'Abnormal' protein could be common link between all forms of motor neuron disease

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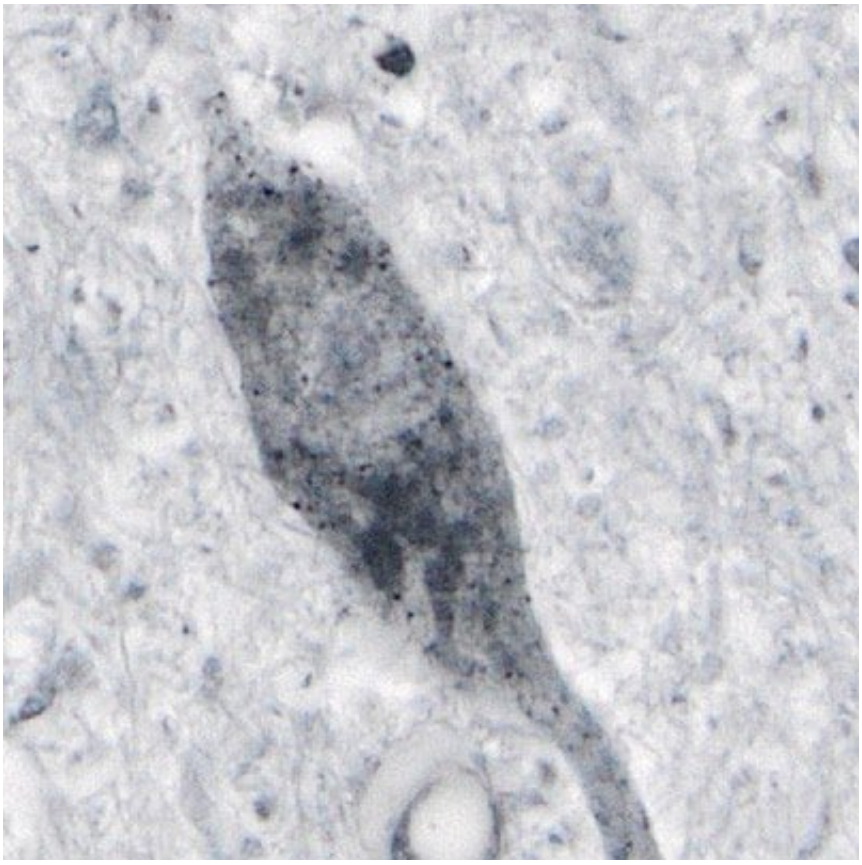

Abnormal SOD1 protein detected in human spinal cord tissue (dark spots). Credit: Trist et al. 2022.

Researchers have found an abnormal protein usually linked to a rare inherited form of motor neuron disease is present in all types of motor neuron disease, suggesting a common link between the different forms

of the disease.

The study, published in the neuroscience journal *Brain*, is the first to confirm toxic changes to the protein in individuals with genetic or non-genetic forms of motor neuron disease.

Amyotrophic lateral sclerosis (ALS) is the most common form of motor neuron disease. Ten percent of ALS cases are hereditary, with remaining cases lacking an apparent genetic cause.

"The results suggest this abnormal protein contributes to cell death in many forms of motor neuron disease, not just rare genetic cases of motor neuron disease," says senior author Professor Kay Double from the Brain and Mind Center, Faculty of Medicine and Health.

"It is a big step in advancing our understanding of motor neuron disease. Our findings will direct further research and could ultimately lead to more effective treatments."

Normally, the protein superoxide dismutase 1 (SOD1) protects cells, but a mutation in its gene is thought to make the protein "toxic"; this toxic protein form is associated with hereditary forms of ALS. Abnormal mutant SOD1 is only found in regions of the spinal cord where nerve cells die, implicating this abnormal protein in cell death.

Previous investigations into the role of toxic forms of SOD1 protein largely focused on mutant forms of the protein and were primarily conducted using animal and cellular models of ALS.

The study, led by a team from the University of Sydney's Brain and Mind Center, advances our understanding of the causes of motor neuron disease by studying this abnormal protein in post-mortem tissues from patients with ALS.

"We have shown for the first time that mechanisms of disease long hypothesized to occur in animal and cellular models are present in patients with motor neuron disease," says lead author Dr. Benjamin Trist from the Brain and Mind Center, Faculty of Medicine and Health.

"This is a significant milestone in our understanding of ALS and motor neuron disease more broadly."

In related experiments, Professor Double and her team are also currently studying how abnormal SOD1 interacts with other disease-linked proteins in motor neuron disease. This work is in press and will be published in *Acta Neuropathologica Communications*.

More information: Benjamin G Trist et al, Altered SOD1 maturation and post-translational modification in amyotrophic lateral sclerosis spinal cord, *Brain* (2022). DOI: 10.1093/brain/awac165

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