Uncovering the cause of a common form of muscular dystrophy

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An international team of researchers led by an investigator from Fred Hutchinson Cancer Research Center has made a second critical advance in determining the cause of a common form of muscular dystrophy known as facioscapulohumeral dystrophy, or FSHD.

In August 2010 the group published a landmark study that established a new and unifying model for the cause of FSHD. The current work, published Oct. 28 in PLoS Genetics, shows that the disease is caused by the inefficient suppression of a gene that is normally expressed only in early development. The work will lead to new approaches for therapy and new insights into human evolution.

The disease-causing gene, called DUX4, previously had been thought to be a completely inactive gene in humans. DUX4 belongs to a special class of genes called retrogenes, which usually represent unused byproducts of evolution that have no remaining biological function, sometimes called "dead genes."

In contrast, the researchers discovered that the DUX4 protein is abundantly expressed in human germ-line cells, the cells that form the sperm and eggs, which indicates a necessary function early in development. Normally, the DUX4 gene is suppressed in all other cells of the body. However, the mutation that causes FSHD makes this suppression less efficient.

"The result is that the DUX4 gene occasionally escapes the inefficient suppression and is expressed in some muscle cells, similar to the Old Faithfull geyser that is usually off but occasionally releases a burst of water," said corresponding author Stephen Tapscott, M.D., Ph.D., a member of the Hutchinson Center's Human Biology Division. "The occasional 'bursts' of DUX4 are thought to be toxic to the muscle cells, which leads to muscle cell death and the muscular dystrophy."

Tapscott led the study in collaboration with Daniel Miller, M.D., Ph.D., at the University of Washington, and co-authors Silvere van der Maarel, Ph.D., and Rabi Tawil, M.D., at Leiden University Medical Center and the Fields Center for FSHD and Neuromuscular Research at the University of Rochester, respectively.

Previously, these same investigators had shown that the reason some people are protected from getting FSHD is that they have mutations in a region of DNA that is necessary to stabilize the DUX4 gene product. These new findings confirm the role of the DUX4 protein in FSHD and reveal a new mechanism of human disease caused by the inefficient suppression of a retrogene that has a role in early development. These findings will provide a focus for future development of therapies for FSHD.

There are broader implications of the new research for understanding human evolution as well. Maintenance of a functional retrogene in humans indicates that it provided some selective advantage during evolution.

"Since FSHD is characterized by excessively weak upper extremity muscles and facial muscles, we speculate that the DUX4 retrogene might have a normal role in causing the weaker and more expressive facial muscles in humans compared to non-human primates," Tapscott said. "If this suggestion is correct, it means that FSHD is caused by increasing the normal role of DUX4 and causing a more extreme weakness of facial and upper extremity muscles. It also means that all humans have a little bit of FSHD and that this contributes to the evolution of these muscles."

The researchers have an ongoing collaboration through a Hutchinson Center-based National Institutes of Health FSHD Program Project Grant, of which Tapscott is principal investigator, and through the Fields Center for FSHD and

Neuromuscular Research, of which Tawil is the director.

"The progress was made possible by an unusual degree of collaboration and data-sharing among the individual groups," Tapscott said.

Provided by Fred Hutchinson Cancer Research Center