Case Study: Mitochondrial disease caused by the A3243G point mutation

Clinical Overview:
A 15-year-old male presents with a complex clinical history, including failure to thrive (FTT), growth retardation (GR), possible sensorineural hearing loss (SNHL), cognitive disabilities, neurological findings, and increased plasma glycine (full history listed below). His mother has a history of diabetes and hearing loss. GeneDx’s sequence analysis of the entire mitochondrial genome was ordered. A heteroplasmic mitochondrial DNA mutation (A3243G) was found in the MT-TL1 gene. The heteroplasmy level was determined to be approximately 8% in the submitted blood specimen. The A3243G mutation is associated with various phenotypes, even within the same family. The level of heteroplasmy in the blood does not correlate with the extent of disease in an individual, as the mutation load can vary widely between tissues.3

Patient Information:
Age: 15 Specimen: Blood

Referral diagnosis: Prematurity, hydrops/chylothorax, failure to thrive, growth retardation/short stature, learning disabilities, possible sensorineural hearing loss, abnormalities of the basal ganglia, dystonia, hypertonia, spasticity, and increased plasma glycine.

Family history: The patient’s mother reports a clinical history of type II diabetes mellitus and sensory neural hearing loss, but was adopted and does not know anything about her biological family. The father’s family history was overall unremarkable.

Diagnostic Summary:
POSITIVE. Heteroplasmic A3243G mutation in the MT-TL1 gene; ~8% heteroplasmy detected.

Sequence Analysis of the Entire Mitochondrial Genome: The entire mitochondrial genome was sequenced and the m.3243 A>G (A3243G) mutation was detected in the mitochondrially-encoded tRNA leucine gene (MT-TL1). The level of heteroplasmy for this mutation in the submitted specimen is approximately 8%. This mutation has been associated with various phenotypes, including 80% of MELAS cases (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes), ~2-7% of patients with MIDD (Maternally Inherited Diabetes and Deafness), Leigh syndrome, and hypertrophic cardiomyopathy (10% of Finnish patients).1,2

GeneDx sequences the entire mitochondrial genome and can detect levels of heteroplasmy as low as 4%. GeneDx also provides the haplogroup information for each patient and a table of observed polymorphisms.

Diagnostic Implications:
Mitochondrial disorders are clinically and biochemically very diverse, but typically present first in tissues with high energy requirements, such as the brain, heart, and skeletal muscle. The patient was counseled for the management of mitochondrial disease. 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. His mother was tested for the A3243G mutation and was found to be positive for the mutation with a level of 12% heteroplasmy in her blood. The family was counseled that although the A3243G mutation was detected at certain levels in the blood, the level of mutation declines over time and may not accurately represent the level of heteroplasmy in other tissues.3

References: