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New gene implicated in neuron diseases

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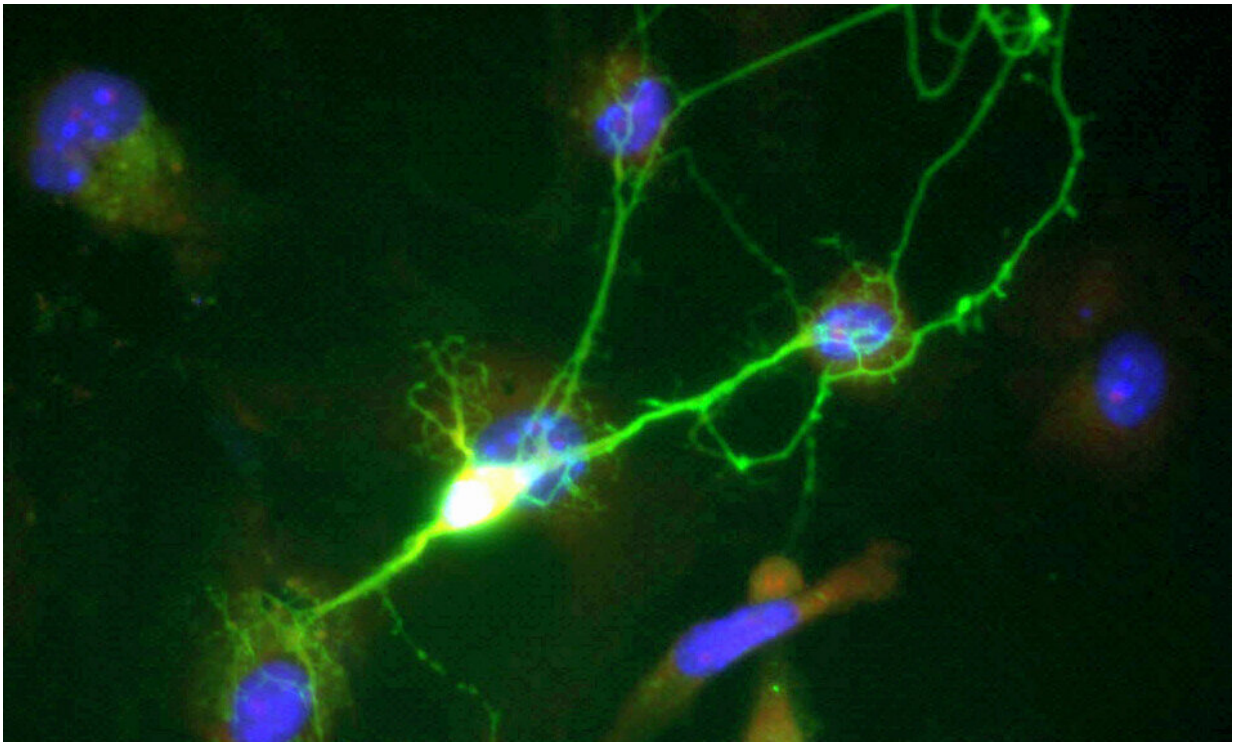

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Failures in a quality control system that protects protein-building fidelity in cells can lead to motor neuron degeneration and related diseases, according to a new study from an international team co-directed by Scripps Research molecular biologist Claudio Joazeiro, Ph.D.

Motor neurons control movement, breathing, swallowing and speaking.

Their death is a hallmark of progressive diseases such as spinal muscular atrophy and ALS, also known as Lou Gehrig's disease. Understanding what can cause motor neurons to die is a key to developing precision treatments. Scientists are finding that the causes of motor neuron diseases are many.

The study, appearing Sept. 15, 2020 in the journal *Nature Communications*, singles out several variants of a gene called NEMF as a new driver of motor neuron diseases. NEMF, short for "nuclear export mediator factor," is known for its role in helping clear glitches that inevitably occur during protein production by cellular organelles called ribosomes.

Healthy NEMF helps the cell recycle garbled protein fragments produced in error. But several mutant forms of NEMF in mice interfered with the system and resulted in neuromuscular, neurodegenerative or other disease, the scientists found.

The research was led by both Joazeiro, who has joint appointments at Scripps Research in Jupiter, Florida and the Center for Molecular Biology of Heidelberg University in Germany, and Gregory Cox, Ph.D., of the Jackson Laboratory of Mammalian Genetics in Bar Harbor, Maine.

A decade ago, Joazeiro discovered an enzyme, the E3 ubiquitin ligase listerin/Ltn1, that works in a specialized quality control process now known as RQC, or ribosome-associated quality control. He and his team also found that inactivation of the enzyme causes motor neuron degeneration in mice. However, whether neurodegeneration resulted from defective ribosome-associated quality control or some other function of listerin remained unclear. At the Jackson Laboratory, Cox had been studying mice with mutations in another quality control factor, NEMF. They exhibited movement difficulties including walking and

gripping. The labs teamed up to investigate whether those defects resulted from a neurodegenerative process. They wanted to find the molecular mechanisms at work.

"The results provide strong evidence that dysfunction of ribosomal quality control causes neurodegeneration," Joazeiro says.

Within cells, millions of ribosomes transform genetic code into proteins by stringing together one amino acid at a time. Mistakes occasionally happen, some of which lead to the production of potentially toxic protein fragments. When that happens, manufacturing may be suspended, and the cell's ribosome protein quality control system chops up the garbled pieces for recycling.

But whether defective ribosome quality control contributed to human disease had remained unknown. Human data backed up the team's mouse and yeast-based investigations.

Working through GeneMatcher, a tool for patients developed at the Baylor-Hopkins Center for Mendelian Genomics in Texas, the team identified nine patients from seven unrelated families who had likely pathogenic NEMF variants and displayed neuromuscular disease, along with a variety of developmental issues including speech delay and intellectual disability.

"It was amazing to see how our early and new mouse data, together with the knowledge acquired on molecular mechanisms, were so predictive of these findings in human patients," Joazeiro says. "We're hopeful these advances will one day prove helpful to families affected by these difficult diseases."

The team is now investigating the role of ribosome-associated quality control in other related diseases, he adds.

Another fascinating takeaway from this research is that this pathway of protein quality control appears to be necessary across species, he adds.

"Last year we reported that it is also present in bacteria, and is likely to have already been active in the last universal common ancestor, the organism that gave rise to all domains of life," Joazeiro says.

Together with the findings that disabling the system results in neurodegeneration, this evolutionary conservation highlights the importance of aberrant protein disposal, and also suggests the system's development may have played a critical role enabling the evolution of complex organisms, Joazeiro says.

"This research shows that failure of ribosome-associated quality control is a cause of motor neuron disease that should be explored in greater detail," he says.

More information: Paige B. Martin et al, NEMF mutations that impair ribosome-associated quality control are associated with neuromuscular disease, *Nature Communications* (2020). DOI: 10.1038/s41467-020-18327-6

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