



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 *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).

Additional Resources:

Cornelia de Lange Syndrome Foundation, Inc.

Phone: 860-676-8166; 800-223-8355

email: info@cclsusa.org

www.cclsusa.org

Test methods:

We offer mutation analysis of all coding exons and intron/exon boundaries of *NIPBL*, *SMC1A*, *SMC3*, *RAD21* and *HDAC8*. 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.

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.

Cornelia de Lange Syndrome Panel (*NIPBL*, *SMC1A*, *SMC3*, *RAD21*, and *HDAC8* sequencing and deletion/ duplication analysis)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$2500
CPT codes:	81407
Turn-around time:	4 weeks

NIPBL sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$1000
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:	\$1000
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

SMC3, RAD21, HDAC8 sequencing

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$1500
CPT codes:	81407
Turn-around time:	4 weeks

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 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:

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.

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