Hereditary Condition Causing Limb Weakness Traced to Gene for Rare Disorder

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(PhysOrg.com) -- A gene that causes a fatal childhood brain disorder can also cause adults to develop peripheral neuropathy, a condition resulting in weakness and decreased sensation in the hands and limbs, according to a study by researchers at the National Institutes of Health and other institutions. The study is the first to show that different mutations in the same gene cause the two seemingly unrelated disorders.

Inherited peripheral neuropathies are a diverse group of disorders that cause loss of muscle tissue in the hands, feet, and lower legs of affected patients, usually starting in adulthood. Various genetic causes have been identified for Charcot-Marie-Tooth disease (CMT), the broad category of inherited peripheral neuropathy that affects approximately 125,000 people in the United States. The peripheral nervous system consists of nerves that reside or extend outside of the brain and spinal cord.

In the current study, the researchers determined that persons with a CMT-like neuropathy have a mutation in the same gene that causes Menkes disease, a severe brain disorder that begins in infancy and is fatal if not treated. This gene, called ATP7A, codes for a protein needed to move the trace metal copper between different compartments within the body's cells, or out of cells altogether.

"The findings provide insight into how peripheral nerves function and may ultimately lead to new treatments for some peripheral neuropathies," said Alan E. Guttmacher, M.D., acting director of the Eunice Kennedy Shriver National Institute of Child Health and Human

Development (NICHD), the NIH Institute that collaborated in the study.

The findings appear in the March 12 American Journal of Human Genetics. The study's first author was Marina L. Kennerson, Ph.D. of the ANZAC Research Institute, University of Sydney, Australia. Another senior author was Stephen G. Kaler, M.D., head of the Unit on Human Copper Metabolism at the NICHD's Molecular Metabolism Program. The NICHD provided funding for the NIH-based portion of the research.

Drs. Kennerson, Kaler, and their colleagues discovered the mutated gene's role in distal motor neuropathy by studying the DNA of two large, unrelated families with multiple affected members. Changes in the DNA of the family members who had the disorder did not appear in the DNA of those who did not have the disorder. Dr. Kaler's Unit at the NICHD helped to identify the location of the ATP7A protein inside human skin cells from patients and characterized the nature of the mutations in the gene. The mutations causing distal motor neuropathy appeared to have much lesser effects than did the mutations found in the infants with Menkes disease.

Menkes disease arises from other mutations in the same gene, which make the resulting protein unable to fulfill its usual function — transporting copper. As a result, children with Menkes disease have abnormal levels of copper: low levels in the blood, the brain and liver, as well as excess amounts in the kidneys and intestines.

But people with distal motor neuropathy do not have abnormal copper levels, Dr. Kaler and his colleagues found. The mutations that cause distal motor neuropathy do not eliminate the protein's function completely — the protein maintains about 70 percent of its normal ability to move copper. Still, the researchers found subtle abnormalities in how the protein itself moves within a cell. The abnormalities

apparently affect people's motor neurons, the nerve cells in the spine that control muscles.

"The ATP7A protein has at least two distinct roles in the nervous system," Dr. Kaler said. "We knew it was critical for central nervous system development. But, before now, there had been no evidence that it played an important role in the function of motor neurons in the peripheral nervous system."

Dr. Kaler and colleagues intend to study the mechanism of how the newly discovered mutations cause the disorder, in hopes of eventually developing treatments.

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