Whole Exome Sequencing
Gene package Disorders of Sex Development (DSD), version 7, 18-2-2019

Technical information
DNA was enriched using Agilent SureSelect Clinical Research Exome V2 capture and paired-end sequenced on the Illumina platform (outsourced). The aim is to obtain 8.1 Giga base pairs per exome with a mapped fraction of 0.99. The average coverage of the exome is ~50x. Duplicate 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).

Erasmus MC
University Medical Center Rotterdam

Dept. Clinical Genetics

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	90	100	100	96
AKR1C4	{46XY sex reversal 8, modifier of}, 614279	600451	59	100	98	91
AMH	Persistent Mullerian duct syndrome, type I, 261550	600957	97	100	100	100
AMHR2	Persistent Mullerian duct syndrome, type II, 261550	600956	105	100	100	98
ANOS1	Hypogonadotropic hypogonadism 1 with or without anosmia (Kallmann syndrome 1), 308700	300836	48	100	92	72
AR	Androgen insensitivity, 300068 Androgen insensitivity, partial, with or without breast cancer, 312300 Hypospadias 1, X-linked, 300633 {Prostate cancer, susceptibility to}, 176807 Spinal and bulbar muscular atrophy of Kennedy, 313200	313700	73	100	98	88
ARX	Epileptic encephalopathy, early infantile, 1, 308350 Hydranencephaly with abnormal genitalia, 300215 Lissencephaly, X-linked 2, 300215 Mental retardation, X-linked 29 and others, 300419 Partington syndrome, 309510 Proud syndrome, 300004	300382	46	91	81	72
ATRX	Alpha-thalassemia myelodysplasia syndrome, somatic, 300448 Alpha-thalassemia/mental retardation syndrome, 301040 Mental retardation-hypotonic facies syndrome, X-linked, 309580	300032	33	100	90	59
BMP15	Ovarian dysgenesis 2, 300510 Premature ovarian failure 4, 300510	300247	47	100	100	94
CBX2	?46XY sex reversal 5, 613080	602770	157	100	100	100

HGNC approved gene symbol	Phenotype description including OMIM phenotype ID(s)	OMIM gene ID	median depth	% covered >10x	% covered >20x	% covered >30x
CCNQ	STAR syndrome, 300707	300708	58	81	81	80
CDKN1C	Beckwith-Wiedemann syndrome, 130650 IMAGE syndrome, 614732	600856	80	92	85	78
CHD7	CHARGE syndrome, 214800 Hypogonadotropic hypogonadism 5 with or without anosmia, 612370	608892	74	100	99	94
CREBBP	Rubinstein-Taybi syndrome 1, 180849	600140	82	100	98	93
CYB5A	Methemoglobinemia and ambiguous genitalia, 250790	613218	65	100	100	97
CYP11A1	Adrenal insufficiency, congenital, with 46XY sex reversal, partial or complete, 613743	118485	99	100	100	100
CYP11B1	Adrenal hyperplasia, congenital, due to 11-beta-hydroxylase deficiency, 202010 Aldosteronism, glucocorticoid-remediable, 103900	610613	206	100	100	100
CYP17A1	17-alpha-hydroxylase/17,20-lyase deficiency, 202110 17,20-lyase deficiency, isolated, 202110	609300	105	100	100	99
CYP19A1	Aromatase deficiency, 613546 Aromatase excess syndrome, 139300	107910	56	100	98	86
CYP21A2	Adrenal hyperplasia, congenital, due to 21-hydroxylase deficiency, 201910 Hyperandrogenism, nonclassic type, due to 21-hydroxylase deficiency, 201910	613815	219	100	100	100
DHCR7	Smith-Lemli-Opitz syndrome, 270400	602858	98	100	100	100
DHH	46XY partial gonadal dysgenesis, with minifascicular neuropathy, 607080 46XY sex reversal 7, 233420	605423	120	100	100	100
DMRT1	No OMIM phenotype	602424	104	100	100	100
DMRT2	No OMIM phenotype	604935	92	100	99	95
DUSP6	Hypogonadotropic hypogonadism 19 with or without anosmia, 615269	602748	129	100	100	100
ESR1	{Atherosclerosis, susceptibility to} {Breast cancer}, 114480 Estrogen resistance, 615363 {HDL response to hormone replacement, augmented} {Migraine, susceptibility to}, 157300 {Myocardial infarction, susceptibility to}, 608446	133430	96	100	100	97
FEZF1	Hypogonadotropic hypogonadism 22, with or without anosmia, 616030	613301	111	100	100	99
FGF17	Hypogonadotropic hypogonadism 20 with or without anosmia, 615270	603725	128	100	100	100
FGF8	Hypogonadotropic hypogonadism 6 with or without anosmia, 612702	600483	133	100	95	94
FGFR1	Encephalocraniocutaneous lipomatosis, 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	94	100	100	98

