Mutations in three genes, *NIPBL* (5p13.1), *SMC1A*, and *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 *SMC1A* and *SMC3* genes often cause a more mild form of CdLS. Classical CdLS is characterized by distinctive facial features (including microbachycelphaly, 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, hirsuitism, and upper limb reduction deficits. Additional features include intellectual disability, cardiac defects, gastrointestinal dysfunction, hearing loss, myopia, and hypoplastic genitilia. Individuals with a milder phenotype have less severe growth, cognitive, and limb involvement but usually have the classical facial features associated with CdLS.

Please note that this test is for the *NIPBL* gene only. For patients with suspected CdLS, 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 #608667: *NIPBL* gene
- OMIM #122470: CdLS

**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.

**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) 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.

Related Tests

- Deletion/duplication analysis of the NIPBL 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.