Case Study: Fabry Disease presenting as HCM

Clinical Overview
A 37 year-old male presents to his doctor with episodes of presyncope and a family history of hypertrophic cardiomyopathy. An echocardiogram reveals a maximum left ventricular wall thickness of 17.6 mm. Full panel testing was ordered for hypertrophic cardiomyopathy (HCM). A hemizygous mutation was found in the GLA gene, which is known to cause Fabry disease, an X-linked disorder caused by deficient activity of the enzyme α-galactosidase (α-Gal A). Concentric hypertrophy is a finding that can be associated with Fabry disease. Studies suggest that approximately 3-10% of cases of unexplained left ventricular cardiac hypertrophy (LVH) in adult males may be caused by underlying Fabry disease. Full gene sequencing of GLA detects mutations in all affected males with decreased α-Gal A enzyme activity and most heterozygous females.

Patient Information:
Age: 37  Specimen: Blood

Referral diagnosis: Left ventricular hypertrophy on echocardiogram. Patient has normal weight and no history of smoking or hypertension.

Family history: Patient’s family history is notable for a sister and mother with hypertrophic cardiomyopathy. Paternal family history is unremarkable.

Diagnostic Summary:
POSITIVE. Hemizygous Gly373Ser in GLA. GeneDx tests not only for genes associated directly with HCM, but also genes associated with disorders such as amyloidosis, Danon disease, and Fabry disease. Distinguishing the different genetic causes of heart muscle thickening is extremely important, as the treatment for HCM differs markedly from the treatment of other conditions.

HCM gene sequencing panel: Sequence analysis of 18 genes associated with HCM revealed the hemizygous Gly373Ser mutation in the GLA gene, associated with Fabry syndrome. The Gly373Ser mutation has been previously reported in association with a Fabry disease phenotype. Hemizygous males typically have a more “classic” onset of Fabry disease with periodic pain crises, vascular cutaneous lesions, corneal/lenticular opacities, hypohidrosis, stroke, renal insufficiency and/or LVH. Heterozygous females typically have a milder presentation, including isolated LVH, and have a later age of onset than males. This milder phenotype is attributed to the presence of a normal allele on the second X chromosome; however there is wide clinical spectrum in heterozygous females presumably due to variation in X-inactivation from one individual to another.

Diagnostic Implications:
Hypertrophy of the left ventricle is a finding common to several conditions, including athlete’s heart, hypertensive heart disease, Fabry disease, cardiac amyloidosis, cardiac sarcoidosis, or when all other conditions are excluded, idiopathic hypertrophic cardiomyopathy. 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 Fabry disease including the availability of enzyme replacement therapy (ERT) which prevents disease progression and other associated disease manifestations including renal disease and strokes. Patient was counseled that all his daughters would carry the mutation for Fabry disease and might manifest symptoms if untreated. The patient’s sister and mother were offered known mutation testing to confirm that their “hypertrophic cardiomyopathy” was actually LVH secondary to Fabry disease and, if positive, could also be eligible for ERT.

References: