Scientists encouraged by new mouse model's similarities to human ALS

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A new mouse model of amyotrophic lateral sclerosis (ALS) closely resembles humans with the paralyzing disorder, researchers at Washington University School of Medicine in St. Louis report.

Like humans with ALS, the new genetically engineered mouse develops progressive paralysis; loses muscle mass and specific types of motor neurons, which are nerve cells that control muscles; and dies of the disorder, which is currently fatal in humans.

"As far as we know, this is the first mouse model that recapitulates 'typical' ALS to be produced in more than a decade," says senior author Robert Baloh, M.D., Ph.D., assistant professor of neurology. "That could make it very helpful for our efforts to better understand and identify treatments for this terrible disorder."

Scientists report the details of the new mouse model online this week in Proceedings of the National Academy of Sciences.

Baloh's work with the mice was made possible in part by the Hope Center for Neurological Disorders, a collaboration between the School of Medicine and Hope Happens, a non-profit foundation that raises funds for research into neurodegenerative disorders such as ALS. The foundation was established by Christopher Hobler, a St. Louisan who died of ALS, and his family.

The mouse model has a point mutation or single letter of erroneous DNA

code in the gene for a protein called TDP-43. Researchers at the University of Pennsylvania linked TDP-43 to inherited forms of ALS in 2006. Washington University scientists Nigel Cairns, Ph.D., and Alison Goate, Ph.D., sequenced a point mutation in the TDP-43 gene of a St. Louis family with an inherited form of ALS, and Baloh's lab created a mouse line with the family's mutation.

"Ten percent of all ALS cases are inherited, but only a small portion of the known inherited forms of the disorder are clinically indistinguishable from sporadic ALS," Baloh says. "TDP-43 is only the second gene to be linked to an inherited form of ALS that appears clinically identical to sporadic ALS, and it's very promising that this similarity allows the symptoms of sporadic ALS to be accurately modeled in mice."

While mice typically live more than two years, mice with the TDP-43 mutation live only five months. Like humans, the mice develop problems with walking, lose muscle mass and eventually become paralyzed.

"The mice have damage to both upper motor neurons, which extend from the brain to the spinal cord, and lower motor neurons, which reach from the spinal cord to the muscles," Baloh says. "In humans, damage to both upper and lower motor neurons is required for a diagnosis of ALS."

Clumps of unidentified proteins develop within the motor neurons of the mice, another symptom that echoes human ALS pathology.

Scientists know that the TDP-43 protein is both a transcription and a splicing factor, which means that it binds to both RNA and DNA to regulate the creation of particular proteins. But they don't yet know enough details about its normal function to determine how TDP-43 mutations cause ALS.

"The mutation could be making the TDP-43 protein toxic to nerve cells,

or it could be blocking a normal function of the protein that is essential for those cells," Baloh says. "The mice will help us test both of these possibilities."

The new mouse model may also provide an important tool for screening new drugs, according to Baloh. Scientists already have another mouse model of ALS with a mutation in SOD1, the first gene to be linked to an inherited form of ALS with typical symptoms, but, according to Baloh, it hasn't always been the best tool for predicting if treatments will work in humans.

"If we use the two models together to test potential treatments, though, that might provide us with a much finer screen," says Baloh. "This could help relieve some frustration in the field, because there are a number of new drugs ready to be tested in humans, and we urgently need ways to determine which should be tried first."

The TDP-43 mutant mice also have brain damage similar to patients with frontotemporal dementia, a disorder sometimes associated with ALS. Baloh and his colleagues will use the mice to explore the potential connection.

Source: Washington University School of Medicine (news : web)

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