

Assay Summary

STK9/CDKL5 Gene Mutation Analysis

Atypical Rett, Infantile Spasms, Autism, and X-linked Mental Retardation

Synopsis

Rett syndrome is an X-linked dominant, progressive neurological disorder that primarily affects females, due to the lethality of severe mutations in males. It is characterized by normal development early on in life, followed by an arrest in development, and subsequently, a regression in language and motor skills. Most individuals typically develop loss of purposeful hand movements, and instead develop stereotypical repetitive hand motions. Approximately 50% of these individuals will also develop seizures, including infantile spasms. Rett syndrome may present in its “classic form”, usually associated with mutations in the MECP2 gene. It may also be classified as “atypical” Rett syndrome, considered to be a milder form of this disease with clinical features including mental retardation, mild learning disabilities and/or autism. Many different syndromes have been described where much overlap occurs between the clinical presentations, making it difficult to place some individuals in a particular diagnostic box. A number of recent publications have reported associations of mutations in the STK9/CDKL5 gene, which a protein containing a conserved serine/threonine kinase domain, with phenotypic presentations ranging from severe mental retardation with infantile spasms to variable neurodevelopmental disorders with overlapping symptoms found in Rett and Angelman syndrome^{1, 2, 3}.

Indications for testing

Individuals with a diagnosis of “classic” or “atypical” Rett syndrome (without MECP2 mutations), infantile spasms, or X-linked mental retardation, with or without a family history of the disease are candidates for STK9/CDKL5 testing. To help a diagnosis in suspected Rett syndrome, infantile spasms, or X-linked mental retardation. Once a specific mutation is known in a family, presymptomatic testing for appropriate family members can be performed.

Methodology

All coding exons and associated intron junctions of the STK9 gene, are analyzed by direct DNA sequence analysis using an automated fluorescent sequencer. When a mutation is detected, confirmation is carried out by sequencing in the opposite direction, in an independent PCR amplification. If no mutation is found sequence analysis is performed in both directions. At-risk family members can be offered DNA sequence analysis of only the region of the gene with the previously identified mutation.

Performance/Limitations

For mutation analysis, the method will not detect mutations located in regions of the genes that are not analyzed (non-coding exon sequences, intron sequences other than the splice junctions, and upstream and downstream sequences). The method also will not detect gross genetic alterations including most large deletions, duplications, and inversions. Some sequence alterations that may be detected (such as those causing missense or synonymous changes) will be of unknown clinical significance. Interpretation of test

results should be in the context of the patient's ethnicity, clinical and family histories, and other laboratory test results.

Specimen Requirements

(a) Blood samples: 2 tubes with a total of 6 ccs in ACD (yellow top) or EDTA (lavender top) tubes. Keep at ambient temperature and ship by overnight courier. Samples must be received in our laboratory within 72 hours of draw.

Note:

- i) for infants, a minimum of 3 ccs is sufficient.
- ii) we accept DNA; at least 10 micrograms is required.

(b) Prenatal samples: 2 T25 flasks of confluent cells sent padded to arrive on M/Tu/W. A blood sample from the mother maybe required (2 tubes with a total of 6 ccs in ACD (yellow top) or EDTA (lavender top) tubes) for use as positive control. Maternal cell contamination studies are not done here but are required for autosomal disorders and dosage analysis on X-linked disorders. We would be happy to assist in coordinating sending out a specimen for this purpose.

Test Request Form (TRF)

A completed MDL [TRF](#) is required for each specimen. Please submit the completed TRF with the specimen. Complete testing and billing information must be provided before the specimen is processed.

<i>Order Codes</i>	<i>CPT Codes</i>	<i>TAT</i>
STK9-SEQ (STK9 gene, full gene sequencing)	83890, 83898(x23), 83894, 83904(x23), 83912	8 wks
STK9-CAS (STK9 gene, targeted mutation analysis, known mutation)	83890, 83898, 83894, 83904, 83912	3 wks
STK9-PD (STK9 gene, known mutation detection, prenatal)	83890, 83898, 83894, 83904, 83912	2 wks

References

1. Kalscheuer, V.M. et al. (2003) Am. J. Hum. Genet. 72:1401-1411.
2. Tao, J. et al. (2004) Am. J. Hum. Genet. 75:1149-1154.
3. Scala, E. et al., (2005) J. Med. Genet. 42:103-107.

NOTE: This test is performed pursuant to a license agreement with Roche Molecular Systems, Inc.