Whole Exome Sequencing
Gene package Craniosynostosis, version 1.1, 22-11-2017

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

Erasmus MC
University Medical Center Rotterdam

Dept. Clinical Genetics

HGNC approved gene symbol	Phenotype description including OMIM phenotype ID(s)	OMIM gene ID	Transcript	median depth	% covered >10x	% covered >20x	% covered >30x
ABCC9	Cardiomyopathy, dilated, 1O, 608569 Atrial fibrillation, familial, 12, 614050 Hypertrichotic osteochondrodysplasia, 239850	601439	NM_020297.3	46	100	95	80
ACTB	?Dystonia, juvenile-onset, 607371 Baraitser-Winter syndrome 1, 243310	102630	NM_001101.3	135	100	100	100
ACTG1	Deafness, autosomal dominant 20/26, 604717 Baraitser-Winter syndrome 2, 614583	102560	NM_001199954.1	121	100	100	100
ADAMTSL4	Ectopia lentis, isolated, autosomal recessive, 225100 Ectopia lentis et pupillae, 225200	610113	NM_001288608.1	70	100	99	98
AKT1	Breast cancer, somatic, 114480 Colorectal cancer, somatic, 114500 Ovarian cancer, somatic, 167000 {Schizophrenia, susceptibility to}, 181500 Proteus syndrome, somatic, 176920 Cowden syndrome 6, 615109	164730	NM_005163.2	72	100	100	97
ALPL	Hypophosphatasia, infantile, 241500 Hypophosphatasia, childhood, 241510 Odontohypophosphatasia, 146300 Hypophosphatasia, adult, 146300	171760	NM_000478.4	64	100	100	96
ALX3	Frontonasal dysplasia 1, 136760	606014	NM_006492.2	87	100	94	90
ALX4	Parietal foramina 2, 609597 Frontonasal dysplasia 2, 613451 {Craniosynostosis 5, susceptibility to}, 615529	605420	NM_021926.3	83	100	100	100

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BUB1	Colorectal cancer with chromosomal instability, somatic	602452	NM_004336.4	58	100	98	88
C5orf42	Joubert syndrome 17, 614615 Orofaciodigital syndrome VI, 277170	614571	NM_023073.3	54	100	98	88
CCBE1	Hennekam lymphangiectasia-lymphedema syndrome 1, 235510	612753	NM_133459.3	58	100	98	90
CDC45	No OMIM phenotype	603465	NM_001178010.2	64	100	99	95
CDKN1C	Beckwith-Wiedemann syndrome, 130650 IMAGE syndrome, 614732	600856	NM_000076.2	56	91	83	74
CEP57	Mosaic variegated aneuploidy syndrome 2, 614114	607951	NM_014679.4	47	100	97	82
CHST3	Spondyloepiphyseal dysplasia with congenital joint dislocations, 143095	603799	NM_004273.4	83	100	100	100
CLCN7	Osteopetrosis, autosomal recessive 4, 611490 Osteopetrosis, autosomal dominant 2, 166600	602727	NM_001287.5	73	100	100	98
COLEC11	3MC syndrome 2, 265050	612502	NM_024027.4	84	100	100	100
CTSK	Pycnodysostosis, 265800	601105	NM_000396.3	45	100	100	93
CYP26B1	Craniosynostosis with radiohumeral fusions and other skeletal and craniofacial anomalies, 614416	605207	NM_019885.3	84	100	100	100
EFNA4	No OMIM phenotype	601380	NM_005227.2	73	100	100	100
EFNB1	Craniofrontonasal dysplasia, 304110	300035	NM_004429.4	55	100	100	97
EIF4A3	Robin sequence with cleft mandible and limb anomalies, 268305	608546	NM_014740.3	44	100	98	76
ERF	Craniosynostosis 4, 600775	611888	NM_006494.2	97	100	100	100
ESCO2	Roberts syndrome, 268300 SC phocomelia syndrome, 269000	609353	NM_001017420.2	48	100	99	87
FAM111A	Kenny-Caffey syndrome, type 2, 127000 Gracile bone dysplasia, 602361	615292	NM_022074.3	62	100	100	99
FAM58A	STAR syndrome, 300707	300708	NM_152274.4	50	81	81	80
FBN1	Marfan syndrome, 154700 Ectopia lentis, familial, 129600 MASS syndrome, 604308 Weill-Marchesani syndrome 2, dominant, 608328 Aortic aneurysm, ascending, and dissection Stiff skin syndrome, 184900 Acromicric dysplasia, 102370 Geleophysic dysplasia 2, 614185	134797	NM_000138.4	111	100	100	100
FGFR1	Pfeiffer syndrome, 101600 Jackson-Weiss syndrome, 123150 Hypogonadotropic hypogonadism 2 with or without anosmia, 147950 Osteoglophonic dysplasia, 166250 Trigonocephaly 1, 190440 Hartsfield syndrome, 615465	136350	NM_023110.2	70	100	100	96

