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UVA reports surprising findings related to myotonic muscular dystrophy

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New research from the University of Virginia Health System shows that, in cases of Type 1 myotonic muscular dystrophy (DM1), a well known heart protein does several surprising things. DM1 is the most common form of muscular dystrophy in adults and affects approximately 40,000 adults and children in the U.S.

The protein, NKX2-5, is a biomarker for heart stem cells. It is also very important for the normal development of the heart. “Too little of it causes major cardiac problems including slow and irregular heartbeats,” observes Dr. Mani Mahadevan, a human genetics researcher and Professor of Pathology at UVa who led the study.

The researchers were surprised to find that mice and individuals with DM1 actually overproduce NKX2-5, yet experience the same kind of heart problems associated with too little of it.

Excessive NKX2-5 may explain why as many as 60 to 70 percent of individuals with DM1 develop heart problems which cause their heartbeats to become slow and irregular, often necessitating the need for pacemakers. If these irregular heartbeats are not detected, sudden death can occur.

By using the mouse model of DM1 and mice genetically engineered to produce less NKX2-5, Dr. Mahadevan and his team showed that reducing the excessive levels of NKX2-5 seemed to protect the mice from the heart problems.

Researchers were also surprised to find NKX2-5 in the muscles of mice and individuals with DM1. “Usually, NKX2-5 is found only in the heart of adults,” Dr. Mahadevan notes. “It’s like the muscle is having some kind of ‘identity crisis’ and starting to make proteins that shouldn’t be there normally.”

This discovery could prove beneficial, says Dr. Mahadevan, and lead to development of a simple diagnostic test to follow a patient’s response to potential therapies.

Myotonic muscular dystrophy is recognized as the first example of a disease caused by a toxic RNA. RNAs are intermediary molecules that convey the genetic code in the DNA to the rest of the cell. RNAs are normally “cut and pasted together” by a process called RNA splicing. It is currently thought that the toxic RNA causes DM1 by disrupting normal RNA splicing.

“Much of the research on DM1 is focused on factors that cause RNA splicing defects. Our work may provide explanations for pathogenic effects not accounted for by RNA mis-splicing,” Mahadevan explained.

Source: University of Virginia Health System