HGNC approved gene symbol	Phenotype description including OMIM phenotype ID(s)	OMIM gene ID	median depth	% covered >10x	% covered >20x	% covered >30x
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	63	100	99	90
FOXL2	Blepharophimosis, epicanthus inversus, and ptosis, type 1, 110100 Blepharophimosis, epicanthus inversus, and ptosis, type 2, 110100 Premature ovarian failure 3, 608996	605597	112	100	95	89
FSHB	Hypogonadotropic hypogonadism 24 without anosmia, 229070	136530	69	100	100	100
FSHR	Ovarian dysgenesis 1, 233300 Ovarian hyperstimulation syndrome, 608115 Ovarian response to FSH stimulation, 276400	136435	58	100	100	94
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	71	100	88	78
GNRH1	?Hypogonadotropic hypogonadism 12 with or without anosmia, 614841	152760	48	100	100	99
GNRHR	Hypogonadotropic hypogonadism 7 without anosmia, 146110	138850	85	100	100	97
HDAC8	Cornelia de Lange syndrome 5, 300882	300269	40	100	97	80
HFM1	Premature ovarian failure 9, 615724	615684	55	100	94	74
HOXA13	Guttmacher syndrome, 176305 Hand-foot-uterus syndrome, 140000	142959	79	86	79	75
HS6ST1	{Hypogonadotropic hypogonadism 15 with or without anosmia}, 614880	604846	145	100	100	99
HSD17B3	Pseudohermaphroditism, male, with gynecomastia, 264300	605573	56	100	98	88
HSD3B2	Adrenal hyperplasia, congenital, due to 3-beta-hydroxysteroid dehydrogenase 2 deficiency, 201810	613890	122	100	100	100
IL17RD	Hypogonadotropic hypogonadism 18 with or without anosmia, 615267	606807	94	100	100	96
INSL3	Cryptorchidism, 219050	146738	65	91	78	78
KISS1	?Hypogonadotropic hypogonadism 13 with or without anosmia, 614842	603286	124	100	100	99
LHB	Hypogonadotropic hypogonadism 23 with or without anosmia, 228300	152780	108	100	100	100

