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## Researchers Identify Defect that Causes Rare Muscular Dystrophies

Subtle defects in the processing of a single protein that provides structural integrity to muscle cells can lead to several devastating forms of muscular dystrophy, according to studies by Howard Hughes Medical Institute researchers and their colleagues at the University of Iowa.

The scientists reported in two papers published in the July 25, 2002, issue of the journal *Nature* that defects in enzymes responsible for the processing of the structural protein dystroglycan are the underlying cause of several rare forms of muscular dystrophy that affect muscles and cause additional developmental brain abnormalities including mental retardation.

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— **Kevin P. Campbell**

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The new findings will immediately help doctors in providing accurate diagnosis and appropriate genetic counseling to patients and their families. In the longer term, knowing the underlying cause of the muscular dystrophies will help researchers tailor their interventions, according to Howard Hughes Medical Institute investigator Kevin Campbell. The disorder also disrupts an important component of learning and memory, so Campbell is hopeful that his team's studies will improve understanding of possible links between muscle physiology and neurobiology.

In the two articles, Campbell and his colleagues describe experiments that demonstrate that dystroglycan is defective in muscle-eye-brain disease and Fukuyama congenital muscular dystrophy. Separate genes had already been identified as defective in these syndromes, but researchers did not understand the underlying mechanism despite having information on the genes involved.

Campbell and his colleagues approached the problem by studying the large complex of proteins involved in several known muscular dystrophies. These proteins, called the dystrophin-glycoprotein complex, protect individual muscle cells from damage as they stretch and contract. They also help hold the cells in place by acting like a molecular Velcro that binds individual cells

to the extracellular matrix, providing a bridge critical for the physical integrity of muscle. In the most common form of muscular dystrophy, Duchenne muscular dystrophy, the dystrophin protein, which provides an anchorage inside the cell, is absent. In the dystrophies Campbell studied, the defect is in anchoring the cell to the extracellular matrix that surrounds it.

The researchers discovered that while the core dystroglycan protein is present on cell surfaces, it is missing distinctive sugar molecules that decorate the protein. The process of adding sugars to proteins, called glycosylation, is an important finishing step in the processing of many proteins and provides a distinctive marking that allows binding partners to recognize the proteins. "When the sugars are missing, it is like Velcro without the loops — it can't stick," said Campbell. "As a result, the cells don't adhere properly to the extracellular matrix and are easily damaged." Campbell and his colleagues hypothesize that several genes defective in these rare forms of muscular dystrophy are involved in the biochemical pathway that leads to glycosylation of dystroglycan.

Additional evidence for the importance of dystroglycan glycosylation came when first author Daniel E. Michele, and his colleagues discovered that a commonly used mouse model of muscular dystrophy, called the *myd* mouse, also has a defect in the biochemical pathway that adds sugar molecules to the dystroglycan protein in muscle and brain. In addition to muscular dystrophy, this mouse had neuronal migration defects very similar to that seen in the patients Michele studied. The loss of the binding of dystroglycan to matrix disrupts anchoring sites at the surface of the brain that are crucial for normal neuronal migration. In human patients, this type of neuronal migration defect results in abnormal smoothing of the brain surface.

"In both the mouse and patients, the only defect is in glycosylation; all the other (dystrophin-glycoprotein complex) components are there," said Campbell. "This shows the importance of the dystroglycan link to the extracellular matrix."

To measure the effect of dystroglycan loss in a controlled way, Steven Moore, a professor of pathology at the University of Iowa, studied mice in which the dystroglycan gene was deleted selectively in brain. In these mice, they found a remarkable similarity to both the *myd* mouse and the patients' brain abnormalities. The finding strengthened the group's hypothesis that dystroglycan is crucial for normal brain function by showing that its absence is sufficient to cause the neuronal migration defects seen in muscular dystrophy patients.

The findings of these two studies raise additional questions about the role of the dystrophin-glycoprotein complex in other developmental brain disorders that result in a smooth brain, some of which are caused by chemical or biological damage. For example, Campbell and his colleagues published a paper in the *Journal of Cell Biology* in 2001 showing that lymphocytic choriomeningitis virus can disrupt the dystroglycan link with the extracellular matrix. LCMV can infect humans, cross the placenta and infect the

developing fetus. The infection produces developmental abnormalities remarkably similar to muscle-eye-brain disease and Walker-Warburg Syndrome.

Finally, the scientists have shown that mice without brain dystroglycan also have defects in an important process called long-term potentiation, which helps form long-term memory by strengthening the links between nerve cells. "This work demonstrates that dystroglycan has two roles in the brain: a developmental role and a synaptic role," said Campbell. "It is interesting because it opens up the whole area of learning and memory and raises questions about the link between neurobiology and muscle physiology."