Cornelia de Lange Syndrome: Sequencing Panel

Test Code: MM460
Turnaround time: 6 weeks
CPT Codes: 81479 x4

Condition Description

Mutations in five genes, \( \text{HDAC8}, \text{NIPBL} \) (5p13.1), \( \text{RAD21}, \text{SMC1A} \), and \( \text{SMC3} \) are currently reported to cause Cornelia de Lange syndrome (CdLS). Mutations in the NIPBL gene more often cause the classical form of CdLS, while mutations in the \( \text{HDAC8}, \text{RAD21}, \text{SMC1A}, \) and \( \text{SMC3} \) genes often cause a milder form of CdLS. Classical CdLS is characterized by distinctive facial features (including microbrachycephaly, arched eyebrows, long, thick eyelashes, low-set posteriorly rotated and/or hirsute ears with thickened helices, depressed or broad nasal bridge, long smooth philtrum, high arched or cleft palate, small widely-spaced teeth, micrognathia, and a short neck), growth retardation, hirsutism, and upper limb reduction deficits. Additional features include intellectual disability, cardiac defects, gastrointestinal dysfunction, hearing loss, myopia, and hypoplastic genitalia. Individuals with a milder phenotype have less severe growth, cognitive, and limb involvement but usually have the classical facial features associated with CdLS.


References:
- GeneReviews
  - OMIM #608667: NIPBL gene
  - OMIM #122470: CdLS

Genes

\[ \text{HDAC8}, \text{NIPBL}, \text{RAD21}, \text{SMC1A}, \text{SMC3} \]

Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of Cornelia de Lange syndrome.
- Carrier testing in adults with a family history of Cornelia de Lange syndrome.

Methodology

**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.

Detection

**Next Generation Sequencing:** 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/duplications will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype.

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

Specimen Requirements

Submit only 1 of the following specimen types

**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: Ship sample at room temperature with overnight delivery.

**Type: Isolated DNA**

Specimen Requirements:
In microtainer: 60 ug

Isolation using the Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping: Refrigerate until time of shipment in 100 ng/ul of TE buffer. Ship sample at room temperature with overnight delivery.

**Related Tests**

- Sequencing and deletion/duplication analysis is available for *NIPBL* and *SMC1A*
- Cornelia de Lange Syndrome: Deletion/Duplication Panel