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FGFR2	Crouzon syndrome, 123500 Jackson-Weiss syndrome, 123150 Beare-Stevenson cutis gyrata syndrome, 123790 Pfeiffer syndrome, 101600 Apert syndrome, 101200 Saethre-Chotzen syndrome, 101400 Craniosynostosis, nonspecific Gastric cancer, somatic, 613659 Craniofacial-skeletal-dermatologic dysplasia, 101600 Antley-Bixler syndrome without genital anomalies or disordered steroidogenesis, 207410 Scaphocephaly and Axenfeld-Rieger anomaly LADD syndrome, 149730 Scaphocephaly, maxillary retrusion, and mental retardation, 609579 Bent bone dysplasia syndrome, 614592	176943	NM_000141.4	49	100	98	81
FGFR3	Achondroplasia, 100800 Hypochondroplasia, 146000 Thanatophoric dysplasia, type I, 187600 Crouzon syndrome with acanthosis nigricans, 612247 Muenke syndrome, 602849 Bladder cancer, somatic, 109800 Colorectal cancer, somatic, 114500 Cervical cancer, somatic, 603956 LADD syndrome, 149730 CATSHL syndrome, 610474 Nevus, epidermal, somatic, 162900 Thanatophoric dysplasia, type II, 187601 Spermatocytic seminoma, somatic, 273300 SADDAN, 616482	134934	NM_000142.4	84	100	100	98
FLNA	Heterotopia, periventricular, 300049 Otopalatodigital syndrome, type I, 311300 Otopalatodigital syndrome, type II, 304120 Intestinal pseudoobstruction, neuronal, 300048 Melnick-Needles syndrome, 309350 Frontometaphyseal dysplasia, 305620 Heterotopia, periventricular, ED variant, 300537 FG syndrome 2, 300321 Cardiac valvular dysplasia, X-linked, 314400 Terminal osseous dysplasia, 300244 Congenital short bowel syndrome, 300048	300017	NM_001110556.1	79	100	100	100

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FLNB	Spondylocarpotarsal synostosis syndrome, 272460 Larsen syndrome, 150250 Atelosteogenesis, type I, 108720 Atelosteogenesis, type III, 108721 Boomerang dysplasia, 112310	603381	NM_001164317.1	71	100	99	94
FREM1	Bifid nose with or without anorectal and renal anomalies, 608980 Manitoba oculotrichoanal syndrome, 248450 Trigonocephaly 2, 614485	608944	NM_144966.5	58	100	99	92
GLI3	Greig cephalopolysyndactyly syndrome, 175700 Pallister-Hall syndrome, 146510 Polydactyly, preaxial, type IV, 174700 Polydactyly, postaxial, types A1 and B, 174200 {Hypothalamic hamartomas, somatic}, 241800	165240	NM_000168.5	92	100	100	97
GNPTAB	Mucolipidosis III alpha/beta, 252600 Mucolipidosis II alpha/beta, 252500	607840	NM_024312.4	47	100	97	86
GPC3	Simpson-Golabi-Behmel syndrome, type 1, 312870 Wilms tumor, somatic, 194070	300037	NM_001164617.1	42	100	94	79
GPC4	No OMIM phenotype	300168	NM_001448.2	50	100	95	81
GUSB	Mucopolysaccharidosis VII, 253220	611499	NM_000181.3	74	100	95	85
HRAS	{Bladder cancer, somatic}, 109800 Costello syndrome, 218040 {Thyroid carcinoma, follicular, somatic}, 188470 Congenital myopathy with excess of muscle spindles, 218040 {Nevus sebaceous or woolly hair nevus, somatic}, 162900 Schimmelpenning-Feuerstein-Mims syndrome, somatic mosaic, 163200 {Spitz nevus or nevus spilus, somatic}, 137550	190020	NM_005343.2	105	100	100	100
IFT122	Cranioectodermal dysplasia 1, 218330	606045	NM_052985.3	72	100	100	95
IFT43	Cranioectodermal dysplasia 3, 614099	614068	NM_052873.2	54	100	100	92
IHH	Acrocapitofemoral dysplasia, 607778 Brachydactyly, type A1, 112500	600726	NM_002181.3	97	100	100	100
IL11	No OMIM phenotype	147681	NM_000641.3	43	100	93	80
IL11RA	Craniosynostosis and dental anomalies, 614188	600939	NM_001142784.2	69	100	100	99
IMPAD1	Chondrodysplasia with joint dislocations, GPAPP type, 614078	614010	NM_017813.4	70	100	100	93
IRX5	Hamamy syndrome, 611174	606195	NM_005853.5	62	100	100	97
JAG1	Alagille syndrome, 118450 Tetralogy of Fallot, 187500 ?Deafness, congenital heart defects, and posterior embryotoxon	601920	NM_000214.2	62	100	100	92
KCNJ8	No OMIM phenotype	600935	NM_004982.3	86	100	100	97
KDM6A	Kabuki syndrome 2, 300867	300128	NM_001291415.1	48	100	95	83
KMT2D	Kabuki syndrome 1, 147920	602113	NM_003482.3	97	100	100	99
KPTN	Mental retardation, autosomal recessive 41, 615637	615620	NM_007059.3	73	100	100	94

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KRAS	Lung cancer, somatic, 211980 Bladder cancer, somatic, 109800 Pancreatic carcinoma, somatic, 260350 Gastric cancer, somatic, 137215 Leukemia, acute myeloid, 601626 Noonan syndrome 3, 609942 Cardiofaciocutaneous syndrome 2, 615278 Breast cancer, somatic, 114480 Schimmelpenning-Feuerstein-Mims syndrome, somatic mosaic, 163200 RAS-associated autoimmune leukoproliferative disorder, 614470	190070	NM_033360.3	61	100	97	64
LRP5	Osteoporosis-pseudoglioma syndrome, 259770 [Bone mineral density variability 1], 601884 Hyperostosis, endosteal, 144750 van Buchem disease, type 2, 607636 Osteosclerosis, 144750 {Osteoporosis}, 166710 Exudative vitreoretinopathy 4, 601813 Osteopetrosis, autosomal dominant 1, 607634	603506	NM_002335.3	81	100	98	96
MACROD2	No OMIM phenotype	611567	NM_080676.5	42	100	94	73
MASP1	3MC syndrome 1, 257920	600521	NM_001879.5	70	100	100	92
MCPH1	Microcephaly 1, primary, autosomal recessive, 251200	607117	NM_024596.3	59	94	94	85
MEGF8	Carpenter syndrome 2, 614976	604267	NM_001271938.1	80	100	100	99
MSX2	Craniosynostosis, type 2, 604757 Parietal foramina 1, 168500 Parietal foramina with cleidocranial dysplasia, 168550	123101	NM_002449.4	68	100	100	100
NFIX	Sotos syndrome 2, 614753 Marshall-Smith syndrome, 602535	164005	NM_001271043.2	78	100	99	90
NOTCH2	Alagille syndrome 2, 610205 Hajdu-Cheney syndrome, 102500	600275	NM_024408.3	75	100	100	96
NSD1	Sotos syndrome 1, 117550 Leukemia, acute myeloid, 601626 Beckwith-Wiedemann syndrome, 130650	606681	NM_022455.4	56	100	99	92
OSTM1	Osteopetrosis, autosomal recessive 5, 259720	607649	NM_014028.3	58	100	100	88
P4HB	Cole-Carpenter syndrome 1, 112240	176790	NM_000918.3	63	100	100	98
PHF21A	No OMIM phenotype	608325	NM_001101802.1	46	99	93	77
PIGT	?Paroxysmal nocturnal hemoglobinuria 2, 615399 Multiple congenital anomalies-hypotonia-seizures syndrome 3, 615398	610272	NM_015937.5	88	100	100	100
POLR1A	Acrofacial dysostosis, Cincinnati type, 616462	616404	NM_015425.3	69	100	99	93
POLR1C	Treacher Collins syndrome 3, 248390 Leukodystrophy, hypomyelinating, 11, 616494	610060	NM_203290.2	76	100	100	91
POLR1D	Treacher Collins syndrome 2, 613717	613715	NM_015972.3	50	100	100	100

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POR	Antley-Bixler syndrome with genital anomalies and disordered steroidogenesis, 201750 Disordered steroidogenesis due to cytochrome P450 oxidoreductase, 613571	124015	NM_000941.2	84	100	100	100
PTCH1	Basal cell nevus syndrome, 109400 Basal cell carcinoma, somatic, 605462 Holoprosencephaly-7, 610828	601309	NM_000264.3	70	100	97	92
PTEN	Cowden syndrome 1, 158350 Lhermitte-Duclos syndrome, 158350 Bannayan-Riley-Ruvalcaba syndrome, 153480 {Meningioma}, 607174 {Glioma susceptibility 2}, 613028 Macrocephaly/autism syndrome, 605309 PTEN hamartoma tumor syndrome VATER association with macrocephaly and ventriculomegaly, 276950 {Prostate cancer, somatic}, 176807 Malignant melanoma, somatic, 155600 Endometrial carcinoma, somatic, 608089 Squamous cell carcinoma, head and neck, somatic, 275355	601728	NM_000314.4	85	92	81	77
PTH1R	Metaphyseal chondrodysplasia, Murk Jansen type, 156400 Chondrodysplasia, Blomstrand type, 215045 Eiken syndrome, 600002 Failure of tooth eruption, primary, 125350	168468	NM_000316.2	80	100	100	99
RAB23	Carpenter syndrome, 201000	606144	NM_016277.4	71	100	100	97
RAI1	Smith-Magenis syndrome, 182290	607642	NM_030665.3	99	100	100	100
RECQL4	Rothmund-Thomson syndrome, 268400 RAPADILINO syndrome, 266280 Baller-Gerold syndrome, 218600	603780	NM_004260.3	95	100	100	98
SALL1	Townes-Brocks syndrome, 107480 Townes-Brocks branchiootorenal-like syndrome, 107480	602218	NM_002968.2	99	100	100	100
SCARF2	Van den Ende-Gupta syndrome, 600920	613619	NM_153334.6	75	99	97	93
SEC23A	Craniolenticulosutural dysplasia, 607812	610511	NM_006364.2	44	100	95	77
SEC24D	Cole-Carpenter syndrome 2, 616294	607186	NM_014822.2	54	100	96	80
SH3BP2	Cherubism, 118400	602104	NM_001145856.1	62	91	91	91
SH3PXD2B	Frank-ter Haar syndrome, 249420	613293	NM_001017995.2	93	100	100	97
SKI	Shprintzen-Goldberg syndrome, 182212	164780	NM_003036.3	76	100	100	99
SLC35C1	Congenital disorder of glycosylation, type IIc, 266265	605881	NM_018389.4	89	100	100	99
SOX6	No OMIM phenotype	607257	NM_017508.2	55	100	100	96
SOX9	Campomelic dysplasia with autosomal sex reversal, 114290 Acampomelic campomelic dysplasia, 114290 Campomelic dysplasia, 114290	608160	NM_000346.3	66	100	100	99
TCF12	Craniosynostosis 3, 615314	600480	NM_207037.1	50	100	99	87
TCIRG1	Osteopetrosis, autosomal recessive 1, 259700	604592	NM_006019.3	79	100	100	92

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TCOF1	Treacher Collins syndrome 1, 154500	606847	NM_001135243.1	78	100	100	98
TGFBR1	Loeys-Dietz syndrome 1, 609192 {Multiple self-healing squamous epithelioma, susceptibility to}, 132800	190181	NM_004612.2	96	95	93	92
TGFBR2	Colorectal cancer, hereditary nonpolyposis, type 6, 614331 Esophageal cancer, somatic, 133239 Loeys-Dietz syndrome 2, 610168	190182	NM_001024847.2	124	100	100	100
TLK2	No OMIM phenotype	608439	NM_001284333.1	41	95	77	54
TMEM216	Joubert syndrome 2, 608091 Meckel syndrome 2, 603194	613277	NM_001173991.2	61	100	99	76
TNR	No OMIM phenotype	601995	NM_003285.2	68	100	100	96
TWIST1	Saethre-Chotzen syndrome, 101400 Saethre-Chotzen syndrome with eyelid anomalies, 101400 Craniosynostosis, type 1, 123100 Robinow-Sorauf syndrome, 180750	601622	NM_000474.3	72	100	90	77
USB1	Poikiloderma with neutropenia, 604173	613276	NM_024598.3	47	100	99	85
WDR19	Nephronophthisis 13, 614377 ?Cranioectodermal dysplasia 4, 614378 ?Short-rib thoracic dysplasia 5 with or without polydactyly, 614376 Senior-Loken syndrome 8, 616307	608151	NM_025132.3	50	100	98	85
WDR35	Cranioectodermal dysplasia 2, 613610 Short-rib thoracic dysplasia 7 with or without polydactyly, 614091	613602	NM_001006657.1	43	100	97	77
ZIC1	Craniosynostosis 6, 616602	600470	NM_003412.3	110	100	100	100
ZIC3	Heterotaxy, visceral, 1, X-linked 306955 Congenital heart defects, nonsyndromic, 1, X-linked, 306955 VACTERL association, X-linked, 314390	300265	NM_003413.3	60	100	97	86
ZSWIM6	Acromelic frontonasal dysostosis, 603671	615951	NM_020928.1	46	95	90	80

- Gene symbols according HGCN
- OMIM release used: 17-3-2016
- "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 96 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