Mutation may cause inherited neuropathy

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Mutations in a protein called dynein, required for the proper functioning of sensory nerve cells, can cause defects in mice that may provide crucial clues leading to better treatments for a human nerve disorder known as peripheral neuropathy, which affects about three percent of all those over age 60.

Peripheral neuropathy results from damage to the nerves and nerve processes that are located outside the brain and spinal cord. Symptoms include pain in the hands and arms, legs and feet--sometimes constant and quite severe--as well as progressive numbness and weakness in the arms and legs. Despite its prevalence, little is known about the precise causes of the disease or how to prevent or treat it.

In the December 26, 2007, issue of the *Journal of Neuroscience*, however, researchers at the University of Chicago Medical Center show that mice with mutations in only one copy of a gene coding for one part of dynein protein have severe defects in proprioception, the ability to perceive the spatial orientation of body parts.

These defects caused a significant reduction in the number of sensory nerve cells in affected mice. They also caused early-onset locomotion problems in the mice's hind legs, a defect that appears to be quite similar to some human neuropathies.

"This gene codes for part of a multi-protein complex," said study author Brian Popko, PhD, Jack Miller Professor in Neurological Diseases at the University of Chicago Medical Center. "So a mutation in any of these

proteins, or disruption in the function of this multi-protein complex through some other mechanism, could also lead to very similar abnormalities" in human patients with sensory neuropathies.

Mutations in the gene for dynein heavy chain 1, Dync1h, led to movement defects in the hind legs of mice. These defect resembled human neuropathies, said Popko, particularly some forms of Charcot-Marie-Tooth disease and hereditary sensory neuropathy.

Charcot-Marie-Tooth disease is one of the most common inherited neurological disorders, affecting approximately 1 in 2,500 people in the United States. It is characterized by loss of muscle tissue and touch sensation, predominantly in the feet and legs. In CMT, both the sensory nerves that carry signals from receptors in the extremities to the brain and spinal cord, as well as motor nerves that relay signals from the brain and spinal cord to the limbs and internal organs are affected.

Hereditary sensory neuropathy affects predominantly sensory nerves. Symptoms included sensation loss, decreased or absent reflexes, foot deformities and various anatomic features.

Dynein appears to be a likely suspect, the authors report. Although it is found throughout the body, Dynein plays an important role in the transport of cargo within axons, the elongated extension of nerve cells that transmit signals from one neuron to another. Dynein is crucial for survival, because mice that lack dynein or have mutations in both Dync1h copies die before birth.

Although dynein is important for the whole body, defects are found only in sensory neurons, and predominantly in hind limbs.

“The key question is why"” said Popko. “This mutation may affect transport proteins in all neurons, but perhaps the region that is mutated is

more important for the proteins that it transports in sensory neurons, whereas other regions could play a role in motor neurons. Also, mutations in different regions of this protein seem to have different effects. That may be due to differences in the cargo-binding domains."

Affected neurons in mice and in patients with sensory neuropathies have very long axons. Such neurons that transmit signals over huge distances depend on dynein, the "cargo-transporter" to carry molecules from the tip of the axon to the neuron's cell bodies. If the cargo-transporter is somehow disturbed, Popko said, like in the case of mutations in Dync1h gene, neurons that transmit signals over "long distances" will suffer more.

"It's very common for neuropathies to affect neurons with the longer axons, for example those that innervate the legs and feet," says Popko. It has been previously suggested that hereditary sensory neuropathy might be connected with disabled trafficking along the axons. There have been mutations found in two genes that form a complex essential for survival of sensory neurons, and this complex is thought to be transported along the neurons by dynein.

"This study lays the groundwork for the search for disruptions of this cargo transporting complex in human patients with sensory neuropathy", write the authors in their paper.

They are already looking at human patients for similar mutations. And they're working further on answering new questions, including: what are the binding partners of dynein that are disrupted in diseases, and why does this affect sensory and not motor neurons"

Source: University of Chicago