THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Cornelia de Lange PLUS Panel

Next Generation Sequencing Panel for Cornelia de Lange Syndrome and related disorders

Overview:
Cornelia de Lange syndrome is characterized by distinctive craniofacial features, developmental delays, variable congenital malformations, and growth retardation (1). Several conditions have considerable overlap with CdLS, including Coffin-Siris syndrome, Rubinstein Taybi syndrome, Robinow syndrome, and Roberts syndrome. The Cornelia de Lange PLUS Sequencing Panel offers sequencing of 22 genes associated with CdLS and related disorders.

Our Cornelia de Lange PLUS Panel include analysis of all 22 genes listed below.

Cornelia de Lange Syndrome PLUS Sequencing Panel genes			
ADNP	EP300	ROR2	SMC3
AFF4	ESCO2	SMARCA2	SOX11
ANKRD11	HDAC8	SMARCA4	TBC1D24
ARID1A	NIPBL	SMARCB1	WNT5A
ARID1B	PHF6	SMARCE1	
CREBBP	RAD21	SMC1A	

Disorder	Genes	Inheritance	Clinical features/molecular genetics
Coffin-Siris syndrome	*ARID1A* *ARID1B* *PHF6* *SMARCA4* *SMARB1* *SMARCE1* *SOX11*	AD, XL	Coffin-Siris syndrome [CSS OMIM #135900] is characterized by intellectual disability, coarse facial features, speech impairment, hypertrichosis, and hypoplastic or absent fifth fingernails or toenails (2). Other findings can include failure to thrive, feeding difficulties, short stature, ophthalmologic abnormalities, microcephaly and hearing loss (3). Several of the genes associated with Coffin-Siris syndrome encode subunits of the SWItch/Sucrose Non-Fermenting (SWI/SNF) complex (4). Most forms of CSS are inherited in an autosomal dominant manner. However, *PHF6* is associated with an X-linked form of CSS (5). The majority of cases of CSS are *de novo*.
Cornelia de Lange syndrome	*NIPBL* *SMC1A* *SMC3* *HDAC8* *RAD21*	AD, XL	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). Dominant CdLS is caused by mutations in *NIPBL, RAD21,* and *SMC3.* Mutations in *HDAC8* and *SMC1A* are associated with X-linked CdLS.

Cornelia de Lange-like syndrome/ KBG syndrome	*ANKRD11*	AD	Heterozygous mutations in *ANKRD11* are associated with KBG syndrome [OMIM #148050], which is characterized by macrodontia of the upper central incisors, vertebral and hand anomalies, short stature, developmental delays and intellectual disabilities. Several individuals with features reminiscent of Cornelia de Lange syndrome have been found to have mutations in *ANKRD11* (6, 7), highlighting the phenotypic overlap between Cornelia de Lange syndrome and KBG syndrome.
CHOPS syndrome	*AFF4*	AD	Heterozygous mutations in *AFF4* are associated with CHOPS syndrome [OMIM#616368], a condition which overlaps phenotypically with CdLS. Individuals with CHOPS syndrome may have features including cognitive impairment, coarse facies, heart defects, obesity, pulmonary involvement, short stature, and skeletal dysplasia (8).
DOORS syndrome	*TBC1D24*		Homozygous or compound heterozygous mutations in *TBC1D24,* a gene encoding a subunit of the SWI/SNF complex, are associated with DOORS (Deafness, Onychodystrophy, Osteodystrophy, Mental Retardation, and Seizures) syndrome [OMIM #220500]. Individuals with DOORS syndrome may exhibit dysmorphic facial features such as a broad nasal bridge, high arched palate, and bulbous nose. Additional features include congenital heart defects and renal anomalies (9).
Helsmoortel-Van der Aa syndrome	*ADNP*	AD	Helsmoortel and Van der Aa, 2014, identified *de novo*, heterozygous truncating mutations in *ADNP* in 10 individuals with mild to severe intellectual disability, autism spectrum disorders, and dysmorphic facial features including prominent forehead, thin upper lip, and broad nasal bridge. Other variable features included hand abnormalities, brain abnormalities, growth retardation, and hypermetropia (10).
Nicolaides-Baraitser syndrome	*SMARCA2*	AD	Nicolaides-Baraitser syndrome (NCBRS) [OMIM #601358] is characterized by severe intellectual disability, microcephaly, short stature, dysmorphic features, sparse hair, and brachydactyly. NCBRS is caused by non-truncating mutations in the ATPase region of *SMARCA2* (11). NCBRS has phenotypic overlap with Coffin-Siris syndrome.
Roberts syndrome	*ESCO2*	AR	Roberts syndrome (RBS) [OMIM #268300] is characterized by limb malformations including tetraphocomelia and hypomelia, hand malformations, prenatal onset growth retardation, and craniofacial findings including cleft lip/palate, micrognathia, microbrachycephaly, downslanting palpebral fissures, beaked nose, and ear malformations. Other features include heart defects, renal anomalies, and variable degrees of developmental delay (12). Roberts syndrome is caused by homozygous or compound heterozygous mutations in *ESCO2. ESCO2* is a member of the conserved Eco1/Ctf7 family of acetyltransferases involved in the establishment of cohesion between sister chromatids and in double-stranded DNA repair (13).
Robinow syndrome	*ROR2* *WNT5A*	AR or AD	Robinow syndrome is characterized by growth retardation, limb defects, genital hypoplasia, and characteristic facial features including broad forehead, midface hypoplasia, short upturned nose, large mouth, and micrognathia (14, 15). Robinow syndrome can be inherited in an autosomal dominant or autosomal recessive manner. Autosomal dominant Robinow syndrome is caused by inherited or *de novo* mutations in *WNT5A* [OMIM #180700]. Autosomal recessive Robinow syndrome is caused by homozygous or compound heterozygous mutations in *ROR2* [OMIM

			#268310].

Rubinstein-Taybi syndrome	*CREBBP* *EP300*	AD	Patients with Rubinstein-Taybi syndrome (RSTS) [OMIM #180849] have short stature, broad thumbs and great toes, moderate to severe intellectual disabilities, and characteristic facial features. Facial features include arched eyebrows, down-slanting palpebral fissures, beaked nose with long columella, high arched palate, and grimacing smile. Many patients with RSTS develop obesity in childhood or adolescence. Other features include eye findings, undescended testes, urinary tract anomalies, and congenital heart defects. Patients with RSTS also have an increased risk for tumors including pheochromocytoma, rhabdomyosarcoma, meningioma, pilomatrixoma, and leukemia (16). RSTS is caused by heterozygous, usually *de novo* mutations in *CREBBP* or *EP300.*

Test methods:
This panel includes full gene sequencing for 22 genes implicated in Cornelia de Lange syndrome and related conditions. Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Cornelia de Lange Syndrome PLUS panel (22 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$3500
CPT codes:	81406 81407
Turn-around time:	8 weeks

Note: We cannot bill insurance directly for the above test

Results:
Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

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