

## Prenatal and Neonatal 46,XY Disorders of Sex Development (DSD) Panel: Sequence Analysis and Exon-level Deletion/Duplication Testing of 19 genes.

Test Code	Test Description
J719	Prenatal 46, XY DSD Panel
T991	Neonatal 46, XY DSD Panel

This panel includes 19 genes; some variants in these genes may manifest with genital ambiguity or external genitalia that are discordant with gender based on genetic testing findings. Pathogenic variants in these genes may be suspected when the fetal karyotype is 46,XY or non-invasive prenatal screening is consistent with the presence of a Y chromosome but ultrasound reveals apparently female or ambiguous external genitalia. Ultrasound detection of abnormalities of the genitalia can be detected as early as the 2nd trimester of pregnancy. Depending on the underlying disorder, renal malformations, congenital heart defects, limb/skeletal malformations, intrauterine growth restriction, cleft lip/cleft palate, and congenital brain defects may also be observed by ultrasound. Note that some ultrasound findings may not be detectable until the 3rd trimester of pregnancy. In addition, some disorders may also present with abnormal findings on second trimester maternal serum screening, such as abnormal maternal serum estriol (MS-uE3) levels.

In the neonatal period, a disorder of sex development may be suspected when prenatal or neonatal karyotyping is male and the neonate has apparently female or ambiguous external genitalia.

As disorders of sex development (DSD) may also be caused by genomic copy number variations, it is recommended that this panel be performed following or concurrent with whole genome chromosomal microarray analysis.

**Note that this panel is not appropriate for children or adults with a suspected DSD as many conditions on this panel may be eliminated from the diagnostic differential in children and adults.**

### ***Genes, Disorders, Inheritance and Reported Ultrasound & Maternal Serum Findings:***

<b>Gene</b>	<b>OMIM References</b>	<b>Inheritance</b>	<b>Prenatal ultrasound/maternal serum findings</b>
AR	300068 (Androgen Insensitivity Syndrome, AIS) 300633 (Hypospadias 1, X-Linked)	X-linked recessive	Complete (CAIS): Male karyotype and female genitalia Partial (PAIS): male karyotype and female or ambiguous genitalia [1]
ARX	300215 (Lissencephaly, X-Linked, 2) 300004 (Agenesis of Corpus Callosum with Abnormal Genitalia)	X - linked	Structural brain anomalies, agenesis of the corpus callosum, ambiguous genitalia, hypospadias [2]

<i>ATRX</i>	301040 (Alpha-Thalassemia/ Mental Retardation Syndrome, X- linked) 309580 (Mental Retardation- Hypotonic Facies Syndrome 1)	X-linked	Microcephaly, genital anomalies [3]
<i>CHD7</i>	214800 (Charge Syndrome) 612370 (Hypogonadotropic Hypogonadism 5 with or without Anosmia)	Autosomal dominant	Heart defects, cleft lip/palate, CNS malformations, renal, gastrointestinal anomalies, and hypogonadism (micropenis) [4]
<i>CYP11A1</i>	613743 (Congenital Adrenal Insufficiency with 46,XY Sex Reversal, Partial or Complete)	Autosomal recessive	Male karyotype and hypospadias to ambiguous genitalia [5,6]
<i>CYP17A1</i>	202110 (Congenital Adrenal Insufficiency due to 17-Alpha- Hydroxylase Deficiency/ Isolated 17,20-Lyase Deficiency)	Autosomal recessive	Male karyotype and female genitalia [7,8]
<i>DHCR7</i>	270400 (Smith-Lemli-Opitz Syndrome)	Autosomal recessive	Male karyotype and female or ambiguous genitalia and IUGR, brain, cardiac, renal, or limb malformation and/or low MS-uE3 levels on maternal serum screening [9]
<i>DHH</i>	233420 (46,XY Sex Reversal 7) 607080 (46,XY Partial Gonadal Dysgenesis with Minifascicular Neuropathy)	Autosomal recessive	Male karyotype and female genitalia [10,11]
<i>DYNC2H1</i>	613091 (Short-Rib Thoracic Dysplasia 3 with or without Polydactyly)	Autosomal recessive / digenic recessive ( <i>NEK1</i> )	Narrow thorax, bilateral short limbs, polydactyly, bilateral enlarged kidneys, and male karyotype and female or ambiguous genitalia [12]
<i>HSD17B3</i>	264300 (17-Beta Hydroxysteroid Dehydrogenase III Deficiency)	Autosomal recessive	Male karyotype and female or ambiguous genitalia [13, 14]
<i>HSD3B2</i>	201810 (Congenital Adrenal Hyperplasia due to 3-Beta Hydroxysteroid Dehydrogenase 2 Deficiency)	Autosomal recessive	Male karyotype and female or ambiguous genitalia [15,16]
<i>NEK1</i>	263520 (Short-Rib Thoracic Dysplasia 6 with or without Polydactyly)	Autosomal recessive/ digenic recessive ( <i>DYNC2H1</i> )	Polydactyly, choroid plexus cysts, short ribs and narrow chest, short fibula, tibial aplasia, and genital abnormalities [17]
<i>NR5A1</i>	612965 (46,XY Sex Reversal 3)	Autosomal dominant/ Autosomal recessive	Male karyotype and female or ambiguous genitalia [18]

