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Researchers give new insight to muscular dystrophy patients

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New research by University of Minnesota scientists has revealed the three-dimensional structure of the DUX4 protein, which is responsible for the disease, facioscapulohumeral muscular dystrophy (FSHD). Unlike the majority of genetic diseases, FSHD is not caused by a protein that is missing or not functioning properly. Rather it is caused when a functioning, normal, protein shows up in a place where it doesn't belong (in muscles).

In the paper "Crystal structure of the double homeodomain of DUX4 in complex with DNA," published in the latest issue of the journal *Cell Reports*, Michael Kyba, Ph.D., professor and Lillehei Endowed Scholar in the University of Minnesota Medical School; and Hideki Aihara, Ph.D., associate professor of Biochemistry, Molecular Biology, and Biophysics in the College of Biological Sciences, crystallized the part of the DUX4 protein that binds to DNA, exposed it to strong X-rays, and used the interference patterns to determine the molecular structure of the protein in three dimensions.

"In many diseases, such structural information has led to the development of drugs to treat those diseases," explained Kyba, "thus this research is an important step on the path to therapy for FSHD."

The structural information also revealed important details about how humans are different from other mammals. "Although all eutherian mammals have a protein equivalent to DUX4, the human protein behaves slightly differently from the mouse protein," says Aihara. "Our

structure showed that a single amino acid difference is responsible for this altered behavior. Furthermore, only primates have this amino acid, meaning that the interaction of the DUX4 protein with DNA in humans, apes and monkeys, is slightly different from that in all other mammals."

By interacting with DNA, the DUX4 protein turns other genes on or off, leading to changes in the function of the cell. Understanding how DUX4 interacts with DNA allows researchers to make predictions about the genes that it regulates and how this causes muscle damage.

Among genetic diseases, FSHD is one of the more common. It is thought to affect close to 1 million people worldwide and currently has no treatment. "Although we have known for many years that DUX4 causes FSHD, we have not had a good explanation for how it damages muscle," said Kyba. "Seeing for the first time what this protein actually looks like when it binds to DNA, and knowing that this is the act that is responsible for so much suffering, was both remarkable and sobering."

More information: John K. Lee et al. Crystal Structure of the Double Homeodomain of DUX4 in Complex with DNA, *Cell Reports* (2018). DOI: 10.1016/j.celrep.2018.11.060

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