Case Study: CPEO caused by a novel deletion in the mitochondrial genome

Clinical Overview:
A 45-year-old female presents to her physician with a clinical diagnosis of chronic progressive external ophthalmoplegia (CPEO) and ragged red fibers on a muscle biopsy. Sequence analysis and deletion testing of the mitochondrial genome was ordered on a muscle sample from the patient. A novel heteroplasmic 9.3 Kb deletion was detected. The level of heteroplasmy was estimated to be ~65%. Single large mitochondrial DNA (mtDNA) deletions typically present as one of three syndromes: Kearns-Sayre syndrome (KSS), progressive external ophthalmoplegia (PEO) in adults, or Pearson syndrome in children. PEO is the only one of these diseases in which the mtDNA deletions are confined to skeletal muscle.

Patient Information:
Age: 45  Specimen: Frozen Muscle Tissue
Referral diagnosis: Chronic progressive external ophthalmoplegia (CPEO) and ragged red fibers on muscle biopsy.
Family history: The patient reported that none of her family members have any history of CPEO, ragged red fibers, or any other eye, muscle, heart or brain disease. Her family history overall was unremarkable.

Diagnostic Summary:
POSITIVE. Heteroplasmic for a 9.3 Kb Deletion of the Mitochondrial Genome; ~65% heteroplasmy.

Sequence Analysis and Deletion Testing of the Mitochondrial Genome: Sequence analysis and deletion testing of the entire mitochondrial genome revealed a 9.3 Kb deletion of the mitochondrial genome. Although this particular deletion had not been previously reported in the literature, large deletions of the mitochondrial genome that are identifiable in muscle tissue have been reported in association with Kearns-Sayre syndrome and chronic progressive external ophthalmoplegia.¹

GeneDx performs both sequence analysis and deletion/duplication analysis of the entire mitochondrial genome and can detect mtDNA mutations at levels of heteroplasmy as low as 4%. For large deletions of the mitochondrial genome, low levels of heteroplasmy can be detected. GeneDx also provides haplogroup information for each patient and a table of observed polymorphisms.

Diagnostic Implications:
In many cases, single large mtDNA deletions occur de novo (i.e., the deletion is newly occurred in that individual and was not inherited from a parent). The patient was counseled that although the risk for transmission of a mitochondrial deletion is typically low², this possibility cannot be excluded. Therefore, deletion analysis (preferably from an involved tissue) is recommended for any at-risk adults (i.e., her mother, children, and siblings) or any family members who may become symptomatic in the future. If any males are found to have the mutation, they are not at risk to pass the deletion to their offspring.

References: