Whole Exome Sequencing
Gene package Disorders of Sex Development (DSD), version 8.1, 31-1-2020

Technical information
DNA was enriched using Agilent SureSelect DNA + SureSelect OneSeq 300kb CNV Backbone + Human All Exon V7 capture and paired-end sequenced on the Illumina platform (outsourced). The aim is to obtain 10 Giga base pairs per exome with a mapped fraction of 0.99. The average coverage of the exome is ~50x. Duplicate and non-unique reads are excluded. Data are demultiplexed with bcl2fastq Conversion Software from Illumina. Reads are mapped to the genome using the BWA-MEM algorithm (reference: http://bio-bwa.sourceforge.net/). Variant detection is performed by the Genome Analysis Toolkit HaplotypeCaller (reference: http://www.broadinstitute.org/gatk/). The detected variants are filtered and annotated with Cartagenia software and classified with Alamut Visual. It is not excluded that pathogenic mutations are being missed using this technology. At this moment, there is not enough information about the sensitivity of this technique with respect to the detection of deletions and duplications of more than 5 nucleotides and of somatic mosaic mutations (all types of sequence changes).

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HGNC approved gene symbol	Phenotype description including OMIM phenotype ID(s)	OMIM gene ID	median depth	% covered >10x	% covered >20x	% covered >30x
AKR1C1	No OMIM phenotype	600449	88	91	91	85
AKR1C4	{46XY sex reversal 8, modifier of}, 614279	600451	67	100	100	94
AMH	Persistent Mullerian duct syndrome, type I, 261550	600957	104	100	100	100
AMHR2	Persistent Mullerian duct syndrome, type II, 261550	600956	123	100	100	99
ANOS1	Hypogonadotropic hypogonadism 1 with or without anosmia (Kallmann syndrome 1), 308700	300836	57	100	95	84
AR	Androgen insensitivity, 300068 Androgen insensitivity, partial, with or without breast cancer, 312300 Hypospadias 1, 300633 {Prostate cancer, susceptibility to}, 176807 Spinal and bulbar muscular atrophy of Kennedy, 313200	313700	81	100	98	94
ARX	Epileptic encephalopathy, early infantile, 1, 308350 Hydranencephaly with abnormal genitalia, 300215 Lissencephaly 2, 300215 Mental retardation 29 and others, 300419 Partington syndrome, 309510 Proud syndrome, 300004	300382	46	89	79	68

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ATRX	Alpha-thalassemia myelodysplasia syndrome, somatic, 300448 Alpha-thalassemia/mental retardation syndrome, 301040 Mental retardation-hypotonic facies syndrome, 309580	300032	40	100	94	78
BMP15	Ovarian dysgenesis 2, 300510 Premature ovarian failure 4, 300510	300247	56	100	100	96
CBX2	?46XY sex reversal 5, 613080	602770	176	100	100	100
CCNQ	STAR syndrome, 300708	300708	62	81	81	81
CDKN1C	Beckwith-Wiedemann syndrome, 130650 IMAGE syndrome, 614732	600856	74	90	83	76
CHD7	CHARGE syndrome, 214800 Hypogonadotropic hypogonadism 5 with or without anosmia, 612370	608892	87	100	100	97
CREBBP	Menke-Hennekam syndrome 1, 618332 Rubinstein-Taybi syndrome 1, 180849	600140	85	100	99	94
CYB5A	Methemoglobinemia and ambiguous genitalia, 250790	613218	77	100	100	100
CYP11A1	Adrenal insufficiency, congenital, with 46XY sex reversal, partial or complete, 613743	118485	108	100	100	100
CYP11B1	Adrenal hyperplasia, congenital, due to 11-beta-hydroxylase deficiency, 202010 Aldosteronism, glucocorticoid-remediable, 103900	610613	209	100	100	100
CYP17A1	17-alpha-hydroxylase/17,20-lyase deficiency, 202110 17,20-lyase deficiency, isolated, 202110	609300	113	100	100	100
CYP19A1	Aromatase deficiency, 613546 Aromatase excess syndrome, 139300	107910	66	100	99	93
CYP21A2	Adrenal hyperplasia, congenital, due to 21-hydroxylase deficiency, 201910 Hyperandrogenism, nonclassic type, due to 21-hydroxylase deficiency, 201910	613815	201	100	100	100
DHCR7	Smith-Lemli-Opitz syndrome, 270400	602858	112	100	100	100
DHH	46XY partial gonadal dysgenesis, with minifascicular neuropathy, 607080 46XY sex reversal 7, 233420	605423	138	100	100	100
DHX37	No OMIM phenotype	617362	103	100	100	96
DMRT1	No OMIM phenotype	602424	106	100	100	100
DMRT2	No OMIM phenotype	604935	92	100	100	96
DUSP6	Hypogonadotropic hypogonadism 19 with or without anosmia, 615269	602748	144	100	100	100
ESR1	{Atherosclerosis, susceptibility to} Breast cancer, somatic, 114480 Estrogen resistance, 615363 {HDL response to hormone replacement, augmented} {Migraine, susceptibility to}, 157300 {Myocardial infarction, susceptibility to}, 608446	133430	115	100	100	99

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FEZF1	Hypogonadotropic hypogonadism 22, with or without anosmia, 616030	613301	116	100	100	100
FGF17	Hypogonadotropic hypogonadism 20 with or without anosmia, 615270	603725	142	100	100	100
FGF8	Hypogonadotropic hypogonadism 6 with or without anosmia, 612702	600483	134	100	94	94
FGFR1	Encephalocraniocutaneous lipomatosis, somatic mosaic, 613001 Hartsfield syndrome, 615465 Hypogonadotropic hypogonadism 2 with or without anosmia, 147950 Jackson-Weiss syndrome, 123150 Osteoglophonic dysplasia, 166250 Pfeiffer syndrome, 101600 Trigonocephaly 1, 190440	136350	102	100	100	98
FGFR2	Antley-Bixler syndrome without genital anomalies or disordered steroidogenesis, 207410 Apert syndrome, 101200 Beare-Stevenson cutis gyrata syndrome, 123790 Bent bone dysplasia syndrome, 614592 Craniofacial-skeletal-dermatologic dysplasia, 101600 Craniosynostosis, nonspecific Crouzon syndrome, 123500 Gastric cancer, somatic, 613659 Jackson-Weiss syndrome, 123150 LADD syndrome, 149730 Pfeiffer syndrome, 101600 Saethre-Chotzen syndrome, 101400 Scaphocephaly and Axenfeld-Rieger anomaly Scaphocephaly, maxillary retrusion, and mental retardation, 609579	176943	74	100	100	95
FOXL2	Blepharophimosis, epicanthus inversus, and ptosis, type 1, 110100 Blepharophimosis, epicanthus inversus, and ptosis, type 2, 110100 Premature ovarian failure 3, 608996	605597	114	100	94	88
FSHB	Hypogonadotropic hypogonadism 24 without anosmia, 229070	136530	81	100	100	100
FSHR	Ovarian dysgenesis 1, 233300 Ovarian hyperstimulation syndrome, 608115 Ovarian response to FSH stimulation, 276400	136435	71	100	100	98
GATA4	Atrial septal defect 2, 607941 Atrioventricular septal defect 4, 614430 ?Testicular anomalies with or without congenital heart disease, 615542 Tetralogy of Fallot, 187500 Ventricular septal defect 1, 614429	600576	81	100	87	80

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GNRH1	?Hypogonadotropic hypogonadism 12 with or without anosmia, 614841	152760	55	100	100	100
GNRHR	Hypogonadotropic hypogonadism 7 without anosmia, 146110	138850	98	100	100	99
HDAC8	Cornelia de Lange syndrome 5, 300882	300269	47	100	100	91
HFM1	Premature ovarian failure 9, 615724	615684	63	100	97	81
HOXA13	?Guttmacher syndrome, 176305 Hand-foot-uterus syndrome, 140000	142959	80	86	78	74
HS6ST1	{Hypogonadotropic hypogonadism 15 with or without anosmia}, 614880	604846	119	100	100	97
HSD17B3	Pseudohermaphroditism, male, with gynecomastia, 264300	605573	67	100	99	94
HSD3B2	Adrenal hyperplasia, congenital, due to 3-beta-hydroxysteroid dehydrogenase 2 deficiency, 201810	613890	143	100	100	100
IL17RD	Hypogonadotropic hypogonadism 18 with or without anosmia, 615267	606807	102	100	100	99
INSL3	Cryptorchidism, 219050	146738	69	93	78	78
KISS1	?Hypogonadotropic hypogonadism 13 with or without anosmia, 614842	603286	127	100	100	100
LHB	Hypogonadotropic hypogonadism 23 with or without anosmia, 228300	152780	99	100	100	100
LHCGR	Leydig cell adenoma, somatic, with precocious puberty, 176410 Leydig cell hypoplasia with hypergonadotropic hypogonadism, 238320 Leydig cell hypoplasia with pseudohermaphroditism, 238320 Luteinizing hormone resistance, female, 238320 Precocious puberty, male, 176410	152790	71	100	100	94
MAMLD1	Hypospadias 2, 300758	300120	96	100	99	95
MAP3K1	46XY sex reversal 6, 613762	600982	69	100	98	94
MCM8	?Premature ovarian failure 10, 612885	608187	52	100	96	87
MCM9	Ovarian dysgenesis 4, 616185	610098	78	100	100	96
MID1	Opitz GBBB syndrome, type I, 300000	300552	89	100	100	93
NR0B1	Adrenal hypoplasia, congenital, 300200 46XY sex reversal 2, dosage-sensitive, 300018	300473	120	100	100	99
NR2F2	Congenital heart defects, multiple types, 4, 615779	107773	232	100	100	100
NR5A1	Adrenocortical insufficiency, 612964 Premature ovarian failure 7, 612964 Spermatogenic failure 8, 613957 46, XX sex reversal 4, 617480 46XY sex reversal 3, 612965	184757	107	100	100	100
NSMF	Hypogonadotropic hypogonadism 9 with or without anosmia, 614838	608137	96	100	95	95
NUP107	Galloway-Mowat syndrome 7, 618348 Nephrotic syndrome, type 11, 616730 ?Ovarian dysgenesis 6, 618078	607617	50	100	99	91

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POLR3A	Leukodystrophy, hypomyelinating, 7, with or without oligodontia and/or hypogonadotropic hypogonadism, 607694 Wiedemann-Rautenstrauch syndrome, 264090	614258	84	100	100	98
POR	Antley-Bixler syndrome with genital anomalies and disordered steroidogenesis, 201750 Disordered steroidogenesis due to cytochrome P450 oxidoreductase, 613571	124015	170	100	100	100
PROK2	Hypogonadotropic hypogonadism 4 with or without anosmia, 610628	607002	61	100	100	99
PROKR2	Hypogonadotropic hypogonadism 3 with or without anosmia, 244200	607123	210	100	100	100
PSMC3IP	Ovarian dysgenesis 3, 614324	608665	108	100	100	100
RNF216	Cerebellar ataxia and hypogonadotropic hypogonadism, 212840	609948	66	100	97	86
RSPO1	Palmoplantar hyperkeratosis and true hermaphroditism, 610644 Palmoplantar hyperkeratosis with squamous cell carcinoma of skin and sex reversal, 610644	609595	93	100	100	100
SEMA3A	{Hypogonadotropic hypogonadism 16 with or without anosmia}, 614897	603961	75	100	100	96
SOX3	Mental retardation, with isolated growth hormone deficiency, 300123 Panhypopituitarism, 312000	313430	64	100	95	89
SOX8	No OMIM phenotype	605923	108	100	100	95
SOX9	Acampomelic campomelic dysplasia, 114290 Campomelic dysplasia, 114290 Campomelic dysplasia with autosomal sex reversal, 114290	608160	157	100	100	100
SPRY4	Hypogonadotropic hypogonadism 17 with or without anosmia, 615266	607984	104	100	100	96
SRD5A2	Pseudovaginal perineoscrotal hypospadias, 264600	607306	56	100	99	86
SRY	46XX sex reversal 1, 400045 dominant 46XY sex reversal 1, 400044	480000	159	100	100	100
STAG3	Premature ovarian failure 8, 615723	608489	89	100	99	96
STAR	Lipoid adrenal hyperplasia, 201710	600617	118	100	100	100
SYCE1	?Premature ovarian failure 12, 616947 ?Spermatogenic failure 15, 616950	611486	86	100	100	100
TAC3	Hypogonadotropic hypogonadism 10 with or without anosmia, 614839	162330	93	100	100	95
TSPYL1	Sudden infant death with dysgenesis of the testes syndrome, 608800	604714	133	100	100	100
WDR11	Hypogonadotropic hypogonadism 14 with or without anosmia, 614858	606417	83	100	100	96
WNT4	Mullerian aplasia and hyperandrogenism, 158330 ?SERKAL syndrome, 611812	603490	231	100	92	92
WT1	Denys-Drash syndrome, 194080 Frasier syndrome, 136680 Meacham syndrome, 608978 Mesothelioma, somatic, 156240 Nephrotic syndrome, type 4, 256370 Wilms tumor, type 1, 194070	607102	117	100	100	98

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ZFPM2	Diaphragmatic hernia 3, 610187 Tetralogy of Fallot, 187500 46XY sex reversal 9, 616067	603693	82	100	100	100
ZNRF3	No OMIM phenotype	612062	155	97	96	95

- Gene symbols according HGCN
- OMIM release used: 8-9-2019
- "No OMIM phenotypes" indicates a gene without a current OMIM association
- OMIM phenotypes between "[ ]", indicate "nondiseases," mainly genetic variations that lead to apparently abnormal laboratory test values
- OMIM phenotypes between "{}", indicate risk factors
- OMIM phenotypes with a question mark, "?", before the disease name indicates an unconfirmed or possibly spurious mapping
- The statistics above are based on a set of 100 samples
- Median depth is the median of the mean sequence depth over the protein coding exons (±10bp flanking introns) of the longest transcript
- % Covered 10x , 20x and 30 x describes the percentage of a gene's coding sequence (±10bp flanking introns) that is covered at least 10x, 20x or 30x