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Scientists create vast data resource to uncover ALS subtypes

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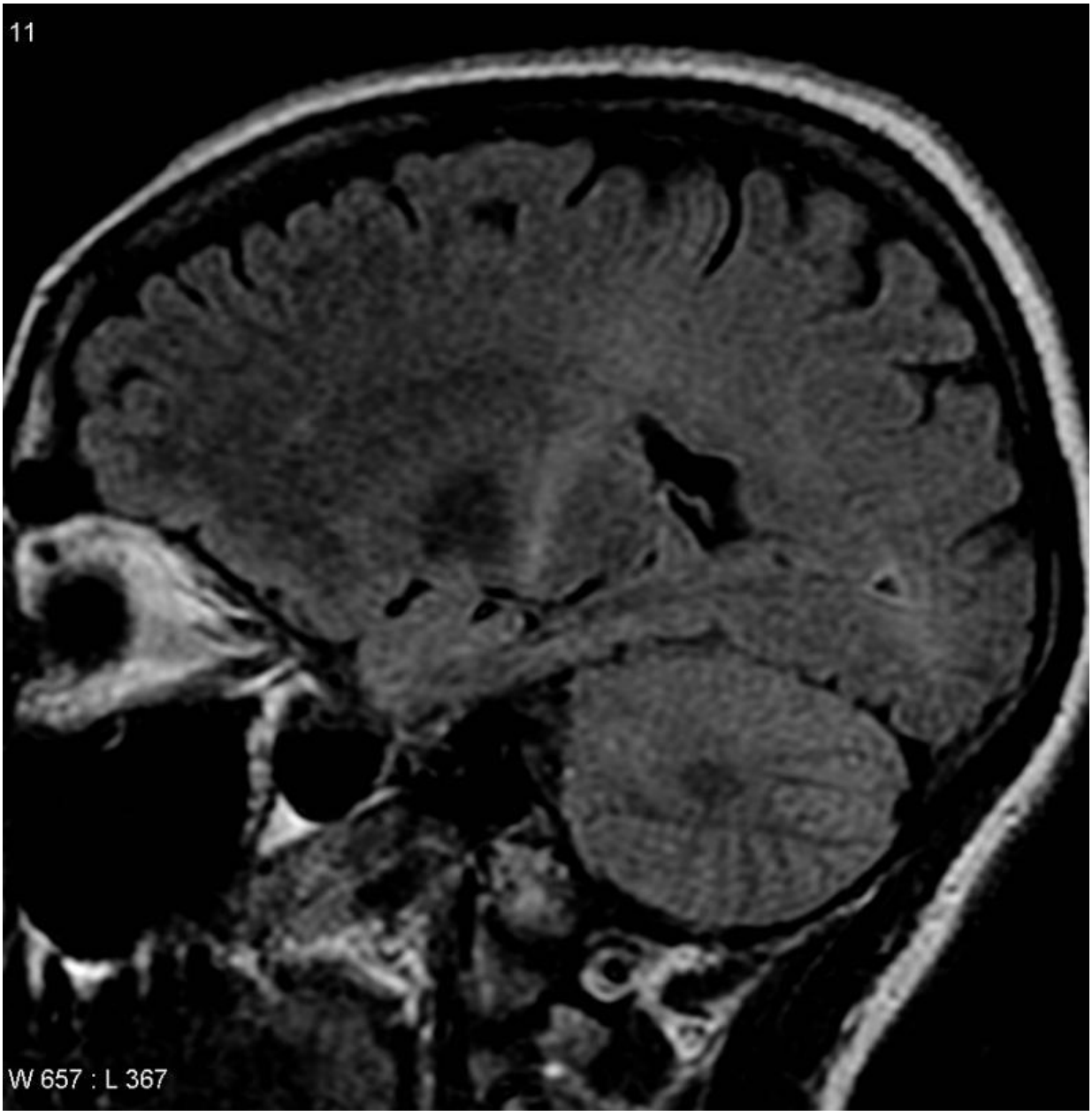

An MRI with increased signal in the posterior part of the internal capsule which can be tracked to the motor cortex consistent with the diagnosis of ALS. Credit: Frank Gaillard/Wikipedia

A new cloud-based data resource co-developed by scientists at Cedars-Sinai provides the research community with a comprehensive set of tools to help identify new subtypes of amyotrophic lateral sclerosis (ALS), a fatal neurological disorder.

