Rett Syndrome, Atypical, CDKL5, Sequencing

Test Code: 2404  Department: Molecular Genetics

Test Synonyms:  CPT Code(s):
Atypical RETT Syndrome  83900
Early Infantile 2 (EIEE2)  83901 x 21
Epileptic Encephalopathy  83892 x 23
Infantile Spasm Syndrome X-linked (ISSX2)  83904 x 23
Rett Syndrome Variant with Infantile Spasms  83909 x 23

Background:
Atypical Rett syndrome (also known as Epileptic Encephalopathy, Early Infantile, 2 (EIEE2); Infantile Spasm Syndrome, X-Linked (ISSX2); and Rett Syndrome, Variant, with Infantile Spasms) is an X-linked, severe progressive neurodevelopmental disorder that generally presents in infancy with early onset seizures during the first weeks to months of life. Infantile spasms and myoclonic jerks are the cardinal feature of this disorder, (with a unique EEG pattern) most frequently marked by hypotonia, poor eye contact, severe mental retardation and profound global developmental delay. Usually there is no period of regression which is often seen in Rett syndrome, the hand movements are less notable but grasp is affected. In the majority, growth is normal except head circumference is variably affected and autonomic disturbances are not noted. This presentation is far more frequent in females than in males although males can be affected. Variable clinical presentation may occur with milder psychosocial phenotypes resembling autistic features and tactile hypersensitivities. Atypical Rett syndrome presenting with early onset seizures may be associated with mutations and this would be a clear indication to consider CDKL5 testing. Approximately 10% of patients with encephalopathy and early onset seizures carry an identified mutation in the CDKL5 gene, cyclin dependent kinase-like 5 gene (CDKL5) on chromosome Xp22.1.

REASONS FOR REFERRAL

- Confirmation of clinical diagnosis in patients with atypical Rett, or suspicion based on infantile spasms AND with a negative MeCP2 mutation screen
- Carrier testing of family members of Atypical Rett patients, given previous CDKL5 mutation identified
- Prenatal diagnosis, given previous CDKL5 mutation identified

Methodology:

Mutation Analysis:

All 21 coding exons, and exon/intron boundaries, of CDKL5 are amplified by PCR. All amplicons are sequenced in both forward and reverse directions using automated fluorescence dideoxy sequencing.

Clinical sensitivity is unknown; however, it is estimated that ~10% of patients with encephalopathy and early onset seizures have a mutation in the CDKL5 gene.
Rett Syndrome, Atypical, *CDKL5*, Sequencing

Test reporting follows the American College of Medical Genetics guidelines.

**Specimen Requirements:**
- Blood: EDTA (purple-top) or ACD (yellow-top Solution A or B) tube
  - *Adult*: 5 mL
  - *Child*: 5 mL
  - *Infant*: 2-3 mL

  **A REQUISITION FORM MUST ACCOMPANY ALL SAMPLES.** Please include detailed clinical information, including ethnicity, clinical history, and family history.

**Test Performed (Days):**
Weekly

**Turn Around Time:**
14 - 21 Days

**Shipment Sensitivity Requirements:**
Package and ship specimen to remain cold, but not frozen. Ship via overnight express, using the FedEx priority overnight label provided. Contact Client Services for shipping kits and instructions at (855) 535-1522.

**Additional Information:**
Confirmation of clinical diagnosis in patients with atypical Rett, or suspicion based on infantile spasms AND with a negative *MeCP2* mutation screen; carrier testing of family members of Atypical Rett patients, given previous CDKL5 mutation identified; or prenatal diagnosis, given previous CDKL5 mutation identified.

**References:**