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Scientists elucidate molecular mechanism contributing to cardiomyopathy

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Cardiomyopathy comprises a deterioration of the heart muscle that affects the organ's ability to efficiently pump blood through the body. Previously researchers have tied forms of the disease to the alternative splicing of titin, a giant protein that determines the structure and biomechanical properties of the heart, but the molecular mechanism remained unknown.

Professor Michael Gotthardt and Professor Norbert Hübner of the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch, Germany, and colleagues have found that the RNA binding motif protein 20 (RBM20), a gene previously tied to hereditary cardiomyopathy, regulates titin splicing. Understanding this molecular mechanism behind heart function and failure, could lead to more efficient molecular diagnosis and therapies for this sometimes insidious disease.

The ventricular filling of the heart is regulated by the different protein isoforms of titin which are produced through alternative splicing, a process in which the protein-coding regions of RNA (the exons) are connected in different ways, resulting in multiple mRNAs (messenger RNAs) that give rise to many proteins.

Professor Marion Greaser of the University of Wisconsin-Madison, USA, had recently identified a naturally occurring rat strain deficient in titin splicing, which resulted in an elongated titin protein. "Titin naturally shortens around birth as the blood flow is redirected through the heart," Professor Gotthardt explained, "but these rats maintained the excessively

long embryonic titin isoforms, which suggests a cause for their cardiomyopathy."

Using genome-wide mapping techniques, the researchers found a loss-of-function mutation in RBM20 in all the rats that expressed the pathological titin isoform. The rats with this mutation also shared many phenotypic similarities with human patients suffering from RBM20 related cardiomyopathy; specifically, ventricular enlargement, arrhythmia, increased rate of sudden death, and extensive fibrosis.

The researchers also identified a set of 31 genes shared by humans and rats that regulate splicing with RBM20. Included in this group was titin, thus validating the group's previous findings. Many of these genes have previously been tied to cardiomyopathy, ion-homeostasis, and sarcomere biology and future analysis will help resolve their individual contribution to the progression of the disease.

Towards utilizing these findings in a clinical setting, Professor Gotthardt has developed a technique to characterize the functional consequences of individual RBM20 mutations. "We can help patients learn if their RBM20 mutation will likely result in the severe form of the disease so that their physician can devise an appropriate therapy," added Professor Gotthardt. "We are currently utilizing this information to develop novel therapeutic strategies for patients suffering from severe forms of cardiomyopathy."

More information: RBM20, a gene for hereditary cardiomyopathy, regulates titin splicing, *Nature Medicine*, dx.doi.org/10.1038/nm.2693xxx

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