Atypical Rett Syndrome: CDKL5 Gene Deletion/Duplication

Test Code: RL  
Turnaround time: 2 weeks  
CPT Codes: 81405 x1

Condition Description

Mutations in the gene CDKL5 (Xp22) (also known as serine threonine kinase 9 or STK9) are associated with an atypical variant of Rett syndrome, which includes intellectual disability and severe neurological symptoms. Characteristics include severe early-onset seizures, loss of communication and motor skills, hypsarrhythmia, and profound global developmental arrest. Hand-wringing and hand-mouthing stereotypies and breathing dysfunction suggestive of Rett syndrome have been reported. Rett syndrome is caused by mutations in the MeCP2 gene, and clinical symptoms include loss of speech and purposeful hand use, microcephaly, seizures, ataxia, and stereotypic hand movements. Similar to MeCP2, CDKL5 mutations manifest a wide range of clinical phenotypes in female and rare male patients, with features overlapping other intellectual disability disorders. Identical twin females with atypical Rett syndrome have been reported in which one was more severely affected, with profound intellectual disability, mixed seizure disorder, and small hands and feet, while the other had mild intellectual disability and autistic features, but no seizures.

CDKL5 mutations have been found in affected individuals with phenotypic features of atypical Rett syndrome. De novo mutations and evidence of germline mosaicism have been reported. It has been demonstrated that in the mouse brain, Cdk5 expression overlaps that of Mecp2, suggesting that these two gene products play a role in a common pathogenic process. Mutation analysis of the CDKL5 gene should be considered in patients who previously tested negative for comprehensive mutation analysis in the MeCP2 gene.

For patients with suspected atypical Rett syndrome, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

Genes

CDKL5

Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of atypical Rett syndrome in an individual in whom sequencing analysis was negative
- Carrier testing in adult females with a family history of atypical Rett syndrome in whom sequencing analysis was negative

Methodology

Targeted CGH Array: DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a "backbone" of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient’s phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

Detection

Detection is limited to duplications and deletions. Array CGH will not detect point mutations or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:
Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Sequence analysis of the *CDKL5* gene is available and is required before deletion/duplication analysis (RJ).
- A CGH array-based test for deletion/duplication analysis of 64 different X-linked intellectual disability genes is available (OL).
- Sequencing and deletion/duplication analysis is available for the *MeCP2* gene for Rett syndrome (SR, KT).
- Prenatal testing is available to adult females who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.