The University of Chicago Genetic Services Laboratories

5841 S. Maryland Ave., Rm. G701, MC 0077, Chicago, Illinois 60637
Toll Free: (888) UC GENES (888) 824 3637
Local: (773) 834 0555 FAX: (773) 702 9130
ucgslabs@genetics.uchicago.edu dnatesting.uchicago.edu
CLIA #: 14D0917593 CAP #: 18827-49

Genetic Testing for Cornelia de Lange Syndrome

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 uptilted 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 *HDAC*8 [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).

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* by direct sequencing of amplification products in both the forward and reverse directions. We also offer deletion/ duplication analysis of the *NIPBL* gene by either MLPA or oligonucleotide array-CGH, and deletion/duplication analysis of the *SMC1A, SMC3, RAD21, HDAC8* genes by oligonucleotide array-CGH to identify copy number changes involving one or more exons. 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. Please note that if ordering both *NIPBL* and *SMC1A* deletion/duplication concurrently, analysis will be performed by oligonucleotide array-CGH.

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

Test strategy:

Our Cornelia de Lange syndrome series employs testing of *NIPBL, SMC1A, SMC3, RAD21* and *HDAC8* in a sequential manner. Tier 1 is mutation analysis of all coding exons and intron/exon boundaries of *NIPBL* by direct sequencing of amplification products in both the forward and reverse directions as well as *NIPBL* deletion/ duplication analysis by MLPA or oligonucleotide array-CGH to identify copy number changes involving one or more exons. Tier 2 is mutation analysis of all coding exons and intron/exon boundaries of *SMC1A* by direct sequencing of amplification products in both the forward and reverse directions as well as *SMC1A* deletion/ duplication analysis by oligonucleotide array-CGH to identify copy number changes involving one or more exons. Tier 3 is mutation analysis of all coding exons and intron/exon boundaries of *SMC3, RAD21* and *HDAC8* gene by direct sequencing of amplification products in both the forward and reverse directions as well as *SMC3, RAD21* and *HDAC8* deletion/ duplication analysis by oligonucleotide array-CGH to identify copy number changes involving one or more exons.

Cornelia de Lange Syndrome Series

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $2000-5000
CPT codes: see below
Turn-around time: 4 weeks (per Tier)

Tier		CPT codes	Cost
1	*NIPBL* sequencing and deletion/duplication	81479	$2000
2	*SMC1A* sequencing and deletion/duplication	81479	$1500
3	*SMC3, RAD21, HDAC8* sequencing and deletion/duplication	81479	$1500

Sequencing and/or deletion/duplication analysis of the *NIPBL* and *SMC1A* gene as well as the Tier 3 panel (*SMC3, RAD21, HDAC8*) can also be ordered separately.

NIPBL sequencing analysis

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $2100
CPT codes: 81407
Turn-around time: 4 weeks

NIPBL deletion/duplication analysis

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $1000
CPT codes: 81406
Turn-around time: 4 weeks

SMC1A sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1500
CPT codes:	81406
Turn-around time:	4 weeks

SMC1A deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405
Turn-around time:	4 weeks

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 to10 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

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.

References:

1. Deardorff M, Clark D, Krantz I. Cornelia de Lange Syndrome. In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washington, 2005.
2. Krantz ID, McCallum J, DeScipio C et al. Cornelia de Lange syndrome is caused by mutations in NIPBL, the human homolog of Drosophila melanogaster Nipped-B. Nat Genet 2004: 36: 631-635.
3. Tonkin ET, Wang TJ, Lisgo S et al. NIPBL, encoding a homolog of fungal Scc2-type sister chromatid cohesion proteins and fly Nipped-B, is mutated in Cornelia de Lange syndrome. Nat Genet 2004: 36: 636-641.
4. Gillis LA, McCallum J, Kaur M et al. NIPBL mutational analysis in 120 individuals with Cornelia de Lange syndrome and evaluation of genotype-phenotype correlations. Am J Hum Genet 2004: 75: 610-623.
5. Russo S, Masciadri M, Gervasini C et al. Intragenic and large NIPBL rearrangements revealed by MLPA in Cornelia de Lange patients. Eur J Hum Genet 2012: 20: 734-741.
6. Musio A, Selicorni A, Focarelli ML et al. X-linked Cornelia de Lange syndrome owing to SMC1L1 mutations. Nat Genet 2006: 38: 528-530.
7. Deardorff MA, Kaur M, Yaeger D et al. Mutations in cohesin complex members SMC3 and SMC1A cause a mild variant of cornelia de Lange syndrome with predominant mental retardation. Am J Hum Genet 2007: 80: 485-494.
8. Deardorff MA, Wilde JJ, Albrecht M et al. RAD21 mutations cause a human cohesinopathy. Am J Hum Genet 2012: 90: 1014-1027.
9. Deardorff MA, Bando M, Nakato R et al. HDAC8 mutations in Cornelia de Lange syndrome affect the cohesin acetylation cycle. Nature 2012: 489: 313-317.

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