Loss of MHCI in motor neurons leads to ALS astrocyte toxicity

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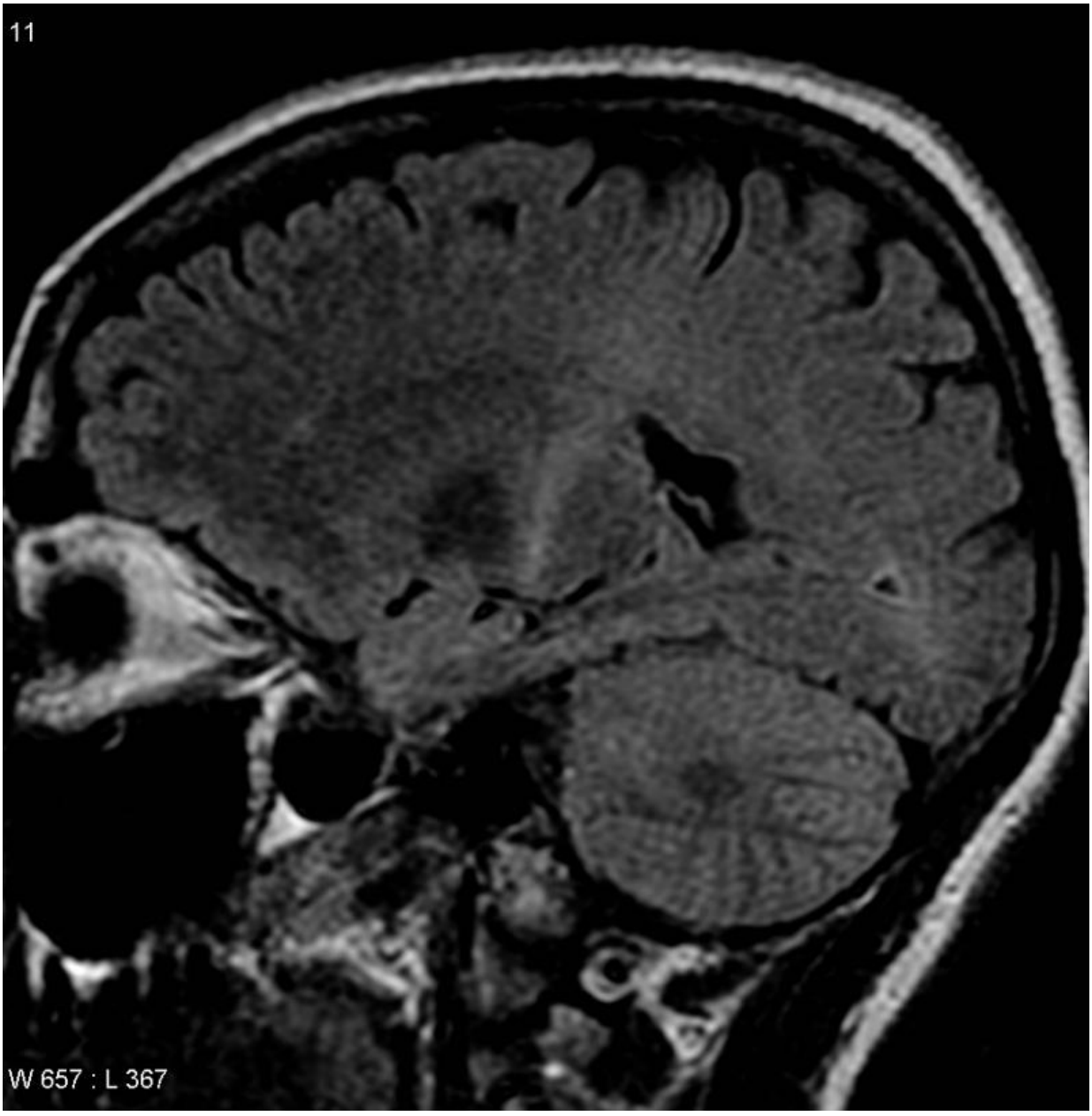

An MRI with increased signal in the posterior part of the internal capsule which can be tracked to the motor cortex consistent with the diagnosis of ALS. Credit: Frank Gaillard/Wikipedia

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a devastating progressive neurodegenerative disease that results in the death of motor neurons, the nerve cells that control muscles. Eventually, individuals with ALS will lose their ability to walk, move, swallow and breathe.

Until recently, the role of astrocytes, glial cells that normally support motor neurons, in motor neuron death has been a mystery, but research from scientists at Nationwide Children's Hospital sheds new light on molecular mechanisms responsible for motor neuron death in ALS. In a study published in *Nature Medicine*, Brian Kaspar, PhD, principal investigator in the Center for Gene Therapy in The Research Institute at Nationwide Children's, and his team demonstrate the explicit loss of major histocompatibility complex I (MHCI) expression in the outer membrane of motor neurons in ALS, leading to motor neuron vulnerability to ALS astrocyte toxicity.

"We wanted to find out what astrocytes were doing—or not doing—to kill motor neurons," explains Dr. Kaspar. "We found unequivocal evidence of the role of MHCI on the motor neurons in signaling the astrocytes."

For each subtype of MHCI protein, there is a receptor that binds to it, much like a lock and key. If MCHI proteins are the keys, then killer inhibitory receptors (KIRs) are the locks. In their study, Dr. Kaspar and his team not only provide evidence of the protective effect of MHCI

against astrocyte toxicity in ALS but also identify the killer inhibitory receptors (KIRs) associated with the specific subclass of MHCI (HLA-F) involved in human motor neurons.

"We showed, in both animal and human studies, the loss of MHCI is destructive to the motor neurons and increases in MHCI are protective," says Dr. Kaspar, who is also associate professor in the Department of Pediatrics and Department of Neuroscience at The Ohio State University College of Medicine. "We knew from past research that ALS astrocytes were responsible for killing motor neurons. Now we have another piece to the puzzle."

According to the study, a dramatic loss of MHCI (HLA-F) from motor neurons is observed in the spinal cords of subjects affected by ALS. This finding is supported by evidence obtained in animal models and in vitro experiments using animal and human cells, which give insight on the protective nature of MHCI (HLA-F). Specifically, MHCI expression in the animal model was modulated using adeno-associated viral vector serotype 9 (AAV9), resulting in increased expression of MHCI and markedly extended survival.

The protective nature of MHCI (HLA-F) points to a potential translational target to delay the progression of ALS, since HLA-F expression may significantly impact disease progression in patients. In the in vitro experiments, human motor neurons expressing higher levels of HLA-F experienced reduced astrocyte toxicity. However, it remains to be seen whether or not this can be translated into a clinical trial and meaningful therapy for patients.

"Taken together, the results provide strong evidence that a single MHCI molecule, HLA-F, can protect motor neurons from both inherited and spontaneous ALS astrocyte-induced toxicity, which is a prerequisite for delaying motor neuron death in these patients," Dr. Kaspar says.

Not only is this work opening doors to new possibilities in ALS research and therapeutics, MHCI has also been shown to be instrumental in neural development. According to Dr. Kaspar, studies now indicate that it may be integral in neurodegenerative situations as well.

"While we have gained much information about the role of MHCI and astrocyte toxicity through this research, we are really just scratching at the surface of all we need to understand," Dr. Kaspar says.

More information: "Major histocompatibility complex class I molecules protect motor neurons from astrocyte-induced toxicity in amyotrophic lateral sclerosis," *Nature Medicine* (2016). DOI: 10.1038/nm.4052

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