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 531. 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 (cryptoorchidism) and heart anomalies.[1] Mild to severe forms of CdLS have been observed. The estimated prevalence is 1/10,0002. 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.[2]

Inheritance Pattern/Genetics:
Autosomal dominant, 99% sporadic. Somatic and gonadal mosaicism has been described.[4,5,6]

Test Methods:
Using genomic DNA, analysis is performed by bi-directional sequencing of the coding region (exons 2-47) and the flanking splice sites of the NIPBL gene. Concurrently, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed to evaluate for a deletion or duplication of one or more exons of the NIPBL gene. Any variant or deletion/duplication is confirmed by repeat sequence analysis, restriction fragment analysis, qPCR, or another appropriate method. For known familial variants, the relevant portion of the NIPBL gene will be analyzed in duplicate.

Test Sensitivity:
Several large studies have identified variants in 37-47% of patients with a clinical diagnosis of CdLS by NIPBL sequencing.[12,13,14] Pooling data from two small studies, 5% of patients with no NIPBL point variants had large deletions encompassing one or more exons of NIPBL.[8,9] 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.[17,18,19]

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