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.

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). NIPBL has 46 coding exons and spans 188 kb. 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). SMC1A has 25 coding exons. Only missense mutations and in-frame deletions have been identified in the SMC1A gene.

A small, in-frame deletion of the SMC3 gene [OMIM #606062] gene has been reported in a patient with atypical facial characteristics and absent limb anomalies (7). SMC3 has 29 coding exons.

Mutations of the RAD21 [OMIM #606462] gene have been reported in 1% or less of CdLS patients (8). RAD21 has 13 coding exons. Missense mutations and whole gene deletions have been identified in the RAD21 gene.

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). HDAC8 has 11 coding exons and both missense and nonsense mutations have been identified.

Patients with mutations in NIPBL tend to be more severely affected than those with mutations in SMC3, SMC1A and RAD21. Individuals with mutations in HDAC8 demonstrate growth, cognitive and facial features consistent with those caused by mutations in NIPBL (9). No patients with mutations in SMC1A or SMC3 have been reported with limb reduction defects (7). Individuals with mutations in RAD21 tend to have milder cognitive and physical abnormalities (8).

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).

Test methods/strategy:
Our Cornelia de Lange Syndrome Series employs testing of NIPBL, SMC1A, SMC3, RAD21 and HDAC8 in a sequential manner. Tier 1 includes sequencing and deletion/duplication analysis of the NIPBL gene. Tier 2 includes sequencing and deletion/duplication analysis of SMC1A. Tier 3 includes sequencing and deletion/duplication analysis of SMC3, RAD21, and HDAC8.

**Test methods:**
Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed 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 novel and/or potentially 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 20 bp. Deletion/duplication analysis of genes in the Cornelia de Lange Syndrome Series is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

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<thead>
<tr>
<th>Cornelia de Lange Syndrome Series</th>
<th>Sample specifications:</th>
<th>3 to10 cc of blood in a purple top (EDTA) tube</th>
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<td>Cost:</td>
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<td>Turn-around time:</td>
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<tr>
<td>2</td>
<td>SMC1A sequencing and deletion/duplication</td>
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<tr>
<td>3</td>
<td>SMC3, RAD21, HDAC8 sequencing and deletion/duplication</td>
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Tier 3: SMC3, RAD21, HDAC8 sequencing
Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $2900
CPT codes: 81407
Turn-around time: 4 weeks

Note: We cannot bill insurance for SMC3, RAD21 and HDAC8 sequencing.
Tier 3: SMC3, RAD21, HDAC8 deletion/duplication

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $1545
CPT codes: 81407
Turn-around time: 4 – 6 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.

Additional Resources:
Cornelia de Lange Syndrome Foundation, Inc.
Phone: 860-676-8166; 800-223-8355
email: info@cdlsusa.org
www.cdlsusa.org

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. You can also contact us at 773-834-0555 or ucgslabs@genetics.uchicago.edu

References:

Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS’ NEEDS