



Genetic Testing for Coffin-Siris syndrome

Clinical Features:

Coffin-Siris syndrome [CSS OMIM #135900] is characterized by developmental delay, coarse facial features, speech impairment, hypertrichosis, hypoplastic or absent fifth fingernails or toenails, and agenesis of the corpus callosum (1). Other findings can include failure to thrive, feeding difficulties, short stature, ophthalmologic abnormalities, microcephaly and hearing loss (2). There are several conditions that exhibit significant overlap with Coffin-Siris syndrome, including Nicolaides-Baraitser syndrome (NCBRS), DOORS syndrome, KBG syndrome, and *ADNP*-related autism/ID (3). NCBRS has significant phenotypic overlap with CSS, including intellectual disability, speech impairment, sparse scalp hair, and short stature. Patients with NCBRS typically present with prominent finger joints (4). DOORS syndrome (deafness, osteodystrophy, mental retardation, and seizures) syndrome is characterized by sensorineural deafness, shortened terminal phalanges with small fingernails and toenails, intellectual disability, and seizures (5). KBG syndrome is characterized by macrodontia of the upper incisors, short stature, skeletal anomalies, and intellectual disability (6).

Our Coffin-Siris Syndrome Panel includes analysis of the 11 genes listed below.

COFFIN-SIRIS SYNDROME PANEL			
ADNP	ARID1B	SMARCA4	SOX11
ANKRD11	PHF6	SMARCB1	TBC1D24
ARID1A	SMARCA2	SMARCE1	

Molecular Genetics:

Tsurusaki *et al.*, 2012 identified *de novo* mutations in *SMARCB1* in 2/5 individuals with CSS (7). *SMARCB1* encodes a subunit of the SWIitch/Sucrose Non-Fermenting (SWI/SNF) complex, and screening of additional genes encoding subunits of this complex revealed mutations in *SMARCA4*, *SMARCE1*, *ARID1A* and *ARID1B*. Overall, Tsurusaki *et al.*, 2012 identified mutation in 20/23 (87%) patients with CSS (7). Wieczorek *et al.*, 2013, identified *de novo* mutations in *PHF6* in two patients with Coffin-Siris syndrome (8). Heterozygous mutations in *SOX11*, which is a downstream transcription factor of the SWI/SNF complex, have been found to cause a mild CSS phenotype (9). Other genes encoding components of the SWI/SNF complex have been implicated in disorders with features that overlap with Coffin-Siris syndrome. Mutations in *SMARCA2* have since been identified in patients with Nicolaides-Baraitser syndrome (Van Houdt *et al.*, 2012). Additionally, heterozygous mutations in *ADNP*, which encodes a transcription factor in the SWI/SNF complex, have been identified in patients with dysmorphic facies, autism, intellectual disability, hypotonia, and congenital heart defects (10).

Some conditions with significant overlap with CSS are caused by genes that are not in the SWI/SNF complex. DOORS syndrome has significant clinical overlap with CSS and is caused by mutations in *TBC1D24*, which has no apparent relationship with the SNF/SWI complex (5). KBG syndrome also exhibits phenotypic overlap with CSS and is caused by heterozygous mutations in *ANKRD11*, which is involved in inhibition of ligand-dependent transcriptional activation (11, 12).

Inheritance:

Most forms of CSS and CSS-related conditions are rare autosomal dominant conditions. However, *PHF6* is associated with an X-linked form of CSS. The majority of cases appear to be *de novo*. An additional exception is DOORS syndrome, which is an autosomal recessive condition.

Test methods:

This panel includes full gene sequencing for 11 genes implicated in CSS and related disorders; *ADNP*, *ANKRD11*, *ARID1A*, *ARID1B*, *PHF6*, *SMARCA2*, *SMARCA4*, *SMARCB1*, *SMARCE1*, *SOX11*, and *TBC1D24*. 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.

Coffin-Siris syndrome panel (11 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$2500
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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9. Tsurusaki Y, Koshimizu E, Ohashi H et al. De novo SOX11 mutations cause Coffin-Siris syndrome. *Nat Commun* 2014; 5: 4011.
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12. Zhang A, Yeung PL, Li CW et al. Identification of a novel family of ankyrin repeats containing cofactors for p160 nuclear receptor coactivators. *J Biol Chem* 2004; 279: 33799-33805.

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