Researchers link specific protein mutations to ataxia disease symptoms

November 6 2019

Jonathan Schisler, MS, PhD. Credit: UNC School of Medicine

For the first time, the UNC School of Medicine lab of Jonathan Schisler, MS, Ph.D., linked the specific biochemical changes to a protein called CHIP to specific disease characteristics of patients with a wide range of rare disorders. The symptoms of patients with CHIP mutations include

accelerated aging, hypogonadism, and early onset cerebellar ataxia, which is characterized by difficulties with speech, eye movement, swallowing, and a lack of muscle control or coordination of voluntary movements.

Published in the *Journal of Biological Chemistry*, the research shows it is possible to merge analyses of protein biochemistry with patient characteristics to better understand spinocerebellar ataxia autosomal recessive 16, or SCAR16, a debilitating disease that occurs in children when part of the nervous system becomes dysfunctional.

SCAR16 is a monogenetic disorder—a condition resulting from modifications in a single gene known as STUB1. This gene produces the protein CHIP and is found in nearly all cells of the body. CHIP is a multi-functional enzyme, monitoring and regulating the quality of proteins important for human health, particularly in age-related diseases. It was unclear if changes in the different activities of CHIP contribute to the clinical spectrum of SCAR16 and what activities may be potential therapeutic targets.

"We found that the severity of ataxia did not correlate with age of onset," said Schisler, senior author and assistant professor of pharmacology at UNC-Chapel Hill. "However, cognitive dysfunction, increased tendon reflex, and ancestry were able to predict 54 percent of the variation in ataxia severity. We identified specific biochemical activities involving CHIP that correlated with increased tendon reflex or cognitive dysfunction, suggesting that specific changes to CHIP dynamics contribute to the clinical spectrum of SCAR16."

In 2013, Schisler led the study that identified the first mutations in STUB1 responsible for a new disease in two sisters—the disease now known as SCAR16. Since then, researchers have identified more than two dozen additional mutations in people with this disease from all

regions of the world. His lab's most recent work lends credence to the concept that further inhibiting mutant CHIP activity lessens disease severity and may be useful in the design of patient-specific targeted approaches to treat SCAR16 and other age-related diseases involving protein quality control.

More information: Sabrina C. Madrigal et al. Changes in protein function underlies the disease spectrum in patients with CHIP mutations, *Journal of Biological Chemistry* (2019). DOI: 10.1074/jbc.RA119.011173

Provided by University of North Carolina Health Care