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Researchers identify first gene linked to heart muscle disease in children

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Scientists at Icahn School of Medicine at Mount Sinai, along with collaborators at institutions in India, Italy, and Japan, have identified the first gene linked to childhood-onset familial dilated cardiomyopathy (DCM), one of the most common heart muscle diseases in children. It is a progressive and potentially fatal heart condition resulting from an enlarged and weakened heart muscle.

The study, published in *Nature Genetics*, also revealed a link between DCM and excessive activation of the protein, mTOR. Currently, there are several existing FDA-approved blocking drugs for this protein including rapamycin, currently used primarily as an immunosuppressant after solid organ transplantation. Promising preliminary research indicate that at least one of these mTor inhibitors may be effective in halting progression of the disease.

"One day we hope to have therapeutic treatments for all of the different genetic variations that contribute to this complex disease, not just medications that delay heart failure," said Valentin Fuster, MD, PhD, Director of Mount Sinai Heart, the Zena and Michael A. Wiener Cardiovascular Institute, and the Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, and Physician-in-Chief at The Mount Sinai Hospital. "This extraordinary study may lead to the first of those treatments and offers new hope to a group of patients with no other medical recourse."

DCM is a disease characterized by progressive weakening and

enlargement of the heart muscle, which can lead to heart failure and premature death. Experts estimate that it likely affects about one in every 250 individuals. The genetically complex disease is associated with variants in at least 40 genes, with the underlying causes of 50-60 percent of cases remaining unknown. Currently, DCM has no cure as the available medicines only delay the onset of congestive heart failure or the need for aggressive therapies like heart transplantation.

In this research effort, scientists conducted DNA sequencing on more than 500 adults and children with DCM and more than 1,100 healthy controls from several ethnically distinct cohorts to learn about the genetic profile of the disease. They identified changes in the RAF1 gene as a cause of DCM and found that patients with these mutations were more likely to have been diagnosed with the disease as children. These genetic variants accounted for approximately 10 percent of childhood-onset DCM cases in the populations studied. Also, the RAF1 variants increased activity of the protein mTOR, which can be inhibited with several drugs already approved by the FDA.

To validate their findings, the scientists modeled these genetic changes in zebrafish. When treated with the medication, rapamycin, one of the FDA-approved drugs used to inhibit the mTOR protein, the zebrafish heart defects were partially reversed and protein levels shifted to a healthy profile.

"There are currently virtually no treatments for dilated cardiomyopathy targeted to genetic changes, so the finding that commercially available drugs may be effective for patients with childhood-onset, RAF1-induced DCM is a remarkable advance," said Bruce Gelb, MD, Director and Gogel Family Professor of the Mindich Child Health and Development Institute at Mount Sinai and senior author. "The critical next step is to study this biological mechanism in a mammalian model and generate data to support a clinical trial of rapamycin or a related drug for DCM

patients who have these genetic variants."

More information: RAF1 mutations in childhood-onset dilated cardiomyopathy, *Nature Genetics*, DOI: 10.1038/ng.2963

Provided by The Mount Sinai Hospital

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