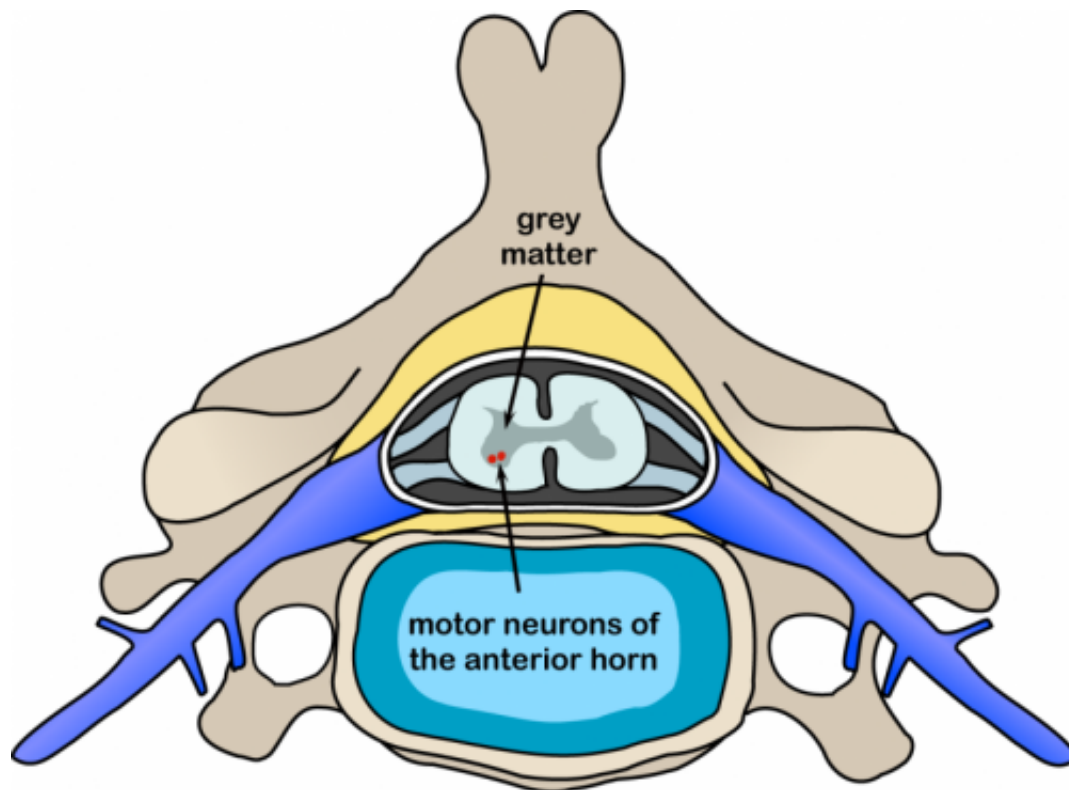


Research reveals the scale of disorder underpinning motor neuron disease

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Polio spinal diagram. The poliovirus affects the motor neurons of the anterior horn cells, or the ventral (front) grey matter section in the spinal column, which control movement of the trunk and limb muscles including the intercostal muscles. Credit: Wikipedia/CC BY-SA 3.0

Researchers at the Francis Crick Institute and UCL have shown that hundreds of proteins and mRNA molecules are found in the wrong place

in nerve cells affected by motor neuron disease (MND), also known as amyotrophic lateral sclerosis (ALS).

ALS is a rapidly progressing and devastating condition that causes paralysis by affecting motor neurons, with limited treatment options. Until now, scientists were aware that a few proteins, especially a protein called TDP-43, were found in unexpected locations in ALS nerve cells.

But new research published in *Neuron* shows that the problem is much broader. This "mislocalization" affects many more proteins than first thought, especially those involved in RNA binding. The mislocalization extends to mRNAs too, molecules that deliver instructions to make proteins from the DNA in the nucleus.

The researchers used [stem cells](#) from patients to create [motor neurons](#) with ALS-causing mutations in the TARDBP and VCP genes. They then separated the two main compartments of the cell (nucleus and cytoplasm), and analyzed all the mRNA and protein within each. They found that in ALS cells, hundreds of mRNAs and proteins were mislocated compared to [healthy cells](#).

They observed proteins and mRNAs relocating from the cell's nucleus into the cytoplasm or vice versa, hinting at potential transport issues within the cell.

The researchers also saw that mislocated mRNAs and proteins interacted more with each other, compared to those in the right place. They speculate that as the mRNAs and proteins mislocalize, they may drag each other with them, creating a [domino effect](#).

Oliver Ziff, Clinician Scientist at the Crick and UCLH, said, "We were surprised to see the extent of the mislocalization, particularly for mRNAs, as this hasn't been reported before. The goal now is to find

where this problem starts and there are many intriguing possibilities—one being a breakdown in the transport between the nucleus and cytoplasm. This study was an exceptional team effort, and I'm immensely grateful to my colleagues, particularly co-first authors, Drs Jasmine Harley, Yiran Wang, and Jacob Neeves."

Remarkably, the mislocalization of proteins and mRNAs was partially improved with a drug called ML240, which blocks the action of the VCP enzyme. Blocking this enzyme also led to other beneficial effects on cell function, such as reducing the level of damage to DNA.

Rickie Patani, Senior Group Leader of the Human Stem Cells and Neurodegeneration Laboratory at the Crick, Professor at UCL and Consultant Neurologist at the National Hospital for Neurology, said, "For the patients I see, it's devastating that there aren't yet impactful treatments available for ALS. This research represents a shift in our thinking about what causes ALS—it doesn't involve abnormal movement of just a few proteins, but the abnormal localization of hundreds of proteins and mRNAs. This opens new avenues for research and potential therapies."

"As ML240 improved the mislocalization and other disease features in ALS, we now need to understand if this can be a tractable therapy for ALS more widely. This is just the beginning and there is lots more to do, but our work provides some hope for effective therapies."

The researchers will next investigate [protein](#) and mRNA location in other ALS genetic backgrounds. There is also much more work ahead before VCP inhibitors could be used clinically—ML240 hasn't yet been tested in animals, and potential chemical changes may be necessary to make sure it enters [nerve cells](#) without causing side effects.

More information: Oliver J. Ziff, Nucleocytoplasmic mRNA

redistribution accompanies RNA binding protein mislocalisation in ALS motor neurons and is restored by VCP ATPase inhibition, *Neuron* (2023). [DOI: 10.1016/j.neuron.2023.06.019](https://doi.org/10.1016/j.neuron.2023.06.019).

[www.cell.com/neuron/fulltext/S0896-6273\(23\)00478-6](https://www.cell.com/neuron/fulltext/S0896-6273(23)00478-6)

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