

**Supplementary Table 1. HUGO Gene Nomenclature Committee (HGNC) gene symbols of genes included in the targeted next-generation sequencing assay**

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**Genes included in the diagnostic sub-panel**

AIRE ALPL ALX3 AMBN AMELX AMELY AMTN ANKRD11 ANTXR1 APC ATR AXIN2 BCOR BLM BMP4 C4ORF26 CA2 CCBE1 CCDC8 CEP152 CFPD1 CHD7 CLCN7 CLDN1 CNNM4 COL17A1 COL1A1 COL1A2 COL5A1 COL5A2 COL7A1 COL9A1 COL9A2 COX7B CREBBP CRTAP CTNNA1 CTSC CTSK CUL7 CYP27B1 DLX3 DSP DSPP EDA EDAR EDARADD ELN ENAM EP300 EVC EVC2 EXT1 FAM20A FAM83H FERMT3 FGF10 FGF23 FGF3 FGF8 FGFR1 FGFR2 FGFR3 FKBP10 FOXC1 GALNT3 GAS1 GDF5 GJA1 GLA GLI2 GNAS GTF21 GTF2IRD1 IFT43 IKBKG IL11RA IRF6 KAL1 KANSL1 KDM6A KLK4 KMT2D KRT14 KRT5 LAMA3 LAMB3 LAMC2 LEF1 LEMD3 LEPRE1 LIMK1 LRP5 LTBP3 MID1 MMP1 MMP20 MSX1 MSX2 MUTYH NFKBIA NHS NSD1 OBSL1 ODAM OFD1 ORAI1 OSTM1 PAX9 PCNT PHEX PITX2 PLEC PLEKHM1 PLXNB2 POLR1C POLR1D POLR3A POLR3B PORCN PPIB PRKAR1A PROK2 PROKR2 PTCH1 PTCH2 PTH1R PVRL1 PVRL4 RAB23 RAI1 RASGRP2 RBBP8 RECQL4 RFC2 ROGDI ROR2 RUNX2 SALL4 SAT1 SATB2 SEC23A SERPINF1 SERPINH1 SH3BP2 SHH SIX3 SLC24A4 SLC26A2 SMARCAL1 SMO2 SP6 SP7 SPARC SPARCL1 SUFU SUMO1 TBX22 TCIRG1 TCOF1 TGIF1 TNFRSF11A TNFRSF11B TP63 TRPS1 TSC1 TSC2 TUFT1 UBR1 VDR WDR72 WNT10A WNT5A WRN ZIC2

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**Genes included in the discovery sub-panel**

ACVR1 ACVR2A ACVR2B ADAMTS10 ADAMTS2 ADARA AGPAT2 AGXT AHCY AIP ALDH3A2 ALKBH1 AMER1 ANKH AP2B1 AP3B1 APAF1 APCDD1 ARHGAP6 ARSB ASXL1 ATP6V0A2 ATP7A ATRIP ATRX B3GALT B3GAT3 B4GALT7 BANF1 BARX1 BCL11B BGLAP BGN BMP2 BMP7 BMPR1A BNC2 BOC BRAF CACNA1C CARD9 CASK CASP7 CCL2 CD96 CDC42 CDC6 CDH1 CDH23 CDH3 CDKN1A CDKN1C CDON CDSN CENPJ CHR1 CHST3 CHSY1 CHUK CIB2 CLCN5 CLEC7A COL10A1 COL11A1 COL11A2 COL2A1 COL3A1 COX4I2 CRISPLD2 CRK CSF1 CTGF DCAF17 DCN DFNB31 DHCR24 DHCR7 DHODH DKC1 DKK1 DKK4 DLG1 DLL1 DLX1 DLX2 DLX4 DLX5 DLX6 DMP1 DPYSL4 DSC3 DSG4 EDNRB EFN1 EHMT1 EXT2 EXTL3 EYA1 FAM20C FBN1 FERMT1 FGD1 FGF13 FGF18 FGF20 FGF4 FGF9 FKBP6 FLNA FLNB FMOD FOS FOXE1 FOXF2 FOXO1 FRAS1 FREM2 FRZB FST FUZ FZD1 FZD2 FZD6 G6PC3 GAB1 GAD1 GALNS GDNF GJB6 GLB1 GLI1 GLI3 GNPTAB GORAB GPC3 GRB2 GSC GSK3B GUSB HAND1 HAND2 HCCS HDAC4 HGSNAT HHAT HOXC13 HOXD13 HR HRAS HYAL IBSP ICAM1 IDS IDUA IFT122 IFT88 IGF1 IHH IL17F IL17RA INHBA INHBB INPP5E INSR ISL1 ITGA11 ITGA6 ITGAV ITGB2 ITGB4 ITGB6 ITGB8 JAG1 JAG2 KAT6B KAZN KCNJ2 KIF7 KISS1 KISS1R KL KRAS KRT1 KRT10 KRT16 KRT17 KRT6A KRT6B KRT74 KRT83 KRT9 LAMA5 LHX6 LHX8 LIFR LIPH LMNA LOR LPAR6 LRP4 LRP6 LTBP2 LUM LUZP1 MAP2K1 MAP2K2 MAP3K11 MASP1 MBTPS2 MED12 MED25 MEPE MGP MITF MMP14 MMP16 MMP2 MMP3 MMP9 MN1 MNT MSC MVP MYO7A NAGLU NCOA2 NCOR1 NELL1 NF2 NFE2L2 NFIC NIPBL NKX2-3 NKX3-2 NLRP1 NOG NOP10 NOTCH1 NOTCH2 NOTCH3 OCRL ORC1 OSR2 PAF1 PCDH15 PDGFA PDGFC PDGFRA PDS5A PDS5B PHC1 PIGL PITX1 PKDCC PKP1 PLCD1 PLG PLOD1 PLOD3 PLXNA1 PLXNA2 PLXNA3 PLXNA4 PLXNB1 PLXNB3 PLXNC1 PLXND1 POLD1 POSTN POU1F1 PRDM1 PRDM16 PRKCI PRRX1 PRRX2 PTHLH PTPN11 PTPRF PTPRS PVRL3 RAPS RBL1 RBL2 RBM28 RFNG RGS2 RIN2 RMRP RPS6KA3 RSPO2 RSPO4 SCARF2 SFN SGSH SH3PXD2B SHOX2 SIM2 SLC20A2 SLC32A1 SLC34A2 SLC35B2 SLC35C1 SLC39A13 SLC4A2 SLC4A4 SLC4A5 SMAD2 SMAD3 SMAD5 SMG1 SMO SMPD3 SNAI1 SNAI2 SOS1 SOST SOSTDC1 SOX10 SOX11 SOX18 SOX2 SOX3 SOX5 SP3 SPP1 SPRY2 SPRY4 SQSTM1 SSTR5 ST14 STAG1 STAT1 STAT3 STIM1 SUOX TAB2 TACR3 TBCE TBX1 TBX10 TBX15 TBX2 TBX3 TCF21 TCP1 TERC TERT TFAP2A TFIP11 TGFA TGFB1 TGFB2 TGFB3 TGFB1 TGFB2 THRA TINF2 TMC01 TMEM107 TNFRSF19 TNFSF11 TRAF6 TRIM37 TRIP11 TRPV3 TSHZ1 TWIST1 TWIST2 UBB USH1C USH1G USH2A WDR19 WDR35 WHSC1 WNT1 WNT10B WNT3 WNT4 WNT6 WNT7B ZEB1 ZEB2 ZMPSTE24 ZNF469

