Menkes Disease: \( \text{ATP7A} \) Gene Deletion/Duplication

Test Code: SJ  
Turnaround time: 2 weeks  
CPT Codes: 81228 x1

**Condition Description**

Menkes disease and occipital horn syndrome (OHS) are X-linked disorders of copper transport caused by mutations in the copper-transporting ATPase (\( \text{ATP7A} \)) gene. These disorders result in low concentrations of copper in some tissues due to impaired intestinal copper absorption, accumulation of copper in other tissues, and reduced activity of copper-dependent enzymes such as dopamine beta hydroxylase (DBH) and lysyl oxidase. Temperature instability and hypoglycemia may be present in the neonatal period. Death usually occurs by three years of age.

Infants with classic Menkes disease appear healthy until age two to three months when growth retardation, hypotonia, and seizures occur. Other manifestations include peculiar hair (short, sparse, coarse, twisted, often lightly pigmented) and focal cerebral and cerebellar degeneration.

Occipital horn syndrome is characterized by "occipital horns," which are distinctive wedge-shaped calcifications at the sites of attachment of the trapezius muscle and the sternocleidomastoid muscle to the occipital bone. Occipital horns may be clinically palpable or observed on skull radiographs. Individuals with OHS also have lax skin and joints, bladder diverticula, inguinal hernias, and vascular tortuosity. Intellect is normal or slightly reduced.

The \( \text{ATP7A} \) (Xq12-q13) gene encodes copper-transporting ATPase 1, which transports copper across cellular membranes and is critical for copper homeostasis. \( \text{ATP7A} \) mutations may result in a gene product with no copper transport capability (associated with a severe phenotype) or a reduced quantity of normally functioning gene product (associated with a milder phenotype). Phenotypic variability is observed in families with mild mutations, but not in those with severe mutations. In affected individuals, approximately 80% of known mutations are point mutations, while approximately 15% are deletions. Approximately one-third of males have de novo mutations. The incidence of Menkes disease and its variants is estimated at 1/100,000 births.

For patients with suspected Menkes disease or OHS, 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.

Due to the presence of a pseudogene for the \( \text{ATP7A} \) gene, analysis of deletion or duplication of exon 11 cannot be included in this assay.

Please [click here](#) for the GeneReviews summary on this condition.

**Genes**

\( \text{ATP7A} \)

**Indications**

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of Menkes disease or OHS in an individual in whom sequencing analysis was negative.
- Carrier testing in adult females with a family history of Menkes disease or OHS in whom sequencing analysis was negative.

**Methodology**

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.

**Detection**

Detection is limited to duplications and deletions. The CGH array will not detect point 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*

**Type: DNA, Isolated**

**Specimen Requirements:**

- Microtainer
- Isolation using the Perkin Elmer™Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Specimen Collection and Shipping:**

Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.
Type: Whole Blood (EDTA)

Specimen Requirements:
EDTA (Purple Top)
Infants and Young Children (2 years of age to 10 years old): 3-5 ml
Older Children & Adults: 5-10 ml
Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Special Instructions

Please submit copies of diagnostic biochemical test results along 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

- Menkes Disease: ATP7A Gene Sequencing (RZ) is required before deletion/duplication analysis.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.