<i>POR</i>	613571 (Disordered Steroidogenesis due to Cytochrome P450 Oxidoreductase Deficiency) 201750 (Antley-Bixler Syndrome with Genital Anomalies and Disordered Steroidogenesis)	Autosomal recessive	Ambiguous genitalia, craniosynostosis, brachycephaly, severe midface hypoplasia, multiple joint contractures [19]
<i>SOX9</i>	114290 (Campomelic Dysplasia)	Autosomal dominant	Male karyotype and female or ambiguous genitalia and limb shortening and/or bowing [20]
<i>SRD5A2</i>	264600 (5- $\alpha$ Reductase Deficiency/Pseudovaginal Perineoscrotal Hypospadias)	Autosomal recessive	Male karyotype and female or ambiguous genitalia [21]
<i>SRY</i>	400044 (46, XY Sex Reversal 1/46,XY Complete or Partial Gonadal Dysgenesis)	Y-linked	Male karyotype and female or ambiguous genitalia [18]
<i>STAR</i>	201710 (Lipoid Congenital Adrenal Hyperplasia)	Autosomal recessive	Male karyotype and female genitalia [22,23]
<i>WT1</i>	194080 (Denys-Drash Syndrome) 136680 (Frasier Syndrome) 608978 (Meacham Syndrome) 256370 (Nephrotic Syndrome, Type 4) 194070 (Wilms Tumor, Type 1)	Autosomal dominant	Male karyotype and ambiguous genitalia, Wilms tumor/kidney tumor [24]

### Clinical Features in Newborns and Children:

The 46,XY DSDs are a highly variable group of disorders, which arise from abnormalities in the complex process of sex determination and differentiation. Approximately 1 in 20,000 live male births are affected with a 46,XY DSD, with the severity ranging from mild hypogonadism (such as micropenis) to complete gonadal dysgenesis [18, 25]. The genes included in the Prenatal and Neonatal 46,XY DSD panel include disorders associated with non-syndromic DSD, steroid abnormalities, skeletal dysplasia syndromes, and multiple malformation syndromes where the presenting finding is discrepant/ambiguous gender.

A brief overview of the more common conditions associated with the genes included in this panel is given below:

#### **Gene variants associated with non-syndromic DSD / sex determination abnormalities**

**(DHH, NR5A1, and SRY):** Pathogenic variants in *DHH* result in a 46,XY disorder of sex development (DSD) with or without polyneuropathy. Several individuals with *DHH* variants have presented with isolated 46,XY complete gonadal dysgenesis characterized by female external genitalia, bilateral streak gonads, and the presence of Mullerian structures, including bilateral Fallopian tubes and an immature uterus [10,11]. Variants in *DHH* have also been reported in an individual with 46,XY partial gonadal dysgenesis, resulting in external female genitalia with a blind-ending vagina, one testis and one streak gonad, and an immature uterus. In addition, this individual also exhibited polyneuropathy with extensive minifascicle formation on sural nerve biopsy [26].

Pathogenic variants in *NR5A1* result in a 46,XY disorder of sex development (DSD) with or without adrenal insufficiency. At the severe end of the spectrum, individuals with *NR5A1* mutations have presented with primary adrenal failure and 46,XY complete gonadal dysgenesis characterized by female external genitalia, severe testicular dysgenesis, and the presence of Mullerian structures or in patients presenting at puberty with 46,XY primary amenorrhea. At the milder end of the spectrum, *NR5A1* mutations have been reported in individuals with normal adrenal function and 46,XY partial gonadal dysgenesis resulting in ambiguous genitalia, bilateral testes, and no evidence of Mullerian structures. Mutations in the *NR5A1* gene have also been identified in several patients with severe (penoscrotal) hypospadias and undescended testes, and in males with idiopathic infertility [18].

Pathogenic variants in *SRY* are associated with 46, XY Complete or Partial Gonadal Dysgenesis. 46,XY complete gonadal dysgenesis (CGD) is marked by a lack of testicular development, streak gonads, the presence of well-developed Mullerian structures (a uterus and fallopian tubes), underdeveloped breasts, and female external genitalia. Individuals often are not diagnosed until puberty when they present with amenorrhea and the absence of secondary sexual characteristics. In rare cases, *SRY* mutations have been associated with 46,XY partial gonadal dysgenesis (also called *SRY*-related 46,XY disorder of sex development or *SRY*-related 46,XY DSD). 46,XY DSD is characterized by the presence of ambiguous genitalia, dysgenetic testes, and absent to fully developed Mullerian structures. Both 46,XY CGD and 46,XY DSD are associated with an increased incidence of gonadoblastoma and germinoma [18].

**Gene variants associated with abnormalities of androgen synthesis or action / sex differentiation abnormalities (*AR*, *CYP11A1*, *CYP17A1*, *HSD17B3*, *HSD3B2*, *SRD5A2*, and *STAR*):** These disorders are associated with abnormalities in the steroid pathway and can lead to abnormal levels of glucocorticoids and mineralcorticoids, which can potentially lead to salt-wasting, hypertension, and/or hypokalemia. The steroid abnormalities also affect the production of enzymes need to make hormones involved in sex development. 46,XY individuals can present with a variable phenotype ranging from female external genitalia, blind vaginal pouch, absence of Mullerian structures, to ambiguous genitalia, hypospadias, and cryptorchidism.

Androgen Insensitivity Syndrome (AIS) is caused by pathogenic variants in the *AR* gene and may be complete or partial. Patients with AIS may come to attention in utero or at birth because of inconsistency between prenatal karyotype (male) and ultrasound findings of a female fetus, or at birth because of ambiguous genitalia. Alternatively, patients may present during the pubertal years with a presumed inguinal hernia (abdominal or inguinal testes), absence of pubic/auxiliary hair, or lack of onset of menses. The mature phenotype is often distinctly feminine with very well-developed breasts and abundant scalp hair. In the partial form, patients may exhibit hypospadias, micropenis, or fusion of the labial folds, associated with the occurrence of virilization at puberty [1].

Pathogenic variants in *CYP11A1*, *CYP17A1*, *HSD3B2*, and *STAR* are associated with rare forms of congenital adrenal hyperplasia which impairs steroidogenesis in both the adrenals and gonads which cause varying degrees of salt-loss in both sexes and incomplete

masculinization of the external genitalia in genetic males [5,6,7,8,15,16,22,23].

