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Study Identifies the Molecular Mechanisms by which Noonan Syndrome RAF1 mutations cause Cardiac Hypertrophy

UTICA NY – Investigators from the Masonic Medical Research Institute (MMRI), Weill Cornell Medicine and Beth Israel Deaconess Medical Center (BIDMC) have identified the molecular mechanisms by which RAF1 mutations in patients with Noonan Syndrome (NS) cause hypertrophic cardiomyopathy (HCM), a dangerous thickening of the heart muscle that can lead to heart failure and death. Reported online this week in the American Heart Association Journal *Circulation*, the new findings reveal downstream effectors that could serve as therapeutic targets for treating NS-associated HCM.

Noonan syndrome is a disorder that involves unusual facial characteristics, short stature, and a multitude of heart defects, including pulmonary stenosis and atrioventricular septal defects (AVSD). It is caused by mutations in any one of several genes, including *PTPN11, SOS1, RAF1* and *KRAS,* each of which modulates the function of the canonical RAS-Mitogen Activated Protein Kinase (MAPK) pathway, a protein signaling cascade important for the regulation of cell growth, differentiation and cell death. RAF1-associated NS patients, often infants and young children, usually present with a more devastating cardiac defect, a severe form of HCM that is often lethal.

“NS is the most common of a group of rare congenital disorders termed RASopathies, which include Costello Syndrome, NS with multiple lentigines (formerly LEOPARD) Syndrome, Neurofibromatosis, Cardiofaciocutaneous Syndrome, and others, and has a prevalence of about 1:1,000 to 1:2,500 children born each year worldwide. NS-associated RAF1 mutations specifically are even more rare, but the effects of this mutation are also much more severe than the other mutations thought to be causal to NS,” explained senior author Maria Kontaridis, PhD, Director of Research, Masonic Medical Research Institute and Associate Professor of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School.

"Currently there is no treatment to prevent the onset of NS and protect against the heart defects that are associated with the RAF1 mutations that cause this disease,” said first author Fabrice Jaffré, PhD, Instructor of Cell and Developmental Biology in Surgery at Weill Cornell Medicine.

“Our studies sought to model and understand the molecular mechanisms that trigger the disease and its cardiac hallmarks so that we can identify new targeted treatments.”

In the article, the investigators used patient-derived RAF1$^{S257L/+}$ and CRISPR-Cas9-generated isogenic control inducible pluripotent stem cell (iPSC)-derived cardiomyocytes (iCMs) to model NS RAF1-associated HCM and to further delineate the molecular mechanisms underlying the disease.

“iPSC-derived cardiomyocytes, combined with genome editing technology such as CRISPR, can be a powerful system for modeling cardiac disorders such as NS-associated HCM, in order to decipher the molecular mechanisms underlying the disease and ultimately, to uncover potentially new therapeutic targets,” said Dr. Jaffré.

“Here, the findings show that two parallel signaling pathways are involved in the development of RAF1-associated HCM,” Dr. Kontaridis said. “Specifically, the ERK5 signaling pathway functions to increase cell size, i.e. hypertrophy, whereas the MEK1/2 signaling pathway is involved in the regulation of cardiac sarcomere function. Both are required to cause the HCM phenotype.”

“Together, these data indicate that this disease is not linear; there are multiple, parallel signaling pathways that play important roles in leading to a disease phenotype. One pathway may be necessary, but alone it may not be sufficient to cause that disorder; therefore, use of a potential combinatorial therapy for each of these pathways identified herein could lead to a promising approach in treating NS-associated RAF1 patients with HCM,” said Dr. Kontaridis.

“Rare disease has always been a window to understanding more common disorders,” said Dr. Kontaridis. “By studying rare diseases and delineating what mechanisms cause those diseases, we may reveal potential therapeutic options for other, more common, diseases as well.”

Additional study coauthors include Clint L. Miller, Center for Public Health Genomics, Department of Public Health Sciences, Biochemistry and Molecular Genetics, and Biomedical Engineering, University of Virginia; Anne Schänzer, Institute of Neuropathology, University Hospital Giessen, Justus Liebig University Giessen, Germany; Todd Evans, Department of Surgery, Weill Cornell Medicine; Amy E. Roberts, Department of Cardiology, Division of Genetics, Boston Children's Hospital; and Andreas Hahn, Department of Child Neurology, University Hospital Giessen, Justus-Liebig University, Giessen, Germany.

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