Cornelia de Lange Syndrome:
Sequence Analysis and Exon-Level Deletion/Duplication Testing of 5 Genes

Disorder also known as:
Brachmann-de Lange syndrome

Panel Gene List:
HDAC8, NIPBL, RAD21, SMC1A, and SMC3.

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 also common. Intellectual disability varies greatly, with an average IQ of 53\(^1\). 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\(^1\). CdLS is estimated to occur in 1 in 10,000 to 1 in 100,000 individuals and presents in mild to severe forms with variable expressivity\(^2\). Pathogenic variants in five genes: NIPBL, SMC1A, SMC3, HDAC8 and RAD21 have been identified in patients with clinical features of CdLS\(^3\). The penetrance of NIPBL variants is complete, while variants within other genes are not precisely known, but expected to be high\(^2\).

The clinical course of patients with null variants in the NIPBL gene, including growth and motor delay, is severe\(^8,9\). Phenotypes due to variants in the SMC1A, SMC3, HDAC8 and RAD21 genes generally range from mild to moderate, including non-specific X-linked mental retardation. Because SMC1A escapes X-inactivation, males and females are similarly affected. This correlation also supports dominant negative effects in affected females rather than skewed X-inactivation or haploinsufficiency\(^2,7\). The phenotype in females with pathogenic variants in HDAC8 varies due to the pattern of X-inactivation. Chromosomal abnormalities in various regions that do not involve NIPBL or SMC1A have been reported in patients with the CdLS phenotype\(^10\). These may cause CdLS, 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\(^11\).
Inheritance Pattern/Genetics:

- NIPBL gene: autosomal dominant, 99% sporadic. Somatic and gonadal mosaicism has been described.4,5,6
- SMC1A gene: X-linked dominant.
- SMC3 gene: autosomal dominant, mostly sporadic
- HDAC8 gene: X-linked dominant, mostly sporadic
- RAD21 gene: autosomal dominant, mostly sporadic

Test Methods:

Using genomic DNA obtained from the submitted specimen, the coding exons and flanking splice junctions of the genes on this panel are enriched using a proprietary targeted capture method developed by GeneDx. These targeted regions are simultaneously by massively parallel (NextGen) sequencing on an Illumina platform with paired-end reads. Bidirectional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing is used to confirm all potentially pathogenic variants and to obtain sequence for regions where fewer than 15 reads are achieved by NextGen sequencing. Concurrent deletion/duplication testing is performed for the genes in the panel using exon-level oligo array CGH (ExonArrayDx). Data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. The array is designed to detect most intragenic deletions and duplications. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat array CHG analysis. Sequence and array CGH alterations are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Benign and likely benign variants, if present, are not included in this report but are available upon request.

Test Sensitivity:

Several large studies have identified variants in ~60% of patients with a clinical diagnosis of CdLS8,9,12,13,14. SMC1A variants have been observed in 9-10% of NIPBL-negative patients and in ~5% overall of patients with CdLS2,7,12. SMC3 variants have been observed in ~1-2% of patients with CdLS2,11. HDAC8 variants have been observed in ~4-5% of patients with CdLS2,21. RAD21 variants are the least frequent and have been observed in <1% of CdLS patients2. 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 CGH17,18,19.

The technical sensitivity of the sequencing test is estimated to greater than 99%. It will not detect deletions, insertions, or rearrangements greater than or equal to ten base pairs. The deletion/duplication testing can detect deletions or duplications encompassing one or more exons, including variants as small as 150-300 base pairs. Note that small sections of a few
individual genes have inherent sequence properties that yield suboptimal data and mutations in those regions may not be identified.

References: