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Novel genetic mutation may lead to the progressive loss of motor function

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Researchers from the National Institutes of Health and their colleagues identified the genetic cause and a possible therapeutic target for a rare form of pediatric progressive neuropathy. Neuropathy, damage or disease affecting the peripheral nervous system, can range from rare conditions linked to a patient's exome to more common causes like diabetes and viral infections. Neuropathies can affect both motor and sensory neurons, producing muscle weakness, numbness, pain, and a wide range of symptoms. The study was published in the journal *Science Signaling* and was a collaboration between the NIH's National Institute of Neurological Disorders and Stroke (NINDS); Vanderbilt University, Nashville, Tennessee; and Yale School of Medicine, New Haven, Connecticut.

These types of discoveries underscore the importance of the families who volunteer to participate in clinical research. "This case superbly illustrates how the intensive study of children with very rare neurological disorders can lead quickly to a deep knowledge of a specific genetic condition, as well as uncover mysteries of the nervous system relevant to a wide spectrum of disorders," said Walter J. Koroshetz, M.D., director of NINDS.

In their report, researchers examined a 10-year-old child with early onset, progressive neuropathy primarily affecting his ability to walk, grasp, and perform fine motor skills. When the patient's complete genetic makeup, or genome, was analyzed, a mutation was found in the gene associated with the protein KCC3. This protein is important for the

ability of cells to respond to swelling.

When a neuron swells, KCC3 is involved in the mechanism that drives fluid out, returning the cell to normal. In the absence of this protein (in what is called a loss-of-function mutation), extreme swelling of the neurons can occur, which in turn leads to nerve damage.

In the study, the patient's mutation affected the ability of KCC3 to turn off once it was no longer needed, leading to the opposite effect—shrunken neurons that also fail to communicate properly. This is referred to as a gain-of-function mutation, causing the affected protein to behave in a new and damaging way.

"This protein, KCC3, has been connected to other forms of neuropathy in the past," said Carsten G. Bonnemann, M.D., a senior investigator in the Neuromuscular and Neurogenetic Disorders of Childhood Section at NINDS and a senior author of the paper. "What's unique here is that this is the first time that we have seen a gain-of-function mutation in the KCC3 protein that leads to neuropathy."

Loss-of-function KCC3 mutations often affect the development of the brain, producing detrimental cognitive changes in addition to both sensory and motor neuropathies. In contrast, the patient described in this report had neuropathy only in the motor neurons and showed no behavioral or developmental changes.

"We wanted to take a closer look at the direct effects of this mutation on the muscles and nerves, so we created a mouse model with the same genetic change as our patient," said Dr. Bonnemann. "When we tested this mouse, we saw many of the same physical deficits, including problems with movement and coordination, and a decrease in the ability of neurons to send signals to the muscles. This shows that this mutation is likely to be the main cause for our patient's neuropathy."

While the exact mechanism that causes the neuropathy remains unclear and will be the focus of further study, identifying a specific molecular target, KCC3, opens the door to studies of potential treatments using U.S. Food and Drug Administration-approved drugs. One such drug, furosemide (also known by its trade name, Lasix), is a diuretic that is prescribed to treat fluid retention, kidney disorders, and high blood pressure. Furosemide is part of a class of drugs that inhibits the function of KCC3 in a way that is unaffected and even enhanced by the gain-of-function mutation.

"We were able to identify what this particular mutation does, so we have a specific target for therapeutic development. Because furosemide inhibits the function of the transporter that is improperly activated in our patient, we may one day be able to use drugs like furosemide to intervene in the progression of neuropathies caused by this type of mutation," said Dr. Bonnemann.

More information: K. T. Kahle et al, Peripheral motor neuropathy is associated with defective kinase regulation of the KCC3 cotransporter, *Science Signaling* (2016). DOI: 10.1126/scisignal.aae0546

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