Case Study: Infantile spasms caused by an ARX mutation

Clinical Overview:
A 5-month-old male presents to clinic with a history of infantile spasms and elevated sialic acid levels. His parents reported no family history of similar symptoms. The GeneDx infantile epilepsy panel, which includes sequencing and deletion/duplication analysis of 38 genes, was ordered. A hemizygous duplication was detected in the ARX gene. Mutations in ARX cause a variety of neurological diseases depending on the type of mutation and its location within the gene. This patient had an in-frame addition of 11 amino acids in the first polyalanine tract of ARX which have been associated with early infantile epileptic encephalopathy (EIEE or Ohtahara syndrome) and infantile spasms (West syndrome).1,2

Patient Information:
Age: 5 months   Specimen: Blood
Referral diagnosis: Infantile spasms, elevated sialic acid
Family history: No known family history of similar symptoms

Diagnostic Summary:
POSITIVE. Hemizygous ARX mutation A105_A115dup (c.309_341dup33)

Infantile Epilepsy Panel: Sequence analysis and deletion/duplication analysis of 38 genes revealed the hemizygous c.309_341dup33 mutation, which results in an in-frame addition of 11 Alanine residues in the first polyalanine tract of ARX, thereby leading to a protein with 27 Alanine repeats instead of the normal 16 repeats. In general, expansions in the first polyalanine tract cause early infantile epileptic encephalopathy (EIEE or Ohtahara syndrome) or infantile spasms (West syndrome), while expansions of the second polyalanine tract are associated with nonsyndromic X-linked intellectual disability (XLID) or Partington syndrome (XLID with dystonia).1,2 Therefore, the presence of c.309_341dup33 is consistent with the diagnosis of an ARX-related disorder in this individual.

Diagnostic Implications:
There are many different causes of epilepsy, including genetic disorders, metabolic diseases, and structural brain abnormalities. Knowing the genetic cause of an individual’s seizures can clarify the prognosis, assist in treatment and management of the patient, and predict the risk of a disease in family members. Mutations in ARX are inherited in an X-linked manner, and heterozygous females are typically unaffected or reported to have mild clinical features.2 Mutation-specific testing for the c.309_341dup33 mutation in the ARX gene was performed on the mother of this child and the mutation was determined to be de novo (arising new in that individual and not inherited). This information provides the family with a more accurate recurrence risk, which is now significantly lowered, but not zero due to the possibility of germline mosaicism the mother.

References: