Clinical Features:
Patients with Cornelia de Lange syndrome (CdLS) [OMIM #122470] have characteristic facial features, growth retardation, hirsutism, and upper limb reduction defects. More than 95% of patients with CdLS have limb involvement, but only 25% have severe limb anomalies. Characteristic facial features include synophrys, long eyelashes, depressed nasal bridge with an upturned nasal tip and anteverted nares, thin upper lip with downturned corners of the mouth, and posteriorly rotated low-set ears. Most individuals have severe to profound mental retardation, but more mild cognitive delays have been reported. Many demonstrate autistic or self-destructive behaviors. Other features include heart defects, myopia, hearing loss, gastrointestinal problems and abnormal genitalia (1). Suggested minimal clinical criteria for testing include short stature, developmental delay, and characteristic facial features.

Our Cornelia de Lange Syndrome Sequencing Panel includes mutation analysis of all 5 genes listed below. Our sequencing assay is validated to detect mosaic variants present at levels of 10% or higher*. We recommend testing on buccal samples to enhance detection of mosaic variants. Single gene testing for each of the 5 genes listed is also available in our laboratory. Our Cornelia de Lange Syndrome Sequencing Panel includes mutation analysis of all 5 genes listed below. Our sequencing assay is validated to detect mosaic variants present at levels of 10% or higher*. We recommend testing on buccal samples to enhance detection of mosaic variants. Single gene testing for each of the 5 genes listed is also available in our laboratory.

<table>
<thead>
<tr>
<th>Cornelia de Lange Syndrome Panel</th>
<th>NIPBL</th>
<th>SMC1A</th>
<th>HDAC8</th>
<th>RAD21</th>
<th>SMC3</th>
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*Please note, detection of mosaic variants is not available for prenatal specimen types.

Molecular Genetics:
Mutations of the NIPBL [OMIM #608667] gene have been identified in patients with CdLS (2, 3). Gillis, et al. (4) detected NIPBL mutations in 56 of 120 (47%) patients with characteristic facial features of CdLS. Patients with an identified NIPBL mutation are more severely affected in growth, development and limb anomalies than those in whom an NIPBL mutation is not identified, and patients with a missense mutation are more mildly affected than those with a truncating mutation (4). Nonsense, missense, frameshift and splicing mutations have been identified in the NIPBL gene. Intragenic deletions of one or more exons of NIPBL have been reported in approximately 3% of patients with a clinical diagnosis of CdLS (5). Mutations of the SMC1A [OMIM #300590] gene have been identified in patients with CdLS (6). Deardorff, et al. (7) detected SMC1A mutations in approximately 5% of patients with CdLS (about 9% of those negative for NIPBL mutations). Mutations of the SMC3 gene [OMIM #606062] gene has been reported in 1-2% of patients with CdLS (7). Mutations of the RAD21 [OMIM #606462] gene have been reported in 1% or less of CdLS patients (8). Mutations of the HDAC8 [OMIM #300269] gene have been identified in 5/154 (3%) individuals with CdLS that were negative for mutations in NIPBL, SMC1A, SMC3 and RAD21 (9).

In recent years, somatic mosaicism has been increasingly recognized in patients with CdLS, and in some patients mosaic pathogenic variants may be detected in DNA extracted from buccal samples but not detectable in DNA derived from a blood sample (10, 11). We recommend testing on buccal samples to enhance detection of mosaic variants.

Inheritance:
CdLS occurs in 1 in 10,000-100,000 live births. NIPBL, SMC3 and RAD21 mutations are inherited in an autosomal dominant pattern. SMC1A and HDAC8 mutations are X-linked and have been found in both males and females. Most cases appear to be de novo. Germline mosaicism has been reported; recurrence risk for unaffected parents of an isolated case is approximately 1-5%. Recurrence risk for affected individuals and carrier parents is 50% (1).
Additional Resources:
Cornelia de Lange Syndrome Foundation, Inc.
Phone: 860-676-8166; 800-223-8355
email: info@cdlsusa.org
www.cdlsusa.org

Test methods:
We offer mutation analysis of all coding exons and intron/exon boundaries of NIPBL, SMC1A, SMC3, RAD21 and HDAC8. Our sequencing assay is validated to detect mosaic variants present at levels of 10% or higher. Mosaicism detection is validated for regions sequenced with >500X coverage, which on average includes >98% of the coding regions of the panel genes. Mosaicism detection may be reduced in regions that have less than 500X coverage. Please note, detection of mosaic variants is not available for prenatalsal specimen types. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. The constructed genomic DNA library is sequenced using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20bp.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Please, send a completed Cornelia de Lange Clinical Questionnaire and patient consent form with each sample.

Cornelia de Lange Syndrome Panel (NIPBL, SMC1A, SMC3, RAD21, and HDAC8 mutation analysis)
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $2600
CPT codes: 81406, 81407
Turn-around time: 4 weeks

NIPBL mutation analysis
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $1000
CPT codes: 81406, 81407
Turn-around time: 4 weeks

SMC1A mutation analysis
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $1000
CPT codes: 81406, 81405
Turn-around time: 4 weeks

SMC3, RAD21, HDAC8 mutation analysis
Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $1500
CPT codes: 81407
Turn-around time: 4 weeks

Patients with negative results or variants of unknown significance can enroll in Dr. Ian Krantz’s research study at the Children’s Hospital of Philadelphia for further studies.
Results:
Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References: