Menkes Disease: \textit{ATP7A} Gene Sequencing

\textbf{Test Code:} RZ  
\textbf{Turnaround time:} 4 weeks  
\textbf{CPT Codes:} 81479 \(\times 1\)

\section*{Condition Description}

Menkes disease and occipital horn syndrome (OHS) are X-linked disorders of copper transport caused by mutations in the copper-transporting ATPase gene (\textit{ATP7A}). These disorders result in:

- Low concentrations of copper in some tissues due to impaired intestinal copper absorption
- Accumulation of copper in other tissues
- Reduced activity of copper-dependent enzymes such as dopamine beta hydroxylase (DBH) and lysyl oxidase.

Infants with classic Menkes disease appear healthy until age 2-3 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. Temperature instability and hypoglycemia may be present in the neonatal period. Death usually occurs by three years of age.

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 \textit{ATP7A} gene (Xq12-q13) encodes copper-transporting ATPase 1, which transports copper across cellular membranes and is critical for copper homeostasis. \textit{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 1/3 of males have \textit{de novo} mutations. The incidence of Menkes disease and its variants is estimated at 1/100,000 births.

Please \textbf{click here} for the GeneReviews summary on this condition.

\section*{Genes}

\textbf{ATP7A}

\section*{Indications}

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of Menkes disease or OHS.
- Carrier testing in adult females with a family history of Menkes disease or OHS.

\section*{Methodology}

\textbf{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.

\section*{Detection}

\textbf{Clinical Sensitivity:} It is estimated that sequencing will detect 95\% of mutations in affected males. Mutations in the promoter region, some mutations in the introns, other regulatory element mutations, and large deletions cannot be detected by this analysis.

\textbf{Analytical Sensitivity:} \textasciitilde99\%.

Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

\section*{Specimen Requirements}

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

\textbf{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**

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

**Related Tests**

- Known Mutation Analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing 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.