

Assay Summary

ARX Gene Mutation Analysis

Non-Syndromic X-Linked Mental Retardation, West syndrome (Infantile spasms), Proud syndrome, Partington syndrome, Ohtahara and X-linked lissencephaly with abnormal genitalia (XLAG) syndrome

Synopsis

X-linked mental retardation (XLMR) has a prevalence of 2.6 cases per 1,000 in the general population¹. Recently, mutations in the ARX gene have been found in association with both non-syndromic XLMR^{2,3} and syndromic XLMR such as i) West syndrome (infantile spasms, hypsarrhythmia and mental retardation)⁴ ii) Proud syndrome (mental retardation with agenesis of the corpus callosum, microcephaly, limb contractures, scoliosis, coarse facies, tapered digits, and urogenital abnormalities)⁵; iii) Partington syndrome (mental retardation with dystonic movements, ataxia, and seizures)⁵; iv) X-linked lissencephaly with abnormal genitalia (XLAG)⁶ and v) Ohtahara syndrome (early infantile epileptic encephalopathy with suppression-burst pattern)⁷.

Indications for testing

Individuals with non-syndromic mental retardation, especially those in whom Fragile X disease has been ruled out, or individuals with a diagnosis of West syndrome, Proud syndrome, Partington syndrome or X-linked lissencephaly with abnormal genitalia (XLAG) are candidates for testing. 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 ARX 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.

Performance

If a point mutation or small deletion/insertion is present within the regions of the ARX gene that are scanned, the sensitivity of mutation detection is approximately 99%. Recent studies with ARX screening suggest that the gene is mutated in 9.5% of X-linked families with these disorders⁸. However, the frequency is much lower in patients with sporadic mental retardation. Once a mutation is found, the sensitivity and specificity for carrier detection for families with identified ARX gene mutations are both estimated to be greater than 99%.

Limitations

The method will not detect mutations located in regions of the ARX gene not analyzed (intron sequences other than the splice junctions and upstream and downstream sequences). The method also will not detect

gross alterations in the ARX gene, including most heterozygous 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>
ARX-SEQ (ARX gene, full gene sequencing)	83890, 83898(x5), 83894, 83904(x6), 83912	5 wks
ARX-CAS (ARX gene, targeted mutation analysis, known mutation)	83890, 83898, 83894, 83904, 83912	3 wks
ARX-PD (ARX gene, known mutation detection, prenatal)	83890, 83898, 83894, 83904, 83912	2 wks

References

1. Stevenson RE, Schwartz CE (2002). *Cytogenet Genome Res* 99(1-4):265-75.
2. Mandel JL, et al. (2004). *Eur J Hum Genet* 12(9):689-93.
3. Partington MW, et al. (2004). *Clin Genet* 66(1):39-45.
4. Kato M et al. (2003). *Neurology* 22; 61(2):267-76.
5. Kato M et al. (2004). *Hum Mutat* 23(2):147-59.
6. Uyanik G et al. (2003). *Neurology* 22;61(2):232-5.
7. Kato M et al (2007) *Am J Hum Genet*. 2007 Aug; 81(2):361-6.
8. Poirier K, et al. (2006) *Neurogenetics* 2006, 7:39-46.

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