

Assay Summary

ARX, DLG3, FACL4, FTSJ1, JARID1C, PQBP1, TM4SF2, and ZNF41 genes, Full Mutation Analysis

Non-Syndromic X-Linked Mental Retardation Test

Synopsis

X-linked mental retardation (XLMR) has a prevalence of 2.6 cases per 1,000 in the general population, accounting for over 10% of all cases of mental retardation¹. It is estimated that 2/3 of X-linked mental retardation is non-syndromic (mental retardation without other distinguishing features). Recently, multiple genes have been indicated in non-syndromic XLMR. We have selected eight genes with strong evidence and high mutation rates to form a non-syndromic XLMR test. This test includes ARX (aristaless related homeobox)²⁻⁵, DLG3 (discs, large homolog 3)⁶, FACL4 (fatty acid CoA ligase 4)⁷, FTSJ1 (FtsJ homolog 1)⁸, JARID1C (Jumonji/ARID domain-containing protein 1C)⁹, PQBP1 (polyglutamine binding protein 1)¹⁰, TM4SF2 (transmembrane 4 superfamily member 2)¹¹ and ZNF41 (Zinc finger protein 41)¹². Based on recent literature, the estimated detection rate of this XLMR test is 20-25% of non-syndromic XLMR patients.

Indications for testing

Individuals with a diagnosis of non-syndromic mental retardation, especially those in whom Fragile X disease has been ruled out, 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

Full Mutation Analysis of ARX, DLG3, FACL4, FTSJ1, JARID1C, PQBP1, TM4SF2 and ZNF41 genes: All coding exons and associated intron junctions of the 8 genes are analyzed by direct DNA sequence analysis using automated fluorescent sequencing. 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.

Performances/Limitations

It is estimated that a mutation could be found in about 15-25% of patients with non-syndromic X-linked mental retardation. For mutation analysis, the method 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 large deletions in female, 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) 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.
- b) [Neuropsychiatric Patient Information Form](#): Include a completed Neuropsychiatric Patient Information Form for the proband and a complete pedigree.

| Order Codes | CPT Codes | TAT |
|---|---|--------|
| MRX-Test (ARX, PQBP1, JARID1C, TM4SF2, FACL4 ,DLG3, FTSJ1 and ZNF41, full gene sequencing) | 83890, 83898(x96), 83894, 83904(x96), 83912(x8) | 10 wks |

References

1. Stevenson RE, Schwartz CE (2002). Clinical and molecular contributions to the understanding of X-linked mental retardation. *Cytogenet Genome Res.* 99(1-4):265-75.
2. Stromme P, et al. Mutations in the human ortholog of aristaless cause X-linked mental retardation and epilepsy. *Nature Genet.* 30: 441-445, 2002.
3. Uyanik G, et al. ARX mutations in X-linked lissencephaly with abnormal genitalia. *Neurology* 61: 232-235, 2003.
4. Hirose S, Mitsudome A. X-linked mental retardation and epilepsy: pathogenetic significance of ARX mutations. *Brain Dev.* 2003 Apr;25(3):161-5. Review.
5. Stromme P, et al. Infantile spasms, dystonia, and other X-linked phenotypes caused by mutations in Aristaless related homeobox gene, ARX. *Brain Dev.* 2002 Aug;24(5):266-8.
6. Tarpey P., et al. Mutations in the DLG3 gene cause nonsyndromic X-linked mental retardation. *Am J Hum Genet.* 2004 Aug;75(2):318-24
7. Covault J, et al. Association of a long-chain fatty acid-CoA ligase 4 gene polymorphism with depression and with enhanced niacin-induced dermal erythema. *Am J Med Genet.* 2004 May 15;127B(1):42-7
8. Freude K, et al. Mutations in the FTSJ1 gene coding for a novel S-adenosylmethionine-binding protein cause nonsyndromic X-linked mental retardation. *Am J Hum Genet.* 2004 Aug;75(2):305-9
9. Jensen LR, et al. Mutations in the JARID1C Gene, Which Is Involved in Transcriptional Regulation and Chromatin Remodeling, Cause X-Linked Mental Retardation. *Am J Hum Genet.* 2005 Feb;76(2):227-36
10. Kalscheuer VM, et al. Mutations in the polyglutamine binding protein 1 gene cause X-linked mental retardation. *Nat Genet.* 2003 Dec;35(4):313-5
11. Zemni R, et al. A new gene involved in X-linked mental retardation identified by analysis of an X;2 balanced translocation. *Nat Genet.* 2000 Feb;24(2):167-70
12. Shoichet SA, et al. Mutations in the ZNF41 gene are associated with cognitive deficits: identification of a new candidate for X-linked mental retardation. *Am J Hum Genet.* 2003 Dec;73(6):1341-54.

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