Case Study: Mitochondrial disease presenting as HCM

Clinical Overview
A 26 year-old male presents with hypertrophic cardiomyopathy (left ventricular wall thickness 1.8 cm) on echocardiogram. Full panel testing was ordered for hypertrophic cardiomyopathy (HCM). A homoplasmic mitochondrial DNA mutation (A4300G) was found in the MT-TI gene, which is known to cause maternally inherited HCM. Unlike other mitochondrial mutations which are known to have phenotypic variability, this mutation is currently believed to cause isolated HCM.

Patient Information:
**Age:** 26  **Specimen:** Blood

*Referral diagnosis:* Hypertrophic cardiomyopathy. Patient has normal weight and no history of smoking or hypertension.

*Family history:* Patient has one 28 year-old sister, who is not known to have HCM but has never been evaluated. Patient’s family history is significant for his mother and maternal uncle with cardiomyopathy.

Diagnostic Summary:
**POSITIVE.** Homoplasmic A4300G mutation in MT-TI. GeneDx tests not only for genes associated with isolated HCM, but also genes associated with multisystem disorders such as amyloidosis, mitochondrial disease, and Fabry disease. Distinguishing the different genetic causes of heart muscle thickening is extremely important, as the treatment for HCM can differ based upon the etiology. The GeneDx 18 gene HCM panel detects mutations in over 60% of patients with a clinical diagnosis of hypertrophic cardiomyopathy.

**HCM gene sequencing panel:** Sequence analysis of 18 genes associated with HCM revealed the homoplasmic mitochondrial mutation m.4300 A>G (A4300G) in the mitochondrially encoded tRNA isoleucine gene (MT-TI). The A4300G mutation in the MT-TI gene has been previously reported in at least two families with maternally inherited hypertrophic cardiomyopathy and was absent from controls.1, 2 In addition, the A4300G mutation has been previously observed in multiple unrelated individuals tested for cardiomyopathy at GeneDx. Since mitochondrial DNA (mtDNA) is passed down to the offspring only through the mother, mtDNA-associated disorders exhibit maternal inheritance. It is believed that the A4300G causes isolated cardiomyopathy and does not cause other mitochondrial-related disease.1

Diagnostic Implications:
Mitochondrial disorders are clinically and biochemically very diverse, but typically present in tissues with high energy requirements such as the brain, heart, and skeletal muscle first. In some cases, the patients can present with isolated cardiomyopathy. Genetic testing as part of a clinical evaluation for cardiomyopathy can define the diagnosis, prognosis, and assist in determining appropriate management. Individuals with mitochondrial mutations should be screened for other mitochondrial-related diseases such as myopathy, diabetes, hearing loss, visual impairment, strokes, and cognitive deficits.

This patient was counseled for the management of mitochondrial cardiomyopathy. He was also counseled that any future children would not be at risk for inheriting this mutation, as men do not pass on their mitochondrial DNA to offspring. The patient’s sister can now be offered targeted testing for the A4300G mutation to determine if she and any future children are at high risk to develop HCM.

References: