Atypical Rett Syndrome: *CDKL5* Gene Sequencing

**Test Code:** RJ  
**Turnaround time:** 4 weeks  
**CPT Codes:** 81406 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, hypersomnia, 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 germ-line mosaicism have been reported. It has been demonstrated that in the mouse brain, Cdkl5 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.
- Carrier testing in adult females with a family history of atypical Rett syndrome.

### Methodology

#### Next Generation Sequencing:
In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

### Detection

Clinical sensitivity: unknown. Mutations in the promoter region, some mutations in the introns, other regulatory element mutations, and large deletions cannot be detected by this analysis. Analytical sensitivity: ~99%.

Results of molecular analysis should be interpreted in the context of the patient's 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) or ACD (yellow 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

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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

Please submit copies of diagnostic biochemical test results along 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 Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition form.

Related Tests

- X-Linked Mental Retardation Deletion/Duplication (OL).
- Rett Syndrome: MeCP2 Gene Sequencing (SR).
- Known Mutation Analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal Custom Diagnostics 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.