46,XY individuals with *HSD17B3* pathogenic variants are born with ambiguous or female external genitalia and the absence of a prostate with hypoplastic to normal internal genitalia (epididymis, vas deferens, seminal vesicles, and ejaculatory ducts); however, at the time of puberty, virilization occurs due to an increase in serum testosterone [13,14]. Phenotypic variation can occur within families with the same homozygous pathogenic variants [27].

Individuals with pathogenic variants in *SRD5A2* are affected with 5- $\alpha$  reductase deficiency. Most patients have ambiguous genitalia noted in infancy, individuals with female external genitalia may not present until puberty with primary amenorrhea, a lack of breast development, and virilization of the external genitalia. If the diagnosis of 5- $\alpha$  reductase deficiency is not made, the majority of infants are assigned a female gender based on the appearance of the external genitalia; however, significant virilization of the external genitalia occurs at puberty unless a gonadectomy is performed [21,28].

**Gene variants associated with a skeletal dysplasia (*DYNC2H1*, *NEK1*, *POR*, and *SOX9*):** These disorders may present with additional ultrasound anomalies, although the additional skeletal anomalies may not be detectable until the third trimester of pregnancy, and can be associated with lethality in the neonatal period.

Short-rib thoracic dysplasia (SRTD) is a group of autosomal recessive ciliopathies; some forms are lethal in the neonatal period. SRTD3 and SRTD6 are caused by homozygous, compound heterozygous, or digenic biallelic pathogenic variants in *DYNC2H1* and *NEK1*, respectively, and are characterized by a constricted thoracic cage, short ribs, shortened tubular bones, and a 'trident' appearance of the acetabular roof. Polydactyly may or may not be present. The severity of these disorders varies, even within families. The thoracic abnormalities in SRTD3 tend to improve with age. SRTD6 is characterized by short ribs and limbs, medial cleft lip, pre- and postaxial polysyndactyly, genital abnormalities, polycystic kidneys, and anomalies of the epiglottis and viscera [17,29].

Pathogenic variants in the *POR* gene are associated with autosomal recessive cytochrome P450 oxidoreductase deficiency, a disorder of steroidogenesis associated with a broad range of clinical presentations. Steroid abnormalities can be detected in all affected patients, consistent with a form of congenital adrenal hyperplasia (CAH) causing deficiencies of both 21-hydroxylase and 17-hydroxylase/17,20-lyase. Like classical CAH, the steroid abnormalities may lead to cortisol deficiency, which in some cases can be life-threatening without treatment [30]. Disordered sex development can be observed in both males and females, and ambiguous genitalia is a common finding. At the severe end of the spectrum, patients may also have skeletal and craniofacial findings consistent with Antley-Bixler syndrome, including craniosynostosis, brachycephaly, severe midface hypoplasia, radiohumeral synostosis, and multiple joint contractures [19].

Aberrations involving the *SOX9* gene are associated with campomelic dysplasia (CD), a rare, often lethal skeletal dysplasia characterized by angular bowing and shortening of the long bones, severe respiratory distress, and XY sex reversal. Approximately 75% of patients with CD that have a 46,XY karyotype exhibit partial or complete sex reversal, ranging from

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ambiguous genitalia to normal female external genitalia [20]. In addition to bowing of the long bones, skeletal features of CD include club feet, a bell-shaped and underdeveloped thorax, eleven pairs of ribs, and hypoplastic scapulae. CD is also associated with micrognathia and Pierre-Robin malformation. Many infants die shortly after birth from respiratory compromise. Children who survive the neonatal period often develop hearing loss, developmental delay, short stature and progressive kyphoscoliosis [31].

**Gene variants associated with a multiple malformation syndrome (*ARX*, *ATRX*, *CHD7*, *DHCR7*, and *WT1*):** These disorders may present with additional ultrasound anomalies and/or abnormal maternal serum findings.

Variants in *ARX* are associated with various clinical phenotypes causing intellectual disability, seizures, movement disorders, brain malformations, and/or abnormal genitalia [2].

