Case Study: Danon Disease presenting as DCM

Clinical Overview
A 65 year-old female presents to her cardiologist with a history of cardiomyopathy and cardiac arrest. An echocardiogram reveals a mildly dilated left ventricle and an ejection fraction of 21%. Full panel testing was ordered for dilated cardiomyopathy (DCM). A Heterozygous mutation was found in the LAMP2 gene, which is X-linked dominant and known to cause Danon disease. LAMP2 mutations typically cause multisystem glycogen-storage disease (aka Danon disease), which can present as a primary cardiomyopathy in both men and women. In a study of 24 patients with increased left ventricular wall thickness an ECG suggesting ventricular pre-excitation, approximately 17% had a LAMP2 mutation.

Patient Information:
Age: 65 Specimen: Blood

Referral diagnosis: Dilated left ventricle and reduced ejection fraction.

Family history: Her family history is notable for a daughter with hypertrophic cardiomyopathy and a son who died of sudden cardiac death. Additional family history is unremarkable.

Diagnostic Summary:
POSITIVE. Heterozygous Trp98Stop mutation in LAMP2. GeneDx tests not only for genes associated with isolated DCM, but also genes associated with multisystem disorders such as mitochondrial disease and Danon disease. Distinguishing the different genetic causes of ventricular dilation is extremely important, as the clinical management for DCM may differ based on which gene is the cause of disease.

DCM gene sequencing panel: Sequence analysis of 27 genes associated with DCM revealed the Trp98Stop (W98X) mutation in LAMP2, previously reported in two family members with Danon disease. Fanin (2006) reported the Trp98Stop mutation in a male patient presenting with jaundice at age 12 and developed muscle weakness, Wolff-Parkinson-White (WPW) syndrome and hypertrophic cardiomyopathy (HCM) by his 20s. His mother, who was heterozygous for Trp98Stop, had a history of WPW, mild muscle weakness and HCM progressing to heart failure with subsequent heart transplant by age 52. Males with a hemizygous LAMP2 mutation exhibit severe hypertrophy at an early age of onset (8-17 years of age), and ventricular pre-excitation. The majority of male patients with a LAMP2 mutation have CNS involvement including mental retardation, cognitive impairment and developmental delay. Mutations in females have been associated with a wide phenotypic spectrum, ranging from asymptomatic to severe heart failure and sudden cardiac death, presumably due to variation in X-inactivation from one individual to another.

Diagnostic Implications:
Although DCM can be inherited, ventricular dilation can also be acquired as a result of ischemia heart disease, normal aging, valvular heart disease, toxins such as alcohol and cocaine, infectious disease, and pregnancy. Genetic testing as part of a clinical evaluation can define the diagnosis and assist in determining appropriate management. The patient was counseled for management of Danon disease and the patient’s daughter was offered known mutation testing to confirm that her “hypertrophic cardiomyopathy” was actually LVH secondary to Danon disease.

References: