

The University of Chicago Genetic Services Laboratories



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NIPBL and SMC1A analysis 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. Recently, intragenic deletions of one or more exons of *NIPBL* have been reported in approximately 2% of patients with a clinical diagnosis of CdLS.

Mutations of the *SMC1A* [OMIM #300590] gene have been identified in patients with CdLS [5]. Deardorff, et al. [6] 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.

Patients with mutations in *NIPBL* tend to be more severely affected than those with mutations in *SMC1A*. No patients with mutations in *SMC1A* have been reported with limb reduction defects [6].

Inheritance:

CdLS occurs in 1 in 10-100,000 live births. *NIPBL* mutations are inherited in an autosomal dominant pattern. *SMC1A* 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 full gene sequencing of the entire coding region for *NIPBL* and *SMC1A*. We also offer deletion/duplication analysis of the *NIPBL* gene by MLPA to identify deletions/duplications of one or more exons. The sensitivity of our deletion/duplication assay may be reduced when DNA is extracted by an outside laboratory. For best results, please provide a fresh blood sample for this testing. 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.

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

NIPBL mutation analysis (sequencing)

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: \$2400
CPT codes: 83891, 83898 x 9, 83904 x 9, 83912
Turn-around time: 10 weeks

Note: We cannot bill insurance for NIPBL sequencing.

NIPBL deletion/duplication analysis

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: \$350
CPT codes: 83891, 83900, 83912
Turn-around time: 4 weeks

SMC1A mutation analysis (sequencing)

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: \$2025
CPT codes: 83891, 83898 x 4, 83904 x 9, 83912
Turn-around time: 4 - 6 weeks

Targeted analysis for a known sequence change in additional family members

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: \$390
CPT codes: 83891, 83898 x 2, 83894, 83912
Turn-around time: 2 - 4 weeks

Prenatal testing for a known mutation

Sample specifications: 2 T25 flasks of cultured cells from amnio or CVS or 10ml of amniotic fluid
Cost: \$590
CPT codes: 83891, 83898 x 2, 83894, 83912, 99051
Turn-around time: 1-2 weeks

Molecular Diagnostics Laboratory Faculty and Staff:

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References:

1. Deardorff MA, Yaeger DM, Krantz ID. Cornelia de Lange syndrome (2006) GeneReviews. www.genetests.com
2. Krantz ID, et al. Cornelia de Lange Syndrome is caused by Mutations in *NIPBL*, the human homolog of the *Drosophila* Nipped-B gene (2004) Nature Genetics 36:631-635.
3. Tonkin ET, 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 (2004) Nature Genetics 36: 636-641.
4. Gillis LA, et al. *NIPBL* Mutational Analysis in 120 Individuals with Cornelia de Lange Syndrome and Evaluation of Genotype-Phenotype Correlations (2004). Am J Hum Genet 75:610-623.
5. Musio A, et al. X-linked Cornelia de Lange syndrome owing to *SMC1L1* mutations (2006) Nature Genetics 38:528-30.
6. Deardorff MA, et al. Mutations in cohesin complex members *SMC3* and *SMC1A* cause a mild variant of Cornelia de Lange syndrome with predominant mental retardation (2007) Am J Hum Genet 80: 485-494.

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