Team deciphers how myotonic dystrophy generates lethal heart dysfunctions

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Researchers determined key molecular events that lead to heart abnormalities in myotonic dystrophy. The team included, from left, bioengineering professor Lawrence Dobrucki, postdoctoral fellow Jamila Hedhli, biochemistry professor Auinash Kalsotra, graduate student Sushant Bangru, research scientist Chaitali Misra and graduate student Kin Lam. Credit: L. Brian Stauffer

Roughly 80% of people with myotonic dystrophy—a common form of muscular dystrophy—experience dangerous heart ailments, and heart rhythm defects are the second-leading cause of death in those with the condition. In a new study, researchers traced the molecular events that lead to heart abnormalities in myotonic dystrophy and recreated the disease in a mouse model.

They report their findings in the journal *Developmental Cell*.

"In this study, we discovered that the genetic abnormalities associated with myotonic dystrophy lead to the overproduction of an alternative-splicing factor that regulates how cells process other proteins," said Auinash Kalsotra, a professor of biochemistry at the University of Illinois at Urbana-Champaign who led the work. He is a faculty member in the Carl R. Woese Institute for Genomic Biology and in the Cancer Center at Illinois.

The alternative-splicing factor comes in two forms, called muscle and nonmuscle RBFOX2. Both alter RNA transcripts by splicing them before they are translated into proteins. The nonmuscle form of the protein is elevated in the heart muscles of people with myotonic dystrophy, the researchers found.

"When we engineered mice to express this wrong version of the protein in the heart, they developed the same heart irregularities seen in humans with myotonic dystrophy," Kalsotra said. "We decided to investigate further why expression of the nonmuscle RBFOX2 variant in the heart triggers arrhythmias."

"By looking at cardiac gene-expression data and focusing on which gene transcripts are altered by the nonmuscle RBFOX2 in myotonic dystrophy patients, we discovered that it induces abnormal splicing of proteins that make up the major potassium and sodium channels in heart cells," said

Chaitali Misra, a postdoctoral research scientist in the Kalsotra laboratory and the first author of the study. "These channels are essential to the propagation of electrical signals across heart muscle, and their aberrant splicing causes major cardiac conduction defects."

"This disrupts the normal rhythm and function of the heart in individuals with myotonic dystrophy," Kalsotra said.

"Our results have answered a long-standing question of why myotonic dystrophy patients develop cardiac dysfunctions and offers new insights into previously unknown mechanisms causing arrhythmias in the heart," he said. "We expect these findings will help explore new approaches for treating cardiac arrhythmias and bring us closer to finding a cure for this disease."

More information: Aberrant expression of a non-muscle RBFOX2 isoform triggers cardiac conduction defects in myotonic dystrophy, *Developmental Cell* (2020). DOI: 10.1016/j.devcel.2020.01.037

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