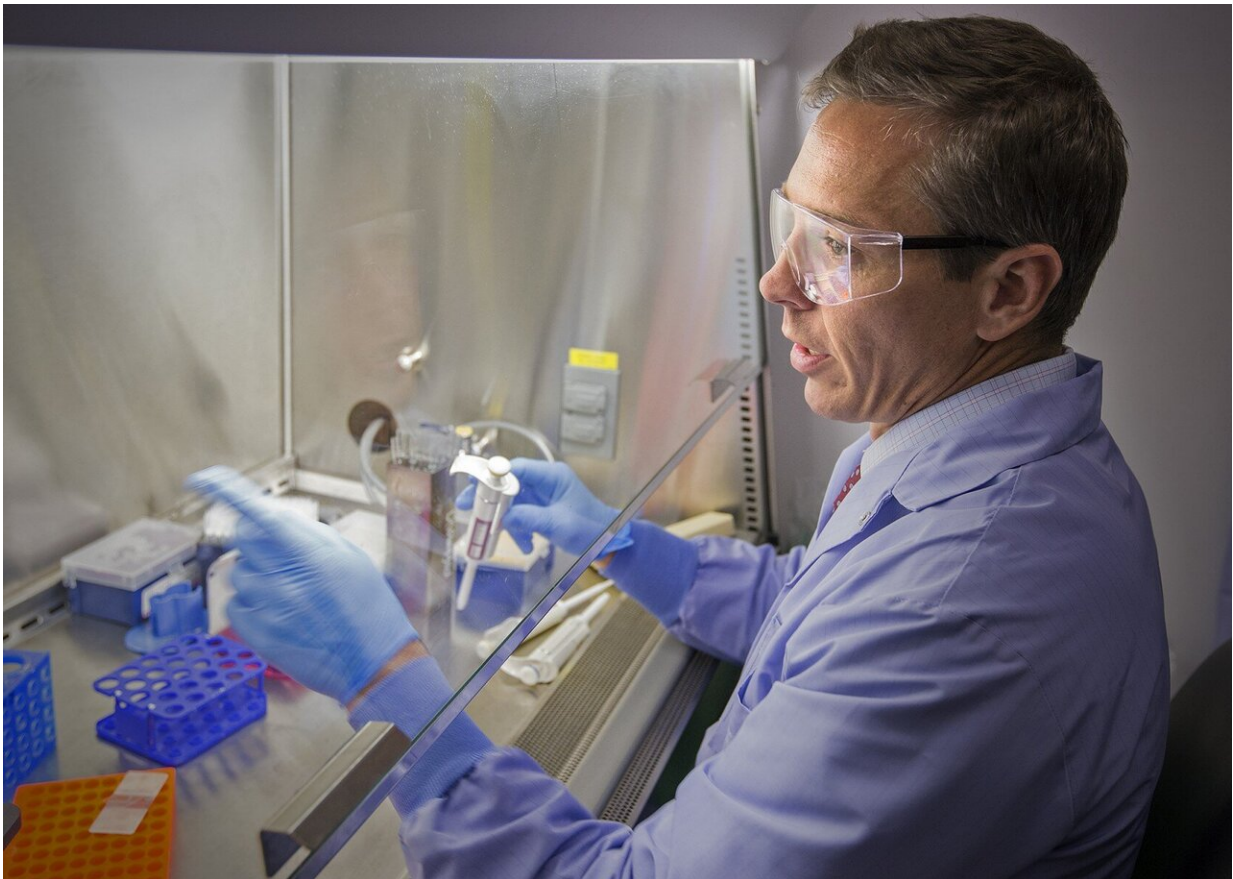


Autoimmune diseases in ALS patients linked to genetic mutation

August 20 2020, by Sarah Lichtman



Robert Baloh, MD, PhD, at work in his laboratory. Credit: Cedars-Sinai

A study published today in the journal *Nature* could help explain why certain people who develop amyotrophic lateral sclerosis (ALS), a deadly

neurological disorder also known as Lou Gehrig's disease, are prone to autoimmune diseases.

ALS, which has no known cure, causes progressive degeneration of nerve cells in the spinal cord and brain. About 5,000 people are diagnosed with the [disease](#) each year.

The new research, led by Cedars-Sinai investigators, focuses on a mutation that decreases expression of a gene called C9orf72, the most common known cause of inherited ALS.

Investigators found that this mutation, found in about 10% of patients with ALS, causes the stimulator of interferon genes (STING) protein, a critical sensor of viral infections in the [immune system](#), to become hyperactive. This hyperactivity led to increased production of interferons. Interferons are key for fighting viral infections, but constant, uncontrolled production of interferons can lead to systemic inflammation and development of autoimmune diseases.

"These findings support that patients with C9orf72 [mutations](#) have a fundamentally different set point of their immune system, with increased propensity to autoimmune diseases, and probably altered responses to viruses and other pathogens in the environment," said Robert Baloh, MD, Ph.D., professor of Neurology and director of the Cedars-Sinai Center for Neural Science and Medicine.

Baloh is the corresponding author of the study, available online today and in the Sept. 3 print edition of the journal.

The C9orf72 mutation, which is believed to have originated in Northern Europe about 1,500 years ago and then spread as a result of Viking travels and wars, is also associated with [frontotemporal lobar degeneration](#), a type of dementia that can accompany ALS.

For the study, investigators examined the brain tissue of laboratory mice with the C9orf72 mutation and also blood and brain tissue from ALS patients who carried the gene. Results included:

- Immune cells isolated from the laboratory mice showed early spontaneous activation. In addition, a certain type of immune cell, called myeloid cells, had increased production of the interferons in response to activation of the STING protein.
- Tissues from ALS patients with the genetic mutation and frontotemporal lobar degeneration showed an elevated immune response compared with samples from patients with a different type of ALS.

Taken together, those findings suggested that ALS patients with the genetic mutation and frontotemporal lobar degeneration have an altered immune system because their reduced levels of C9orf72 cannot suppress the inflammation caused by the hyperactive STING protein, the investigators said.

"These results give us critical insights into the interplay of the immune system and neurodegenerative disease," said Nancy Sicotte, MD, chair of the Department of Neurology at Cedars-Sinai and the Women's Guild Distinguished Chair in Neurology. "They have implications not only for ALS and frontotemporal lobar degeneration, but for other autoimmune and degenerative disorders affecting the nervous system."

Interestingly, the investigators also found that mice with the C9orf72 mutation were more resistant to certain cancers, possibly as a byproduct of a hyperactive immune system. A similar decreased incidence of cancers has also been reported in ALS patients, but the reason remains a mystery.

"This study ties together research about a really important immune

pathway and the genetics of ALS, linking neurodegeneration, [autoimmune diseases](#) and cancer," Baloh said.

Baloh's Neurodegenerative Diseases Laboratory is now studying how this gene mutation and heightened autoimmune response is linked to neurodegeneration. He said that understanding these connections may help investigators lay the groundwork for developing therapies for ALS.

More information: Madelyn E. McCauley et al. C9orf72 in myeloid cells suppresses STING-induced inflammation, *Nature* (2020). [DOI: 10.1038/s41586-020-2625-x](#)

Provided by Cedars-Sinai Medical Center

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