Study highlights gene that could lead to therapies for Amyotrophic Lateral Sclerosis

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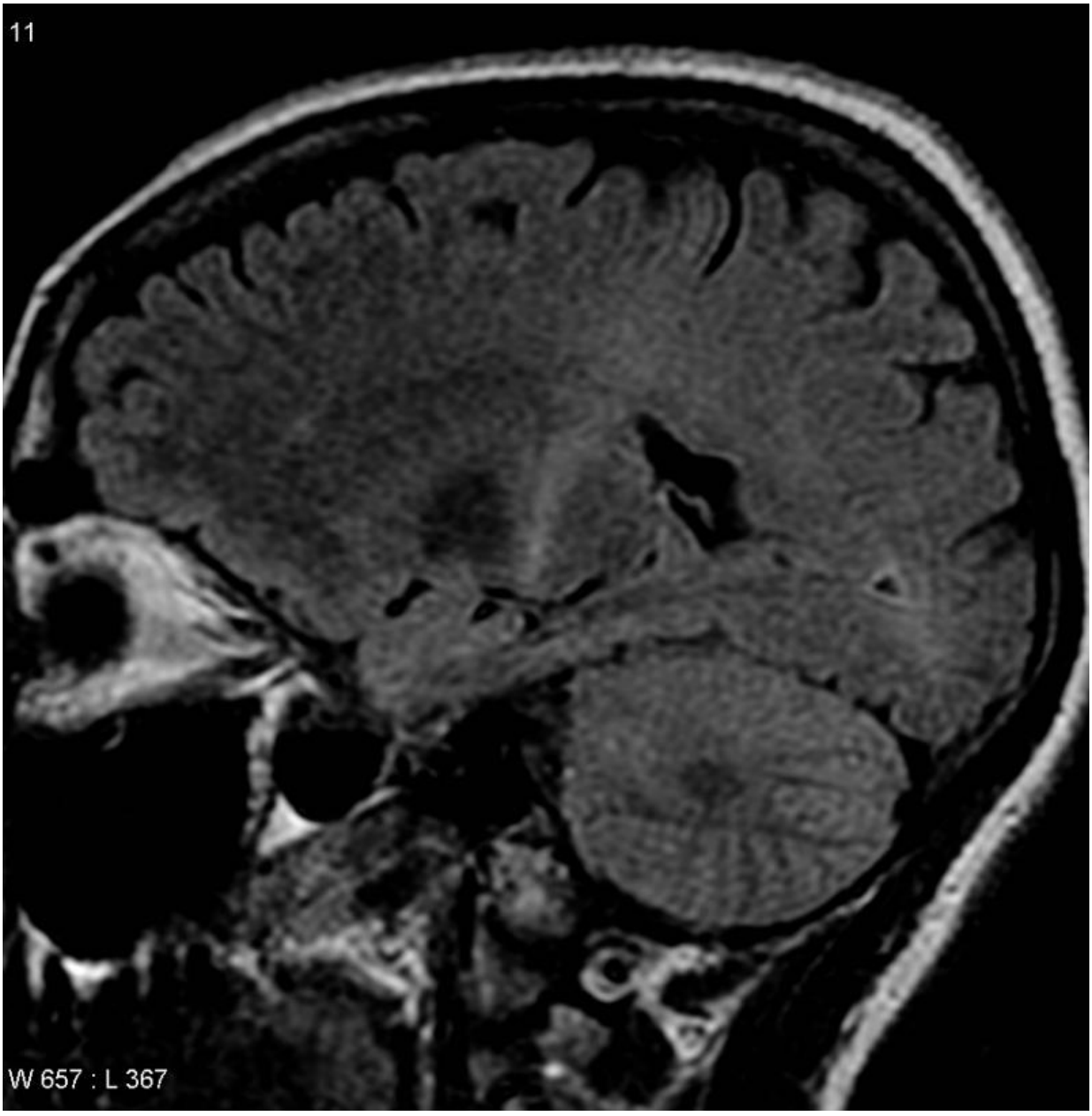

An MRI with increased signal in the posterior part of the internal capsule which can be tracked to the motor cortex consistent with the diagnosis of ALS. Credit: Frank Gaillard/Wikipedia

Researchers from Ben-Gurion University of the Negev (BGU) have published a new study that describes a novel molecular mechanism that could lead to the development of new therapies for Amyotrophic Lateral Sclerosis (ALS). The study was published online in the prestigious *PNAS* (*Proceedings of the National Academy of Sciences*).

ALS, also known as Lou Gehrig's disease, is a fatal neurodegenerative disease that causes death of motor neurons, which control voluntary muscles. Progressive weakness and paralysis due to muscle atrophy lead to difficulty in speaking, swallowing and eventually breathing. The disease typically starts between ages 40 and 60, and the average survival from onset to death is two to five years.

The cause is not known in about 90 percent of cases, but approximately 10 percent are genetically inherited. Approximately 20 percent of these genetic cases are caused by mutations in the SOD1 gene (superoxide dismutase), which lead to the accumulation of "misfolded" SOD1 proteins that provoke selective killing of motor neurons.

"Correct protein folding is critically important, which is why we are focusing on the diverse set of complex cellular mechanisms, including molecular chaperones, that promote efficient folding and prevent toxicity," says Dr. Adrian Israelson, who heads the Cellular and Molecular Neurodegeneration Lab in the BGU Department of Physiology and Cell Biology.

For the first time, this study reported that "endogenous multifunctional protein macrophage migration inhibitory factor (MIF)," a gene that regulates cell inflammation and immunity, acts as a chaperone for misfolded SOD1 in a mouse model. The researchers demonstrated that completely eliminating MIF in a mutant SOD1 mouse model of familial ALS increased misfolded SOD1 accumulation. This also accelerated disease onset and late disease progression and shortened the lifespan of mice expressing mutant SOD1.

"This study provides insight into the potential therapeutic role of MIF in suppressing the selective accumulation of misfolded SOD1 in ALS by modulating MIF levels," Dr. Israelson says.

Dr. Israelson's lab focuses on cellular and molecular mechanisms that lead to the onset and progression of neurodegenerative diseases, such as Alzheimer's, Parkinson's and Huntington's diseases, with special emphasis on ALS.

More information: Marcel F. Leyton-Jaimes et al. Endogenous macrophage migration inhibitory factor reduces the accumulation and toxicity of misfolded SOD1 in a mouse model of ALS, *Proceedings of the National Academy of Sciences* (2016). DOI: 10.1073/pnas.1604600113

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