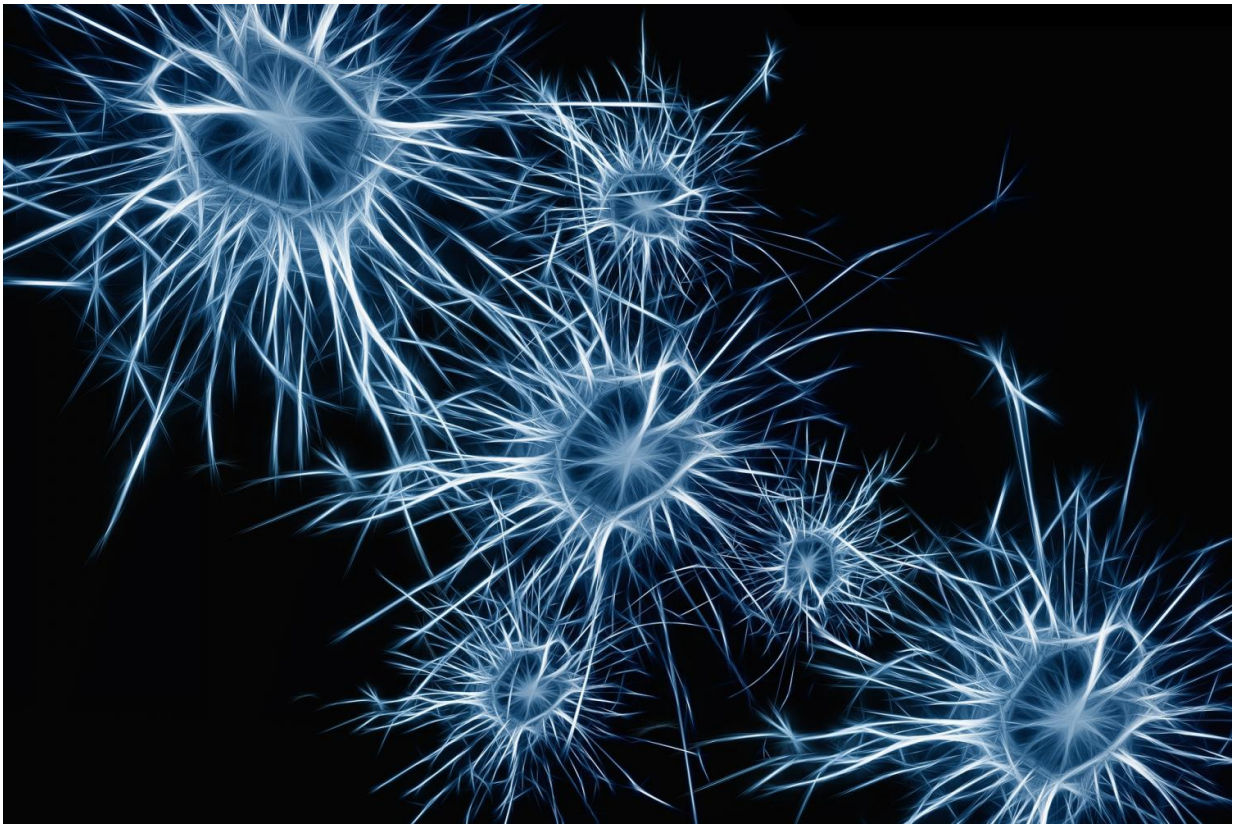

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Though it is exceedingly rare, some people diagnosed with amyotrophic lateral sclerosis (ALS) partially or fully recover from the lethal neurodegenerative disease.

A better understanding of this baffling phenomenon, reported in medical literature for at least 60 years, could point to potential new treatment approaches. To that end, researchers at Duke Health and St. Jude's Research Hospital recently launched a study of ALS recovery patients and found certain genetic factors that appear to protect against the disease's typical assault on motor neurons.

The findings appear in the journal *Neurology*.

"With other neurological diseases, there are now effective treatments," said Richard Bedlack, M.D., Ph.D., the Stewart, Hughes, and Wendt Professor in the Department of Neurology at Duke University School of Medicine. "But we still don't have great options for these patients, and we desperately need to find things. This work provides a starting point to explore how biological reversals of ALS occur and how we might be able to harness that effect therapeutically."

Bedlack and colleagues—including co-lead author Jesse Crayle, M.D., who is now at Washington University in St. Louis—conducted a genome-wide association study of 22 participants who had been diagnosed with ALS and recovered, comparing them to similar patients whose ALS progressed. Researchers at St. Jude Children's Research Hospital led the genetic analysis.

"Our whole genome sequencing pipeline leveraged a multiomics strategy to combine newly available gene expression and epigenetic data, and maximized not just this unique dataset but the CReATe and TargetALS patient databases," explained co-lead author Evadnie Rampersaud, Ph.D., St. Jude Children's Research Hospital Center for Applied Bioinformatics. She stated that the finding was made possible because the patient samples were characterized so well.

The team identified a common genetic variation called a single

nucleotide polymorphism (SNP). The SNP reduces levels of a protein that blocks the IGF-1 signaling pathway, and study participants with this one-letter change in their DNA were 12 times more likely to have experienced a recovery than those without it.

IGF-1 is a growth factor that has long been a target of interest in ALS research because of its role in protecting the motor neurons. ALS patients with fast progression of disease have lower levels of IGF-1 protein, but clinical trials aimed at raising their IGF-1 levels have had disappointing results.

The current finding provides a potential new approach to targeting IGF-1.

"This suggests that the IGF-1 pathway should be further studied as a potential target for future ALS treatments," Crayle said. "While it may not be effective to simply give people IGF-1, our study indicates we might have a way to go about it differently by reducing the levels of this inhibiting protein. It is also possible that the prior studies with IGF-1 were just not adequately dosed or need to be dosed in a different way."

Bedlack said the research team is now exploring whether there is a correlation between the blocking protein and disease progression in a much larger number of patients. Results of that analysis will inform whether a clinical trial targeting this protein could be launched.

In addition to Bedlack and Crayle, study authors include Jason Myers, Joanne Wuu, J. Paul Taylor, Gang Wu and Michael Benatar.

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