ARX-related Disorders: ARX Gene Sequencing

Test Code: RV
Turnaround time: 4 weeks
CPT Codes: 81404 x1

**Condition Description**

Mutations of the ARX gene have recently been identified as contributors to X-linked intellectual disability (XLID), both syndromic and non-syndromic. The phenotypic expression varies, and mutations in ARX have been associated with such syndromic conditions as West syndrome, Partington syndrome, X-linked lissencephaly with abnormal genitalia (XLAG), Ohtahara syndrome, and Proud syndrome.

The West syndrome phenotype includes infantile spasms, hypsarrhythmia, and intellectual disability. Partington syndrome characteristics include intellectual disability with dystonic movements, ataxia, and seizures. Ohtahara syndrome includes early infantile epileptic encephalopathy with suppression-burst pattern. The Proud syndrome phenotype is composed of intellectual disability with agenesis of the corpus callosum, microcephaly, limb contractures, scoliosis, coarse facies, tapered digits, and urogenital abnormalities. Female carriers are not clinically affected.

The ARX gene maps to Xp22.13 and belongs to the family of aristaless-related paired-class homebox genes. These genes are transcription factors and function as key players in vertebrate embryology. The ARX protein is a crucial gene for the development of interneurons in the fetal brain. Mutations identified in ARX have included polyalanine repeat tract expansions, missense mutations, nonsense mutations, premature termination mutations, frameshift mutations, splice site mutations, duplications/insertions, and large deletions.

For patients with a suspected ARX-related disorder, 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. Click here for the OMIM summary on this condition.

**Genes**

**ARX**

**Indications**

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of an ARX-related disorder
- Carrier testing in adult females with a family history of an ARX-related disorder

**Methodology**

Full Gene Sequencing: PCR amplification of 5 exons contained in the ARX gene is performed on patient genomic DNA. Direct sequencing of amplification products is performed in both the forward and reverse directions using automated fluorescence dideoxy sequencing methods. Patient gene sequences are compared to a normal reference sequence. Sequence variations are then classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions or other regulatory elements. Large deletions are not detected by this analysis.

**Detection**

Clinical Sensitivity: Unknown. 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<sup>TM</sup> 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 Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Deletion/duplication analysis of the ARX gene by CGH array is available for those individuals in whom sequence analysis is negative (RW).
- A CGH array-based test for deletion/duplication analysis of 64 different X-linked intellectual disability genes is available (OL). 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.