Microphthalmia with Linear Skin Defects: \textit{HCCS} Gene Sequencing

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\textbf{Test Code:} SHCCS  \\
\textbf{Turnaround time:} 6 weeks  \\
\textbf{CPT Codes:} 81479 x1  \\
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\textbf{Condition Description}

Microphthalmia with linear skin defects (MLS) syndrome (OMIM \#309801) is characterized by unilateral or bilateral microphthalmia and/or anophthalmia and linear skin defects (areas of aplastic skin) which are usually present at birth and involve the face and neck. Overtime these lesions heal and leave minimal residual scarring. Minor criteria of MLS syndrome include other ocular abnormalities such as microcornea and, central nervous system involvement including agenesis of the corpus callosum and microcephaly, intellectual disability, infantile seizures, and congenital heart defects. Short stature, diaphragmatic hernia, nail dystrophy, hearing loss, and genitourinary malformations may also be present.

MLS syndrome is inherited in an X-linked manner and is usually lethal in males. Most cases present as a single occurrence in a family, however, familial occurrences have been described. Both intra- and interfamilial variability is possible.

Diagnosis is based on clinical findings and the detection of either a chromosomal abnormality that results in monosomy for Xp22 or a mutation in the \textit{HCCS} gene (Xp22) (OMIM \#300056), the only gene known to be associated with MLS syndrome. Approximately 77\% of affected individuals have monosomy Xp22 due to either a chromosomal abnormality or an interstitial deletion. Both point mutations and multiple exon deletions of the \textit{HCCS} gene have been reported.

For patients with suspected MLS 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.

References:

- GeneReviews
  - OMIM \#309801: MLS syndrome
  - OMIM \#300056: HCCS gene

\textbf{Genes}

\textit{HCCS}

\textbf{Indications}

This test is indicated for:

- Confirmation of a clinical diagnosis of MLS syndrome.
- Carrier testing in adults with a family history of MLS syndrome.

\textbf{Methodology}

PCR amplification of 6 exons contained in the \textit{HCCS} gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are 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, and does not detect large deletions.

\textbf{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 clinical and/or biochemical phenotype.

Analytical Sensitivity: \( \sim 99\% \)

\textbf{Specimen Requirements}

\textit{Submit only 1 of the following specimen types}

\textbf{Type: Whole Blood (EDTA)}

\textbf{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 uncotted 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.

Type: Saliva

Specimen Requirements:
Oragene™ Saliva Collection Kit
Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Type: DNA, Isolated

Specimen Requirements:
Microtainer
8µg
Isolation using the Perkin Elmer™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.

Related Tests

- Deletion/duplication analysis of the HCCS gene by CGH array is available for those individuals in whom sequence analysis is negative.
- 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 only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.
- X-Linked Intellectual Disability panels are available for 30, 60, and 90 genes.