Alpha-Thalassemia X-Linked MR Syndrome: ATRX Gene Sequencing

**Condition Description**

Alpha-thalassemia X-linked MR (ATRX) syndrome is characterized by intellectual disability and alpha-thalassemia without molecular abnormalities of the alpha-globin gene complex on chromosome 16p. Characteristics include distinctive craniofacial features, genital anomalies, and severe developmental delays with hypotonia. Craniofacial abnormalities include microcephaly, hypertelorism, epicanthus, a small triangular upturned nose, and flat face. Although all affected individuals have a normal 46,XY karyotype, genital anomalies range from hypospadias and ambiguous genitalia to normal-appearing female genitalia. Global developmental delays are evident in infancy and some affected individuals never walk independently or develop significant speech. The degree of red blood cell hypochromia and HbH levels are milder than usually found in alpha-thalassemia.

The ATRX gene (Xq13) encodes a transcriptional regulator, ATRX, a zinc finger domain which functions as a transcription factor. The mutant ATRX protein down-regulates the alpha-globin locus, resulting in thalassemia, and probably suppresses expression of other genes by disturbances in transcription and chromatin structure, leading to malformations and intellectual disability.

Sequence analysis of the ATRX gene has been shown to identify 90-95% of known mutations. Missense mutations appear more commonly than do frameshift and nonsense mutations. Deletions, insertions, and intragenic duplications have also been found (<5% of known mutations). Approximately 25% of individuals tested on the basis of suggestive clinical findings have the diagnosis confirmed by gene testing. Germline mosaicism has been documented, but no data is available on the frequency of de novo mutations. The prevalence of ATRX syndrome is not known. Approximately 200 affected individuals are known to laboratories conducting molecular genetic testing, but substantial under-ascertainment is probably, especially of those individuals with milder phenotypes. No ethnic or racial concentration of individuals has been reported.

ATRX mutations have been found in several named X-linked mental retardation (XLMR) syndromes (Carpenter-Waziri syndrome, Holmes-Gang syndrome, Chudley-Lowry syndrome), XLMR with spastic paraplegia, XLMR with epilepsy, and nonsyndromic XLMR. These entities can be considered to be in the phenotypic spectrum of ATRX syndrome.

Click here for the GeneReviews summary on this condition.

**Genes**

ATRX

**Indications**

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of alpha-thalassemia X-linked MR syndrome
- Carrier testing in adult females with a family history of alpha-thalassemia X-linked MR 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: Approximately 25% of individuals tested on the basis of suggestive clinical findings have the diagnosis confirmed by gene testing. Approximately 95% of known mutations can be identified by sequence analysis while less than 5% are deletions or duplications. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

**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**

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**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

**Related Tests**

- ATRX Gene Deletion/Duplication (SN) is available for those individuals in whom sequence analysis is negative.
- X-Linked Intellectual Disability panels are available for 30, 60, and 90+ genes.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing 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.

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