NIPBL and SMC1A Gene Analysis in Cornelia de Lange Syndrome

Also known as: Brachmann-de Lange syndrome

Mendelian Inheritance in Man Number: 122470 (Cornelia de Lange syndrome); 608667 (NIPBL gene); 300590 (SMC1A)

Clinical features:
Cornelia de Lange syndrome (CdLS) is a pan-ethnic disorder characterized by pre- and postnatal growth retardation and various congenital anomalies. Distinct craniofacial dysmorphisms include microbrachycephaly, synophrys, long eyelashes, long philtrum, thin upper lip, downturned mouth and small upturned nasal tip. Limb anomalies range from oligodactyly and small hands to absence of forearm. Gastrointestinal disorders and hirsutism are common. Intellectual disability varies greatly, with an average IQ of 53. Less common features include psychomotor retardation, high arched palate with cleft, autism-like behavior, self-injurious behaviors, speech impairment, sensorineural hearing loss, and ophthalmological, genito-urinary (cryptorchidism) and heart anomalies. Mild to severe forms of CdLS have been observed. The estimated prevalence is 1/10,000. Mutations in five genes have been identified in patients with clinical features of CdLS: NIPBL, SMC1A, SMC3, PDS5A and PDS5B. The penetrance of NIPBL mutations is complete, while that of SMC1A mutations is not yet known.

Inheritance pattern:

- NIPBL gene: autosomal dominant, 99% sporadic. Somatic and gonadal mosaicism has been described.
- SMC1A gene: X-linked dominant. SMC1A escapes X-inactivation, and males and females are similarly affected. It is likely that the mechanism in affected females is a dominant negative effect rather than to skewed X-inactivation or haploinsufficiency.

Gene/protein information:
The 189-kb NIPBL gene contains 47 exons and is located on 5p13.2. It produces the delangin protein, which is involved in chromatid cohesion processes and in enhancer-promoter communications. The 49-kb SMC1A gene has 25 exons and is located on Xp11.22. It encodes a subunit of the cohesin complex. SMC1A escapes X-inactivation.

Genotype/phenotype correlation:
The clinical course of patients with large deletions in the NIPBL gene, including growth and motor delay, is severe. Mutations in the SMC1A gene lead to mild to moderate phenotypes, including non-specific X-linked mental retardation. Males and females with a mutation in SMC1A are similarly affected. Chromosomal abnormalities in various regions that do not involve NIPBL or SMC1A have been reported in patients with the CdLS phenotype. These may cause CdLS or a CdLS phenocopy, or may be unrelated to the phenotype. Of note, patients with large duplications including all or a portion of NIPBL or SMC1A present with phenotypes distinct from those observed with deletion of the genes. In particular the typical CdLS facial gestalt is absent and some patients have increased weight and long fingers.

Reason for referral:
- Confirmation of a clinical diagnosis
- Prenatal diagnosis in a family with a known mutation

Test Methods:
Sequence analysis of the NIPBL gene is offered in two tiers. Tier 1 analysis of NIPBL includes bi-directional sequencing of select exons where the majority of mutations have been reported. An analysis of the NIPBL-LOVD database suggests that a mutation detection rate of almost 80% could be achieved by this tier 1 test, which includes sequencing of exons 2, 3, 7, 10, 13, 14, 15, 17, 19, 22, 26, 28-31, 35, 36, 39, 40, 42, 43, and 45. Tier 2 analysis encompasses bi-directional sequencing of the remaining 24 exons of NIPBL. If no mutation has been identified by
sequencing of NIPBL, whole genome array CGH (GenomeDx) including exon-level coverage of NIPBL is available to evaluate for a deletion or a duplication of an exon or larger and for other genomic copy number variants. Sequence analysis of the coding exons 1-25 and targeted deletion/duplication analysis of SMC1A are also available as separate tests. Any mutation or deletion/duplication is confirmed by repeat sequence analysis, restriction fragment analysis, qPCR, or another appropriate method.

**Test sensitivity:**
Several large studies have identified mutations in 37-47% of patients with a clinical diagnosis of CdLS by NIPBL sequencing. Pooling data from two small studies, 5% of patients with no NIPBL point mutations had large deletions encompassing one or more exons of NIPBL. SMC1A mutations have been observed in 9-10% of NIPBL-negative patients with an overall prevalence of 5% among patients with CdLS. Additionally, 4-14% of patients with a clinical diagnosis of CdLS have been found to harbor a genomic deletion or duplication not including NIPBL or SMC1A by karyotype or array CGH.

**Mutation spectrum:**
Mutations in NIPBL occur throughout the gene, including a cluster of mutations in exon 10 and in the highly conserved HEAT domain. Approximately 200 unique mutations have been reported in NIPBL, including small deletions (28%), missense (21%), nonsense (17%), splicing (17%), and frameshifts (17%) (www.lovd.nl/CDLS). Only one regulatory change in the 5' UTR region has been reported, and rarely whole or partial gene deletions have been described. Most reported mutations in SMC1A are missense or in-frame deletions that preserve the reading frame. Approximately 30 patients with a CdLS phenotype have been described with chromosomal abnormalities in various regions other than NIPBL or SMC1A. Large duplications including all or a portion of NIPBL have been found in five unrelated patients with a phenotype distinct from CdLS, while another patient has been reported with a duplication on chromosome X including SMC1A.

**Specimen Requirements and Shipping/Handling:**
- **Blood:** A single tube with 1-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for up to 7 days prior to shipping.
- **Buccal Brush:** Can be used as an alternative to blood for NIPBL and SMC1A sequencing only. Use a GeneDx buccal kit (others not accepted). Submit by mail. Buccal brushes are not accepted on children under 6 months of age. Analysis to detect a NIPBL or SMC1A gene deletion or duplication requires submission of a venous blood sample.
- **Prenatal Diagnosis:** For prenatal testing for a known mutation in the NIPBL or SMC1A genes, please refer to the specimen requirements table on our website at: http://www.genedx.com/test-catalog/prenatal/. Ship overnight at ambient temperature, using a cool pack in hot weather.

**Required Forms:**
- **Sample Submission (Requisition) Form** – complete all pages
- **Payment Options Form or Institutional Billing Instructions**

For test codes, prices, CPT codes, and turn-around-times, please refer to the “DISORDER” page on our website: www.genedx.com.

**References:**