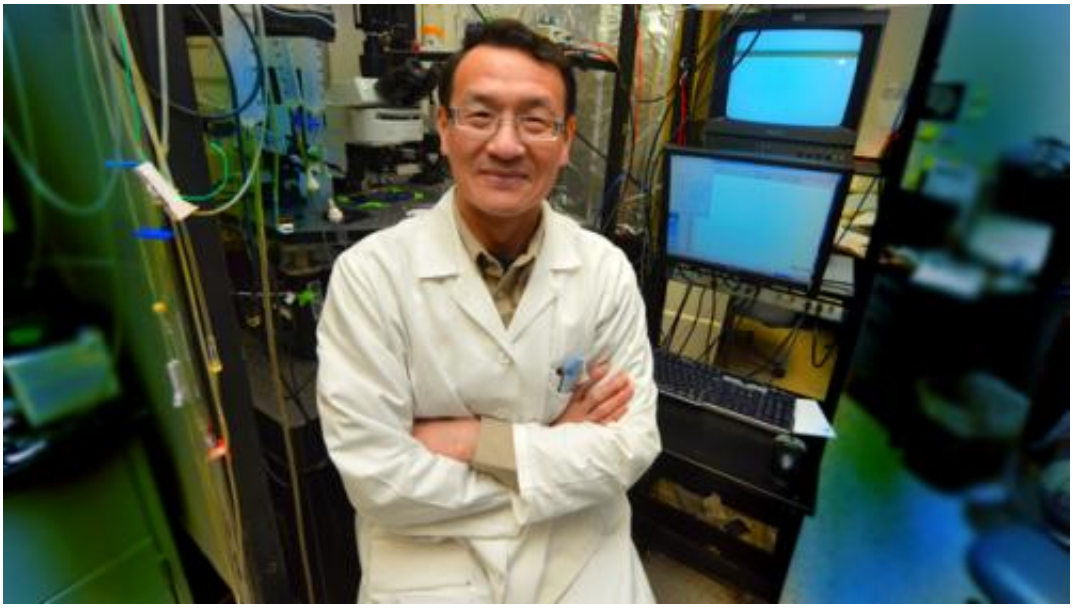
New cause found for muscle-weakening disease myasthenia gravis

November 11 2013



This is Dr. Lin Mei, Director of the Institute of Molecular Medicine and Genetics at the Medical College of Georgia at Georgia Regents University. Credit: Phil Jones

An antibody to a protein critical to enabling the brain to talk to muscles has been identified as a cause of myasthenia gravis, researchers report.

The finding that an antibody to LRP4 is a cause of the most common disease affecting brain-muscle interaction helps explain why as many as 10 percent of patients have classic symptoms, like drooping eyelids and generalized muscle weakness, yet their blood provides no clue of the

cause, said Dr. Lin Mei, Director of the Institute of Molecular Medicine and Genetics at the Medical College of Georgia at Georgia Regents University.

"You end up with patients who have no real diagnosis," Mei said.

The finding also shows that LRP4 is important, not only to the formation of the neuromuscular junction – where the brain and muscle talk – but also maintaining this important connection, said Mei, corresponding author of the paper in *The Journal of Clinical Investigation*.

Mei and his colleagues first reported antibodies to LRP4 in the blood of myasthenia gravis patients in the *Archives of Neurology* in 2012. For the new study, they went back to animals to determine whether the antibodies were harmless or actually caused the disease. When they gave healthy mice LRP4 antibodies, they experienced classic symptoms of the disease along with clear evidence of degradation of the neuromuscular junction.

LRP4 antibodies are the third cause identified for the autoimmune disease, which affects about 20 out of 100,000 people, primarily women under 40 and men over age 60, according to the National Institutes of Health and Myasthenia Gravis Foundation of America, Inc.

An antibody to the acetylcholine receptor is causative in about 80 percent of patients, said Dr. Michael H. Rivner, MCG neurologist and Director of the Electrodiagnostic Medicine Laboratory, who follows about 250 patients with myasthenia gravis. Acetylcholine is a chemical released by neurons which act on receptors on the muscle to activate the muscle. More recently, it was found that maybe 10 percent of patients have an antibody to MuSK, an enzyme that supports the clustering of these receptors on the surface of muscle cells.

"That leaves us with only about 10 percent of patients who are double negative, which means patients lack antibodies to acetylcholine receptors and MuSK," said Rivner, a troubling scenario for physicians and patients alike. "This is pretty exciting because it is a new form of the disease," Rivner said of the LRP4 finding.

Currently, physicians like Rivner tell patients who lack antibody evidence that clinically they appear to have the disease. Identifying specific causes enables a more complete diagnosis for more patients in the short term and hopefully will lead to development of more targeted therapies with fewer side effects, Rivner said.

To learn more about the role of the LRP4 antibody, Mei now wants to know if there are defining characteristics of patients who have it, such as more severe disease or whether it's found more commonly in a certain age or sex. He and Rivner have teamed up to develop a network of 17 centers, like GR Medical Center, where patients are treated to get these questions answered. They are currently pursuing federal funding for studies they hope will include examining blood, physical characteristics, therapies and more.

Regardless of the specific cause, disease symptoms tend to respond well to therapy, which typically includes chronic use of drugs that suppress the immune response, Rivner said. However, immunosuppressive drugs carry significant risk, including infection and cancer, he said.

Removal of the thymus, a sort of classroom where T cells, which direct the immune response, learn early in life what to attack and what to ignore, is another common therapy for myasthenia gravis. While the gland usually atrophies in adults, patients with myasthenia gravis tend to have enlarged glands. Rivner is part of an NIH-funded study to determine whether gland removal really benefits patients. Other therapies include a plasma exchange for acutely ill patients.

Provided by Medical College of Georgia