HGNC approved gene symbol	Phenotype description including OMIM phenotype ID(s)	OMIM gene ID	median depth	% covered >10x	% covered >20x	% covered >30x
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	59	100	99	90
MAMLD1	Hypospadias 2, X-linked, 300758	300120	80	100	98	93
MAP3K1	46XY sex reversal 6, 613762	600982	59	100	98	93
MCM8	?Premature ovarian failure 10, 612885	608187	45	100	94	80
MCM9	Ovarian dysgenesis 4, 616185	610098	69	100	99	94
MID1	Opitz GBBB syndrome, type I, 300000	300552	74	100	97	85
NR0B1	Adrenal hypoplasia, congenital, 300200 46XY sex reversal 2, dosage-sensitive, 300018	300473	110	100	100	98
NR2F2	Congenital heart defects, multiple types, 4, 615779	107773	209	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	104	100	100	100
NSMF	Hypogonadotropic hypogonadism 9 with or without anosmia, 614838	608137	98	100	95	95
NUP107	Nephrotic syndrome, type 11, 616730	607617	44	100	97	83
POLR3A	Leukodystrophy, hypomyelinating, 7, with or without oligodontia and/or hypogonadotropic hypogonadism, 607694	614258	79	100	100	94
POR	Antley-Bixler syndrome with genital anomalies and disordered steroidogenesis, 201750 Disordered steroidogenesis due to cytochrome P450 oxidoreductase, 613571	124015	152	100	100	100
PROK2	Hypogonadotropic hypogonadism 4 with or without anosmia, 610628	607002	52	100	100	96
PROKR2	Hypogonadotropic hypogonadism 3 with or without anosmia, 244200	607123	198	100	100	100
PSMC3IP	Ovarian dysgenesis 3, 614324	608665	99	100	100	100
RNF216	Cerebellar ataxia and hypogonadotropic hypogonadism, 212840	609948	59	100	95	82
RSPO1	Palmoplantar hyperkeratosis and true hermaphroditism, 610644 Palmoplantar hyperkeratosis with squamous cell carcinoma of skin and sex reversal, 610644	609595	86	100	100	100
SEMA3A	{Hypogonadotropic hypogonadism 16 with or without anosmia}, 614897	603961	62	100	99	92
SOX3	Mental retardation, X-linked, with isolated growth hormone deficiency, 300123 Panhypopituitarism, X-linked, 312000	313430	66	100	96	92
SOX8	No OMIM phenotype	605923	88	100	100	95
SOX9	Acampomelic campomelic dysplasia, 114290 Campomelic dysplasia, 114290 Campomelic dysplasia with autosomal sex reversal, 114290	608160	120	100	100	100
SPRY4	Hypogonadotropic hypogonadism 17 with or without anosmia, 615266	607984	101	100	100	94
SRD5A2	Pseudovaginal perineoscrotal hypospadias, 264600	607306	55	100	94	82

HGNC approved gene symbol	Phenotype description including OMIM phenotype ID(s)	OMIM gene ID	median depth	% covered >10x	% covered >20x	% covered >30x
SRY	46XX sex reversal 1, 400045 46XY sex reversal 1, 400044	480000	155	100	100	100
STAG3	Premature ovarian failure 8, 615723	608489	78	100	98	93
STAR	Lipoid adrenal hyperplasia, 201710	600617	106	100	100	100
SYCE1	?Premature ovarian failure 12, 616947 ?Spermatogenic failure 15, 616950	611486	77	100	100	96
TAC3	Hypogonadotropic hypogonadism 10 with or without anosmia, 614839	162330	83	100	100	92
TSPYL1	Sudden infant death with dysgenesis of the testes syndrome, 608800	604714	123	100	100	100
WDR11	Hypogonadotropic hypogonadism 14 with or without anosmia, 614858	606417	72	100	99	92
WNT4	Mullerian aplasia and hyperandrogenism, 158330 ?SERKAL syndrome, 611812	603490	216	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	114	100	100	99
ZFPM2	Diaphragmatic hernia 3, 610187 Tetralogy of Fallot, 187500 46XY sex reversal 9, 616067	603693	66	100	100	99
ZNRF3	No OMIM phenotype	612062	137	97	96	93

- Gene symbols according HGCN
- OMIM release used: 4-7-2018
- "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 95 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 describes the percentage of a gene's coding sequence (±10bp flanking introns) that is covered at least 10x
- % Covered 20x describes the percentage of a gene's coding sequence (±10bp flanking introns) that is covered at least 20x
- % Covered 30x describes the percentage of a gene's coding sequence (±10bp flanking introns) that is covered at least 30x