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SCIENTISTS UNCOVER NEW MECHANIMS RESPONSIBLE FOR HEART DISEASE

MMRI Collaborates to Investigate Rare Mutations to Unlock Answers to Heart Failure

UTICA, NY — Heart disease continues to be the number one cause of death worldwide. Many of those who experience heart failure develop the disease due to underlying, genetic mutations within their DNA. By investigating these rare mutations, researchers and clinicians can better understand the various reasons as to why the disease occurs, and make possible the discovery of life-saving treatments. Recently, Dr. Coralie Poizat, Associate Professor at the Masonic Medical Research Institute (MMRI), studied one of these rare mutations in the heart. “Our findings identified a novel mechanism causal to human heart disease, which upon further examination, will hopefully lead to the development of new therapeutic targets and better options for treatment of children with genetic heart abnormalities,” said Dr. Poizat.

Following on the heels of a paper published in 2016, in which the genetic mutation in question was discovered in a large blood-related family from Saudi Arabia, the manuscript aimed to take the research one step further. The mutation, identified in the FBXO32 gene, was found in 4 out of 10 siblings, and was causal to heart failure in these children. Ultimately, this required the affected children to all need a heart transplant before the age of 21. “After finding this mutation, which was previously unknown, we wanted to know more and figure out why it was that they were developing end stage heart failure at such a young age,” said Dr. Poizat.

The mutation in the FBXO32 protein was discovered by comparing samples from diseased hearts to healthy hearts. The Poizat lab identified that the mutation was preventing its necessary binding to other partner proteins, thereby causing abnormal enlargement and dysfunction of the heart. Moreover, the study revealed that the mutation led to excessive heart cell death due to an abnormal activation of an FBX032 partner protein called CHOP. Interestingly, the mutation did not activate any other of the “usual suspects” associated with cardiac stress. Together, these data suggest that the FBX032 mutation induces alternative stress-mediated signaling pathways in the heart, which lead to the development of dilated cardiomyopathy and heart failure.

This basic biomedical research is crucial to understanding heart failure, as more than 30% of patient cases are directly linked to genetic mutations. Therefore, this type of research provides key insights into the mechanistic pathways causal to heart failure, and helps researchers identify how they can devise ways to repair the cardiac dysfunction in patients. “As researchers, we do the work that is often behind the scenes. However, this work is necessary for clinicians and medical professionals to more effectively and safely treat their patients,” said Dr. Poizat.

The manuscript titled, “Mutation in FBXO32 causes dilated cardiomyopathy through up-regulation of ER-stress mediated apoptosis,” was published in *Communications Biology* on July 16, 2021. Additional authors include Drs. Nadya Al-Yacoub, Dilek Colak, Salma Awad Mahmoud, Kunhi Muhammed, Olfat Al-Harazi, Abdullah M. Assiri, and Jehad Al-Buraiki from King Faisal Specialist Hospital & Research Center; Dr. Waleed Al-Habeeb from King Saud University; and Maya Hammonds, former Research Assistant at the MMRI. The publication can be found at the following website: nature.com/articles/s42003-021-02391-9

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