Researchers identify new form of muscular dystrophy

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A strong international collaboration and a single patient with mild muscle disease and severe cognitive impairment have allowed University of Iowa researchers to identify a new gene mutation that causes muscular dystrophy.

Furthermore, by engineering the human gene mutation into a mouse, the researchers, led by Kevin Campbell, Ph.D., professor and head of molecular physiology and biophysics at the UI Carver College of Medicine and a Howard Hughes Medical Institute investigator, have created a new mouse model that could help screen potential drugs to treat this type of muscular dystrophy.

The study, which is published in the March 10 issue of the New England Journal of Medicine, also ties together almost two decades of research on dystroglycan, an important muscle protein that is abnormal in a group of congenital muscular dystrophies, which often involve brain abnormalities.

Normal dystroglycan protein is extensively modified with added sugar chains. This modification allows dystroglycan to interact with other cellular proteins and by doing so provide structural strength and integrity to cell membranes in many tissues, including muscle and brain.

Several enzymes are involved in adding sugar chains onto the dystroglycan protein, and mutations in these enzymes cause congenital muscular dystrophies collectively known as secondary

dystroglycanopathies. In these disorders, which include Fukuyama Congenital Muscular Dystrophy, Walker-Warburg Syndrome, Muscle-Eye-Brain disease, Congenital Muscular Dystrophy 1C and 1D, and limb-girdle muscular dystrophy 2I, too few sugar groups are added to the dystroglycan protein. The resulting dystroglycan does not attach properly to other proteins leading to muscle and neurological problems.

"In all these muscular dystrophies, the core dystroglycan protein is normal, so there was always the question of, 'Did the sugar-adding enzymes act on other proteins as well as dystroglycan, and could those other unknown proteins be important for muscular dystrophy?'" said Campbell, who also is a UI professor of internal medicine and neurology and holds the Roy J. Carver Chair of Molecular Physiology and Biophysics. "Finding a mutation in the dystroglycan protein itself, which produces similar muscle and brain problems as are seen in these 'secondary' muscular dystrophies, suggests that dystroglycan is the major substrate, and probably the only substrate, in these other diseases."

Campbell's team, including UI postdoctoral fellow Yuji Hara, Ph.D., collaborated with colleagues in Turkey, Switzerland, England, New York and California to study the mutation found in a Turkish patient with a mild muscular dystrophy and severe cognitive impairment.

The team found that all genes for the known sugar-adding enzymes were normal, but there was a single mutation in the gene for the dystroglycan protein. Further analysis showed that the mutated protein did not get its full complement of added sugar molecules, and was not able to interact efficiently with its normal cell partners either in muscle or brain. The researchers showed that the mutation blocked normal interaction between dystroglycan and one of the sugar-adding enzymes, thus disrupting the addition of sugar chains required for dystroglycan to function.

The researchers then engineered the genetic mutation into mouse dystroglycan and found that the animals have muscle and brain abnormalities similar to the Turkish patient and to patients with the secondary dystroglycanopathies. Taken together, the data strongly suggests that the mutation causes neurological problems as well as muscle disease as a consequence of impaired dystroglycan modification.

"A particularly exciting aspect of this study is the new mouse that we have developed, which has the mutation in the dystroglycan protein," Campbell said. "It will give us a really good model to test therapies for their potential to boost the action of the sugar-adding enzymes and see if that helps reduce the severity of the muscle and neurological symptoms."

With the discovery of the mutation in the dystroglycan protein itself, Campbell's team has found an example of a new disease class known as primary dystroglycanopathy.

Although this finding is based on only one patient, Campbell noted that the mutation produced such mild muscle disease, especially compared to the severe cognitive symptoms, that it was not immediately obvious that the patient had a muscular dystrophy.

"This might mean that there are other patients who have not been correctly diagnosed as having a muscular dystrophy because their major symptoms are cognitive rather than muscular," he said. "Sometimes you just need that first patient case for clinicians to recognize that they have patients whose symptoms may also be caused by a particular mutation."

Provided by University of Iowa Health Care