

## Prenatal Testing for NIPBL Gene Variants: Cornelia de Lange Syndrome

### DISORDER ALSO KNOWN AS

Brachmann-de Lange syndrome

### 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 53.1. 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. <sup>1</sup> Mild to severe forms of CdLS have been observed. The estimated prevalence is 1/10,000.2. Pathogenic variants in five genes have been identified in patients with clinical features of CdLS: NIPBL, SMC1A, SMC3, PDS5A and PDS5B3. The penetrance of NIPBL variants is complete. <sup>2</sup>

### INHERITANCE PATTERN/GENETICS

Autosomal dominant, 99% sporadic. Somatic and gonadal mosaicism has been described.<sup>4,5,6</sup>

### TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Additionally, genotype analysis of maternal and fetal DNA for several polymorphic markers to test for maternal cell contamination will be performed. Therefore, in all prenatal cases a maternal sample should accompany the fetal sample.

### TEST SENSITIVITY

Several large studies have identified variants in 37-47% of patients with a clinical diagnosis of CdLS by NIPBL sequencing.<sup>12,13,14</sup> Pooling data from two small studies, 5% of patients with no NIPBL point variants had large

deletions encompassing one or more exons of NIPBL.<sup>8,9</sup> Additionally, 4-14% of patients with a clinical diagnosis of CdLS have been found to harbor a genomic deletion or duplication not including NIPBL by karyotype or array CGH.<sup>17,18,19</sup>

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