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New genetically engineered mice aid understanding of incurable neuromuscular disease

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A team of scientists from the University of Missouri created a genetically modified mouse that mimics key features of Charcot-Marie-Tooth disease, an inherited neuromuscular disease affecting approximately 150,000 people in the United States.

Charcot-Marie-Tooth, or CMT, is a group of progressive disorders that affects the peripheral nervous system, the part of the nervous system that connects the brain and spinal cord to targets such as muscles. The disease largely affects the distal nerves, those running to the feet and hands, and can progress to include the legs and arms.

"Wasting and weakening of the muscles occurs because the distal nerves are either dying or not functioning properly," said Michael Garcia, study leader and associate professor of biological sciences. "The condition can be very debilitating depending on the muscles affected and the degree to which they are affected."

No cure exists for CMT, but Garcia hopes that insights gleaned from the new mouse model may aid the development of therapeutic interventions.

"By learning about the basics of disease initiation and progression, perhaps we can soon test therapeutics designed to stop or reverse the pathology," he said.

Garcia and colleagues created the mouse model by inserting a mutated copy of a human gene into fertilized mouse egg cell. Similar mutations in that particular gene have been linked to a specific form of CMT, known as Type 2e, in humans. The cells were then implanted into female mice. The offspring that contained the mutated human gene were reared and observed for signs of CMT.

At four months of age, the mice developed a condition with several of the same hallmarks of humans with CMT Type 2e, including muscle wasting and weakness, foot deformities, and reduced ability to move. No significant neural problems or detachment of the nerves from the muscle was observed in the mice, which surprised the scientists.

"With such severe muscle atrophy we expected to see a loss of nerve connections on the muscles, but they are all there, and they look relatively healthy," said Garcia, who is also an investigator in the Christopher S. Bond Life Sciences Center.

The finding was also surprising since another mouse model, which also mimicked CMT type 2e, did show nerve detachment. This other mouse model, developed by a team in Canada, had a mutation in the same gene but at a different site in the genetic code. According to Garcia, the lack of nerve detachment observed in his mouse model may point to different underlying mechanisms for CMT type 2e.

In a follow-up study, Garcia and colleagues showed that the mice they engineered also developed an abnormal gait. The scientists evaluated the gait of the mice using a so-called CatWalk system, a device that uses light and a high-speed camera to capture certain dynamics of a running mouse's footfalls. Abnormal gaiting was observed as a decreased paw print overlap and increased hind limb drag on the left side of the body, the authors report in the study.

A high-stepped gait is characteristic of people with CMT. Weakness of the foot and leg muscles often results in foot drop, an inability to move the ankle and toes properly, which is compensated for by raising the foot higher.

"It's an exciting time for CMT type2e," said Garcia. "With two really good mouse models, we're now in a powerful position to begin to ask questions about how the disease initiates and how it progresses."

Findings from the studies are published in the July 1, 2011, issue of the journal *Human Molecular Genetics* and in the January 30, 2012, online issue of the journal *Genes, Brain, and Behavior*.

Provided by University of Missouri-Columbia

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