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New Form of Muscular Dystrophy Found by Two Hughes Teams

Scientists in two HHMI laboratories have found a gene involved in a newly recognized form of muscular dystrophy known as limb-girdle muscular dystrophy.

Kevin P. Campbell's HHMI laboratory at the University of Iowa and Louis Kunkel's HHMI laboratory at Children's Hospital in Boston each found the gene independently. Both groups published their research in separate reports in the November issue of *Nature Genetics*. Muscular dystrophy is a disease of skeletal and cardiac muscle cells, resulting in muscle weakness in persons affected and eventual confinement to a wheelchair. Most muscular dystrophy patients die when the disease affects muscles required for breathing.

"HHMI investigator Kevin P. Campbell (left), HHMI associate Franck Duclos (center) and University of Iowa College of Medicine M.D./Ph.D. student Leland Lim have identified a new form of muscular dystrophy and developed a screening test to detect carriers of the disease."

The new finding zeroes in on the gene for β -sarcoglycan, a protein component of the dystrophin-glycoprotein complex (DGC) which is associated with the muscle cell membrane. The DGC proteins span the muscle cell membrane and link the intracellular cytoskeletal network with the extracellular matrix. "This link stabilizes the cell membrane and plays a crucial role in preserving the integrity of the membrane during muscle cell contraction," Campbell said. A number of muscular dystrophies are caused by defects in genes for components of the DGC. Disruption of this complex, resulting from mutations in one of the DGC components, leads to a greater susceptibility to cell damage from muscle contraction. People with DGC mutations become progressively weaker as more muscle cells become damaged.

Campbell's studies of limb-girdle muscular dystrophy in a group of Amish patients revealed that β -sarcoglycan was absent from the muscle cell membrane in each of the patients. Further studies showed that β -sarcoglycan is normally present in all tissues studied, such as brain, kidney, and liver, suggesting that the protein may be important for other functions which have not yet been determined, Campbell said. The team found the gene encoding β -sarcoglycan in the same region of chromosome 4 that had been associated in previous linkage studies with inheritance of the disease. "These results suggested to us that mutations in the β -sarcoglycan gene are responsible for this new form of muscular dystrophy," said Campbell.

Kunkel's group, which included collaborators in Japan, also found that the gene for β -sarcoglycan was defective in a young, non-Amish girl with limb-girdle muscular dystrophy. The defect was present in the girl and members of her family.

Analysis of the DNA of affected individuals by Campbell's group resulted in the identification of a mutation which caused an amino acid change in the β -sarcoglycan protein. Using a specialized polymerase chain reaction (PCR) diagnostic technique, Campbell's team screened DNA samples of more than 100 unaffected and affected people. The results of the search indicated that only if a person inherited two copies of the mutated gene did he or she develop limb-girdle muscular dystrophy.

Identification of the gene for limb-girdle muscular dystrophy and development of a screening test to identify carriers of the disease in the Amish community has broad implications for the management of the disease. "Because of the rapid and accurate diagnostic procedure, unaffected members of the Amish community can determine their carrier status," Campbell said. "This information can then be used to counsel couples about the risk of having children who might develop muscular dystrophy."

Further efforts are already underway to identify how β -sarcoglycan mutations cause muscular dystrophy. In addition, patients with different forms of muscular dystrophy will be tested for the presence of β -sarcoglycan mutations. The spectrum of mutations and the clinical symptoms that are caused by those mutations will provide further insight into the role of β -sarcoglycan in this disease.