THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Next Generation Sequencing Panels for Disorders of Sex Development

Disorders of Sex Development – Overview

Disorders of sex development (DSDs) occur when sex development does not follow the course of typical male or female patterning. Types of DSDs include congenital development of ambiguous genitalia, disjunction between the internal and external sex anatomy, incomplete development of the sex anatomy, and abnormalities of the development of gonads (such as ovotestes or streak ovaries) (1). Sex chromosome anomalies including Turner syndrome and Klinefelter syndrome as well as sex chromosome mosaicism are also considered to be DSDs.

DSDs can be caused by a wide range of genetic abnormalities (2). Determining the etiology of a patient's DSD can assist in deciding gender assignment, provide recurrence risk information for future pregnancies, and can identify potential health problems such as adrenal crisis or gonadoblastoma (1, 3).

Sex chromosome aneuploidy and copy number variation are common genetic causes of DSDs. For this reason, chromosome analysis and/or microarray analysis typically should be the first genetic analysis in the case of a patient with ambiguous genitalia or other suspected disorder of sex development. Identifying whether a patient has a 46,XY or 46,XX karyotype can also be helpful in determining appropriate additional genetic testing.

Abnormal/Ambiguous Genitalia Panel

Our Abnormal/Ambiguous Genitalia Panel includes mutation analysis of 72 genes associated with both syndromic and non-syndromic DSDs. This comprehensive panel evaluates a broad range of genetic causes of ambiguous or abnormal genitalia, including conditions in which abnormal genitalia are the primary physical finding as well as syndromic conditions that involve abnormal genitalia in addition to other congenital anomalies.

Our Abnormal/Ambiguous Genitalia Panel includes the genes listed below.

Abnormal/Ambiguous Genitalia Panel							
AKR1C2	CREBBP	DYNC2H1	HCCS	LMNA	PTPN11	SRD5A2	WT1
AR	CYB5A	ESCO2	HOXA13	MAP3K1	RIPK4	SRY	ZFPM2
ARX	CYP11A1	FAM58A	HSD17B3	MKKS	ROR2	STAR	
ATRX	CYP11B1	FAT4	HSD3B2	MKS1	RSPO1	TBX15	
B3GALTL	CYP17A1	FEZF1	ICK	NEK1	SALL1	TCTN3	
BCOR	CYP19A1	FIG4	IL17RD	NR0B1	SCARF2	TSPYL1	
BMP4	DHCR24	FRAS1	IRF6	NR5A1	SEMA3A	UBR1	
CDKN1C	DHCR7	FREM2	KAL1	NSMF	SETBP1	WDR60	
CEP41	DHH	GATA4	KISS1R	OPHN1	SOX9	WNT4	
CHD7	DNMT3B	GRIP1	LHCGR	POR	SPECC1L	WNT7A	

46,XY Disorders of Sex Development/Complete Gonadal Dysgenesis Panel

The 46,XY Disorders of Sex Development/Complete Gonadal Dysgenesis (46,XY DSD/CGD) Sequencing Panel includes sequence analysis of 26 genes associated with disorders of sex development (DSD) or complete gonadal dysgenesis (CGD) in patients with a 46,XY karyotype. Individuals with 46,XY CGD (also known as 46,XY sex reversal) have a 46,XY karyotype in conjunction with normal female external genitalia, "streak" gonads, absent sperm production, and presence of a uterus and fallopian tubes. 46,XY CGD has been associated with mutations or copy number variations in several genes, including *SRY, DHH*, *NR5A1,* and *SOX9* (with campomelic dysplasia) (2).

46,XY DSDs are characterized by one or more of the following in an individual with a 46,XY karyotype: ambiguous genitalia with mild to severe penoscrotal hypospadias, dysgenetic gonads, reduced/absent sperm production, and Müllerian structures that range from absent to presence of a uterus and fallopian tubes (4). Example of genes associated with 46,XY DSDs include *AKR1C2, CYB5A, GATA4*, and *SRD5A2*. In addition, a 46,XY DSD phenotype may be syndromic, as in Mowatt-Wilson syndrome (5), X-linked lissencephaly-2 (6), ATR-X syndrome (7), and Smith-Lemli-Opitz syndrome (8).

Our 46,XY DSD/CGD Panel includes the genes listed below.

46,XY DSD/CGD Panel			
AKR1C2	CYB5A	HCCS	SOX9
AMH	CYP11A1	HSD17B3	SRD5A2
AMHR2	CYP17A1	LHCGR	SRY
AR	DHCR7	MAMLD1	WT1
ARX	DHH	MAP3K1	ZFPM2
ATRX	DYNC2H1	NR5A1	
B3GALTL	GATA4	OPHN1	

46,XX Disorders of Sex Development/Complete Gonadal Dysgenesis Panel
The 46,XX Disorders of Sex Development/Complete Gonadal Dysgenesis (46,XX DSD/CGD) Panel includes 9 genes associated with disorders of sex development (DSD) or complete gonadal dysgenesis (CGD) in patients with a 46,XX karyotype. A range of phenotypes may be observed in patients with 46,XX DSD/CGD, from mullerian aplasia and hyperandrogenism (9) or ovarian dysgenesis (10), to adrenal hyperplasia with overvirilization. There are syndromic forms of 46,XX DSDs, including Peters-Plus syndrome (11) and WAGR syndrome (12). 46,XX complete gonadal dysgenesis (also referred to as 46,XX sex reversal, 46,XX true hermaphroditism, or ovotesticular DSD) may be observed in patients with presence of the *SRY* gene (13), in patients with copy number variations in *SOX3 (14),* or due to mutations in other genes, such as *RSPO1* (15). Please note that due to the presence of a pseudogene, the *CYP21A2* gene is not included on this panel.

Our 46,XX DSD/CGD Panel includes the genes listed below.

46,XX DSD/CGD Panel		
B3GALTL	HCCS	RSPO1
CYP11B1	NR5A1	WNT4
CYP19A1	PSMC3IP	WT1

Test methods:
Comprehensive sequence coverage of the coding regions and splice junctions of all genes in the 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.

Abnormal or Ambiguous Genitalia Panel

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$4000
CPT codes:	See test page
Turn-around time:	8 weeks

Note: We cannot bill insurance for the above test

46,XY DSD/CGD Panel

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$3000
CPT codes:	See test page
Turn-around time:	8 weeks

Note: We cannot bill insurance for the above test.

46,XX DSD Panel

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2000
CPT codes:	See test page
Turn-around time:	8 weeks

Note: We cannot bill insurance 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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