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EDITORIAL COMMENT

Focusing in on the Danon Disease Heart

Charles A. Tharp, MD,[a] Matthew R.G. Taylor, MD, PhD[b]

Genetic causes of cardiomyopathy are historically underrecognized, which has contributed to delayed, or missed diagnoses resulting in deferred initiation of evidence-based therapies and missed opportunities for family screening. Panel-based genetic testing, where available, has advanced diagnostic speed and permits an understanding of genotype-phenotype relationships, prognostic considerations, and access to early but promising gene therapy trials (A Gene Therapy Study of RP-A501 in Male Patients With Danon Disease; NCT06092034).[1] Although expansion of clinical testing is essential for improved diagnosis and management of familial cardiomyopathies, the ability to recognize pathogenic mutations is limited by mutations previously reported in literature and in collective registries. Therefore, it is essential that efforts continue to identify and report novel gene mutations that contribute to cardiomyopathy. Additionally, these gene discovery efforts should be inclusive of patient populations from diverse geographic, ethnic, and socioeconomic circumstances so that our understanding of genetic causes of heart failure is comprehensive and representative of the world population. In this issue of *JACC: Case Reports*, the paper by Guerra et al[2] is an example of discovery and reporting of a novel gene mutation associated with clinical Danon disease.

Danon disease is an X-linked dominant disorder caused by mutations and loss of function of the lysosome-associated membrane protein (LAMP2). LAMP2 deficiencies cause impairment of lysosome-mediated cell autophagy leading to accumulation of glycogen and cytoplasmic material within intracellular vacuoles resulting in oxidative stress, cell death, and fibrosis. Cellular changes are more pronounced in cells with high metabolic activity including within the myocardium, skeletal muscle, and brain.[3] Clinical manifestations of Danon disease are often described as a syndrome of cardiac and extracardiac features, including cardiomyopathy, skeletal myopathy, intellectual disability, and retinal diseases which present in men and women in the first and second and second to fourth decades of life, respectively. Typical cardiac manifestations include left ventricular hypertrophy, cardiac fibrosis, systolic dysfunction, conduction abnormalities, and arrhythmias with a severe disease course typically requiring cardiac transplantation for long-term survival.[4]

Guerra et al[2] report a case of a 14-year-old boy who presented with severe cardiac hypertrophy, a short PR interval on electrocardiography, and significant cardiac fibrosis. Initially diagnosed with hypertrophic cardiomyopathy, the patient subsequently developed left ventricular systolic function, left ventricular dilation, and progression of cardiac fibrosis with an acute left ventricular thrombus. Given the rapidly progressive cardiac deterioration, the clinical team appropriately expanded the differential diagnosis for alternative etiologies including genetic causes and completed exon sequencing of 289 genes. The reported results identified a novel mutation in LAMP2 c.645_651del that results in frameshift and early termination of the LAMP2 protein (p.Lys215Asnfs*25) predicted to affect all 3 isoforms of LAMP2. The clinical progression was consistent with Danon disease, and the patient required cardiac transplantation with pathologic findings of the explanted heart demonstrating autophagic vacuoles and cytoplasmic glycogen, which are features associated with Danon disease.

The data of this case report support the novel discovery of a likely pathogenic LAMP2 mutation leading to clinical Danon disease. This mutation is described in a historically underrepresented population from Mexico adding important ethnic and population

From the [a]Division of Cardiology, University of Colorado, Denver Health, Denver, Colorado, USA; and the [b]Adult Medical Genetics Program and Division of Cardiology, Anschutz Medical Center, Aurora, Colorado, USA. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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diversity to the existing genetic knowledge base which has traditionally gathered information from Western European, Caucasian, and Asian populations.[5] There are, however, limitations to the case report that should be highlighted. The first is that a comprehensive family history and pedigree are not included in the report. American College of Medical Genetics and Genomics and the Heart Failures Society of America guidelines for evaluation of patients suspected of having a genetic cause of cardiomyopathy recommend obtaining a detailed family history of at least 3 generations and phenotypic screening for cardiomyopathy of at-risk family members.[6,7] It should be emphasized that a detailed family history and creation of a pedigree should be included not only for academic reporting, but also for clinical management and facilitation of cascade genetic testing in first-degree relatives. The authors claim of a novel pathogenic LAMP2 mutation leading to Danon disease would be strengthened by data including alternative causative mutations and a detailed pedigree demonstrating that the reported mutation cosegregates with a clinical phenotype in other family members.

The authors suggest the novel LAMP2 mutation reported is associated with a cardiac exclusive phenotype without the typical intellectual or skeletal muscle manifestations of Danon disease. LAMP2 mutations leading to a cardiac predominant phenotype have been reported with frameshift mutations occurring at c.741+2T, c.764_765insGA, c. 973delC, and c.35C>A.[8-10] If valid, these cardiac-specific phenotypes represent an interesting topic for future study to identify on the molecular and cellular level why specific truncating mutations may cause a cardiac selective phenotype. Such translational studies may offer a more comprehensive understanding of the molecular pathogenesis of Danon disease and may lead to novel therapeutic targets. Additional information regarding clinical phenotyping would be helpful to definitively conclude that the reported mutation is cardiac exclusive including skeletal muscle testing and cognitive testing.

Overall, the case report by Guerra et al[2] adds to the expanding literature of likely pathogenic mutations contributing to cardiomyopathy and Danon disease. The authors report the discovery of a novel LAMP2 mutation in a 14-year-old boy with left ventricular hypertrophy, myocardial fibrosis, and rapid deterioration resulting in heart transplantation with myocardial pathology consistent with Danon disease. This study highlights the utility of genetic testing for correctly diagnosing and managing patients with cardiomyopathies. In addition, the case serves as an example of exon sequencing as a tool for identifying novel gene mutations which improves individual clinical management and adds to collective knowledge for identification of pathogenic mutations in future patients. Finally, the report suggests that mutation leads to an exclusive cardiac phenotype, which represents an interesting area of future study to determine how specific LAMP2 mutations may have more cardiac selective effects.

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ADDRESS FOR CORRESPONDENCE: Dr Matthew R.G. Taylor, Adult Medical Genetics Program and Division of Cardiology, Anschutz Medical Center, 12700 East 19th Avenue, F442, Aurora, Colorado 80045, USA. E-mail: matthew.taylor@cuanschutz.edu.

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