Pathogenic variants in the *ATRX* gene cause alpha-thalassemia X-linked intellectual disability (*ATRX*) syndrome as well as many other allelic disorders, including syndromic and nonsyndromic intellectual disability, X-linked intellectual disability with epilepsy, and X-linked intellectual disability with spastic paraplegia. The phenotypes of each of these allelic disorders have overlapping clinical features with *ATRX* syndrome and likely should be included as a spectrum of related disorders. *ATRX* syndrome presents in males with intellectual disability, developmental delay, microcephaly, craniofacial abnormalities, genital anomalies, hypotonia, and anemia due to alpha-thalassemia. In addition, brain abnormalities, including brain atrophy and abnormal white matter signals, have also been reported [3].

Individuals with pathogenic variants in *CHD7* present with CHARGE syndrome. CHARGE syndrome is characterized by coloboma of the eye, heart defects, choanal atresia, intellectual disability, growth retardation and ear anomalies or hearing loss. Affected patients may also have genital abnormalities (hypogonadotropic hypogonadism), pre- and post-natal growth deficiency, hypotonia, and characteristic hands (broad palms with “hockey-stick” palmar crease, short fingers and small/unusual thumbs). The characteristic facial appearance includes square face with broad prominent forehead, arched eyebrows, large eyes with or without ptosis, prominent nasal bridge and columella, flat midface, small mouth and facial asymmetry. CHARGE syndrome encompasses additional nonspecific features such as intellectual disability, skeletal abnormalities, hypodontia, orofacial clefting, tracheoesophageal fistula, and urinary tract and renal anomalies [32].

*DHCR7* is associated with Smith-Lemli-Opitz Syndrome (SLOS), a severe developmental disorder. The clinical spectrum is wide and includes both pre- and post-natal growth retardation, mild to severe mental retardation, multiple congenital malformations (both major and minor), and characteristic facies. Frequent additionally observed findings include: microcephaly, micrognathia, cleft palate, cardiac defects, abnormal external genitalia, post-axial polydactyly, and 2-3 toe syndactyly. Infants are often hypotonic with poor suck, and fail to thrive. Older children commonly have behavioral concerns including autism, hyperactivity, aggression, and self-injurious behavior [9].

Pathogenic variants in *WT1* are associated with both isolated Wilms tumor as well as syndromes that include other renal and genitourinary abnormalities such as Denys-Drash  
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(DDS), Frasier syndromes, and isolated nephrotic syndrome [24,33]. Denys-Drash Syndrome (DDS) is characterized by the triad of Wilms tumor, ambiguous genitalia in 46,XY individuals, and early onset nephropathy [24,34,35,36]. Frasier syndrome (FS), involves ambiguous genitalia in 46,XY individuals, nephropathy, occasionally Wilms tumor, and a risk for gonadoblastoma of up to 67% [37,38].

### Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel 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. For the *ARX*, *HSD3B2*, and *NR5A1* genes, only whole gene deletions/duplications can be detected. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. 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 on prenatal samples. ***Therefore, in all prenatal cases a maternal sample should accompany the fetal sample.***

### Test Sensitivity:

The 46,XY DSDs are a genetically heterogeneous group of conditions with a wide variant spectrum. The clinical sensitivity of sequence analysis of the 19 genes included in this panel in prenatal cases ascertained based on fetal ultrasound gender discrepancy/ambiguity is currently unknown, as is the clinical sensitivity of testing on neonates. The clinical sensitivity of analysis of the genes included in the Prenatal and Neonatal 46,XY Disorders of Sex Development depends on the specific gene and the clinical phenotype of the patient.

The technical sensitivity of gene sequencing in prenatal and neonatal cases ascertained based on fetal ultrasound abnormalities/neonatal abnormalities is estimated to be greater than 99%. It will not detect deletions, insertions, or rearrangements greater than or equal to ten base pairs.

Most pathogenic variants identified in these genes include frameshift, nonsense, missense, and splice site variants resulting in protein truncation or loss of expression of the allele with the variation. Pathogenic deletions and/or duplications have also been observed in majority of analyzed genes [39].

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