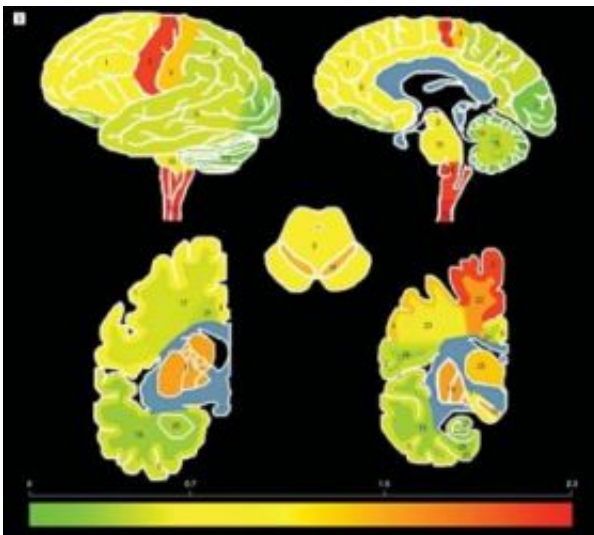


Lou Gehrig's protein found throughout brain, suggesting effects beyond motor neurons

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Whole-brain density map of TDP-43 distribution throughout central nervous system of ALS patients. Red, orange, and yellow depict areas of highest density of TDP-43 pathology. Credit: Felix Geser and Nick Brandmeir, University of Pennsylvania; Archives of Neurology

Two years ago researchers at the University of Pennsylvania School of Medicine discovered that misfolded proteins called TDP-43 accumulated in the motor areas of the brains of patients with amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease. Now, the same group has shown that TDP-43 accumulates throughout the brain, suggesting

ALS has broader neurological effects than previously appreciated and treatments need to take into account more than motor neuron areas. Their article appeared in last month's issue of the *Archives of Neurology*.

"The primary implication for ALS patients is that we have identified a molecular target for new therapies," says co-author John Q. Trojanowski, MD, PhD, Director of Penn's Institute on Aging. "The other implication is that new therapies for ALS now need to go beyond treating only motor neurons."

Traditionally, ALS has been diagnosed based on muscle weakness and neurodegeneration of the upper and lower motor neurons that extend from the motor cortex to the spinal cord and brainstem motor neurons, which directly innervate voluntary muscles. For example, if you want to wiggle your big toe, the signal travels from the motor neuron in the cortex at the top of your head to a synapse on the lower spinal cord motor neurons in the lower back, which, in turn transmit the "wiggle" command by sending a signal to the muscles that move your big toe. Patients with ALS cannot wiggle their big toe or complete other voluntary muscle movements, including those carried out by their other extremities and eventually, by the diaphragm that moves air in and of their lungs.

The study was conducted by examining post-mortem brain tissue of 31 ALS patients. The accumulation of TDP-43 was imaged by detecting TDP-43 with an antibody specific for this protein. TDP-43 pathology was observed not only in the areas of the brain and spinal cord that control voluntary movements, as expected, but also in regions of the brain that involve cognition, executive functioning, memory, and involuntary muscle control. TDP-43 pathology was not observed in any of the controls that did not have ALS.

The pathological TDP-43 observed in ALS brains is different in two

ways from normal TDP-43 that is found in most cells. The ALS-associated TDP-43 includes fragments of normal TDP-43 as well as other abnormally modified forms of TDP-43, and it is located in the cytoplasm of neurons; whereas, normal TDP-43 is found almost exclusively in the cell nucleus. In ALS, the pathological TDP-43 accumulates in large "globs," mainly in cell bodies.

"Our observation of TDP-43 in the brains of ALS patients suggests that ALS and two other neurodegenerative diseases called ALS- PLUS [ALS with cognitive impairments] and FTLD [frontotemporal lobar disease] may all have the same underlying molecular pathology involving abnormal TDP-43," says Trojanowski. "This constitutes a paradigm shift in the way we think about these diseases."

Current research is focused on understanding the basic biology of TDP-43 in cell culture systems. The research team is now trying to find out whether pathological TDP-43 causes nerve cells to lose their normal function or if they take on a toxic function. "The over-riding goal that drives our work is helping ALS patients," says Trojanowski.

Source: University of Pennsylvania

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