The web-based tool is part of a collaborative effort with more than 100 scientists called Answer ALS, which includes biological and clinical data from more than 1,000 ALS patients. The information is intended to help investigators across the globe better understand ALS, also known as Lou Gehrig's disease. Details of the resource are described in the peer-reviewed journal *Nature Neuroscience*.

"This is one of the largest resources for ALS samples in the world," said Clive Svendsen, Ph.D., executive director of the Cedars-Sinai Board of Governors Regenerative Medicine Institute and a co-author of the paper and co-director of the Answer ALS program. "It's a critical step forward in finding new treatments for a very complex disease that has really no effective treatments available."

ALS is a progressive neurodegenerative disease that damages nerve cells known as motor neurons in the brain and spinal cord, leading to the loss of muscle control. With no known cure, it is usually fatal within five years of diagnosis.

Discovering new subtypes of ALS can provide clues to how an individual may respond to treatment. This information is useful for

guiding disease management and can help lead to the development of new drugs that target specific cells and pathways that may only be found in certain subgroups.

"We don't think ALS is one disease," said Svendsen, who is also a professor of Biomedical Sciences and Medicine. "It's very complex and we think there are different subtypes that can be targeted differently. We just need to uncover them."

To successfully build the database, scientists first had to create a model of the disease that could be used to help study how ALS develops. Creating models of neurodegenerative diseases has been notoriously challenging because of the lack of reliable animal models or patient samples at early disease stages.

To overcome this issue, the investigators used induced pluripotent stem cells (known as iPSCs), which can be deployed to produce any type of cell in the body and at any stage of development. The team then converted these stem cells into the neurons of the spinal cord that die in ALS, essentially a personalized neural biopsy. These were then analyzed using the latest molecular techniques, which gave the team the ability to look for proteins that may have been affected in the disease.

"Proteomics is one of the most powerful tools we have to really look at the protein content of a cell, providing us insight into attractive treatment targets," said Jennifer Van Eyk, Ph.D., professor of Cardiology, Biomedical Sciences and Pathology and Laboratory Medicine, and a study author who led the proteomics analysis.

The details of the model were previously published in the peer-reviewed journal *iScience*. The team, with Svendsen as one of the two corresponding authors, showed an integrated multi-omics approach can be used to understand more about motor neurons from iPSCs.

With the model in place, investigators collected blood samples from more than 1,000 ALS patients from around the country. The samples were sent to Cedars-Sinai, where Dhruv Sareen, Ph.D., executive director of the Cedars-Sinai Biomanufacturing Center and director of the induced pluripotent stem cell facility at the Regenerative Medicine Institute, and his team reprogrammed the white blood cells into iPS cells for each patient that were then turned into motor neurons.

"Creating these many iPS cell lines and generating neurons from them has never been done at this scale before," said Sareen, who is also an associate professor of Biomedical Sciences. "We hope this platform will allow us to dive more deeply into the mechanisms leading to ALS. Furthermore, we can now provide these patient cells to the entire research community through our repository."

All of the data is continually being collected and deposited into an online, open-source portal, where scientists can download all the data from every sample.

"This was a huge collaborative effort, and we hope the information we collected will help lead to the discovery of new molecular subtypes of ALS. With this knowledge we may at last be able to develop drugs targeted to these subtypes, laying the groundwork for new and improved therapies," Svendsen said.

The Answer ALS platform was designed by Svendsen and Jeffrey Rothstein, MD, Ph.D., from Johns Hopkins University School of Medicine in Baltimore. Other collaborators include scientists from the University of California, San Francisco, Massachusetts Institute of Technology, University of California, Irvine, Ohio State University Wexner Medical Center, Columbia University, Emory University, Washington University in St. Louis, Northwestern University, On Point Scientific Inc. and Microsoft Corp. A full list of contributions can be

found in the paper.

More information: Emily G. Baxi et al, Answer ALS, a large-scale resource for sporadic and familial ALS combining clinical and multi-omics data from induced pluripotent cell lines, *Nature Neuroscience* (2022). DOI: 10.1038/s41593-021-01006-0

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