

Assay Summary

ATRX Gene Mutation Analysis

Alpha Thalassemia/Mental Retardation Syndrome, Smith-Fineman-Myers Syndrome, Carpenter-Waziri Syndrome, Juberg-Marsidi Syndrome, and Alpha Thalassemia Myelodysplasia Syndrome

Synopsis

ATR_X (ATR-X, X-linked helicase II, XH2, X-linked nuclear protein gene, XNP) belongs to the SNF2 family of proteins, many of which have been demonstrated to have chromatin remodeling activity. ATR_X gene spans about 300kb of genomic DNA and contains 36 exons. Mutations in the transcriptional regulator ATR_X are associated with several X-linked mental retardation syndromes: (1) X-linked alpha-thalassemia/mental retardation syndrome (ATR-X) characterized by severe psychomotor retardation, facial dysmorphism, urogenital abnormalities, alpha-thalassemia, and hemoglobin H erythrocyte inclusions, an essential phenotypic trait¹; (2) Smith-Fineman-Myers syndrome (SFM) with clinical features including severe mental retardation, microcephaly, growth failure, facial anomalies and bilateral cryptorchidism²; (3) Carpenter-Waziri syndrome (CWS) characterized by moderate mental retardation, short stature, brachydactyly with excessive skin creases, and widening of the knuckles³; (4) Juberg-Marsidi syndrome (JM) characterized by severe mental retardation, growth failure, sensorineural deafness, microgenitalism and early death⁴; and (5) alpha-thalassemia myelodysplasia syndrome (ATMDS) in which alpha-thalassemia occurs as an acquired abnormality in association with a multilineage myelodysplasia⁵. Over 200 cases from 182 families have been identified with 113 different mutations⁶.

Indications for testing

Individuals suspect of having any of the syndromic X-linked mental retardation above. After a specific mutation is identified in a family, carrier testing can be performed for appropriate at-risk females and presymptomatic males. With appropriate genetic counseling, prenatal testing can be performed for females with an identified mutation.

Methodology

All coding exons and associated intron junctions of the ATR_X gene are analyzed by direct DNA sequence analysis using an automated fluorescent sequencing machine. 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.

Limitations

The mutation analysis will not detect mutations located in regions of the genes that are not analyzed (non-coding exon regions, intron regions other than the splice junctions, and upstream and downstream regions). The method also will not detect gross genetic alterations including most duplications, inversions or deletions

(in females). 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>
ATRX-SEQ (ATRX gene, full gene sequencing)	83890, 83898(x43), 83894, 83904(x43), 83912	10 wks
ATRX-CAS (ATRX gene, targeted mutation analysis, known mutation)	83890, 83898, 83894, 83904, 83912	3 wks
ATRX-PD (ATRX gene, known mutation detection, prenatal)	83890, 83898, 83894, 83904, 83912	2 wks

References

1. Gibbons, RJ, et al *Cell* 1995; 80: 837-845.
2. Villard L, et al. *Am J Med Genet.* 2000; 6; 91(1):83-5.
3. Abidi F, et al. *Am J Med Genet.* 1999; 30; 85(3):249-51.
4. Villard L, et al. *Nat Genet.* 1996; 12(4):359-60.
5. Gibbons RJ, et al. *Nat Genet.* 2003; 34(4):446-9.
6. Gibbons RJ, et al. *Hum Mutat* 2008; 29(6), 796–802

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