Alpha-Thalassemia X-Linked MR Syndrome: **ATRX** Gene Deletion/Duplication

**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 undescended testicles to severe 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.

For patients with suspected ATRX syndrome, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

**Genes**

**ATRX**

**Indications**

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of alpha-thalassemia X-linked MR syndrome in an individual in whom sequencing analysis was negative
- Carrier testing in adult females with a family history of alpha-thalassemia X-linked MR syndrome in whom sequencing analysis was negative

**Methodology**

Targeted CGH Array: DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

**Detection**

Deletions, insertions, and intragenic duplications have been found in the **ATRX** gene (<5% of known mutations). Detection is limited to duplications and deletions. Array CGH will not detect point mutations or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

**Specimen Requirements**

Submit only 1 of the following specimen types

* **Preferred specimen type**: Whole Blood

**Type**: Whole Blood

Specimen Requirements:
In EDTA (purple 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.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

### Related Tests

- Sequence analysis of the *ATRX* gene is available and is required before deletion/duplication analysis (SL).
- X-Linked Intellectual Disability panels are available for 30, 60, and 90+ genes.
- 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.