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**Genes added to the discovery sub-panel in the screening assay**

ADAM10 AKAP9 ANTXR2 BAZ1B BBX BMP1 CHPF CSRP2BP FAM111A FAM111B FAM73B GALC HMX3 IFITM5 IFT20 ITGA3 ITGB1 KDM4B LTBP1 NSUN2 NTRK1 RHOBTB3 SLC25A21 TMEM38B UBE3B

**Supplementary Table 2. Details of the targeted capture design**

		<b>v1.0</b>	<b>v2.0</b>
<b>Number of loci targeted</b>	Total	560	585
	Diagnosis sub-panel	175	175
	Discovery sub-panel	385	410
<b>Size of targeted regions (Mb)</b>	Total	2.36	2.47
	Diagnosis sub-panel	0.81	0.81
	Discovery sub-panel	1.5	1.66

**Supplementary Table 3. Known variants in samples V1.01-V1.08 identified with v1.0 of the panel**

<b>ID</b>	<b>Gene</b>	<b>Transcript</b>	<b>c.</b>	<b>p.</b>	<b>Inheritance</b>	<b>Reference</b>
V1.01	<i>LTBP3</i>	NM_001130144.2	c.[1531+1G>A];[421C>T]	p.[Q141*];[p.0?]	AR	[1]
V1.02	<i>FAM20A</i>	NM_017565.3	c.[34_35del];[612del]	p.[L12Afs*67];[L205Cfs*11]	AR	[2]
V1.03	<i>DSPP</i>	NM_014208.3	c.[3676del];[=]	p.[S1226Afs*88];[=]	AD	-
V1.04	<i>AMELX</i>	NM_182680.1	c.[11G>A];[0]	p.[W4*];[0]	X-linked	-
V1.05	<i>ENAM</i>	NM_031889.2	c.[588+1del]	p.[N1971fs*81]	AD	-
V1.06	<i>CNNM4</i>	NM_020184.3	c.[586T>C];[586T>C]	p.[S196P];[S196P]	AR	[3]
V1.07	<i>MMP20</i>	NM_004771.3	c.[954-2A>T];[954-2A>T]	p.[0?];[0?]	AR	-
V1.08	Contiguous gene deletion		hg19 chrX:(?_185958)_(12815845- ?)del [*hg19 chrX:10417360- 8699939del]	p.[0?];[=]	AD	-

**Supplementary Table 4. Sequencing statistics from v1.0 of the gene panel on samples V1.01-V1.16**

ID	Total sequenced nucleotides	Total passed filter aligned nucleotides	Total passed filter aligned nucleotides in targeted regions <sup>o</sup>	Mean coverage*			% bases ≥ 1X*			% bases ≥ 20X*			% bases ≥ 50X*			% bases ≥ 100X*		
				Total	Diag. sub-panel	Disc. sub-panel	Total	Diag. sub-panel	Disc. sub-panel	Total	Diag. sub-panel	Disc. sub-panel	Total	Diag. sub-panel	Disc. sub-panel	Total	Diag. sub-panel	Disc. sub-panel
V1.01	2529393600	1935516105	973675975	410.57	443.57	393.18	99.5	99.5	99.6	97.5	98.8	96.8	94.5	97.8	92.8	88.3	95	84.8
V1.02	2441063200	1869714700	937342410	395.32	433.5	375.19	99.6	99.3	99.7	97.9	98.8	97.5	95.6	98.2	94.3	90.1	95.9	87
V1.03	2152958600	1631544311	855687555	360.71	400.9	339.54	99.7	99.6	99.8	98.2	99.1	97.7	95.7	98.4	94.3	89.6	96.2	86.2
V1.04	1703053800	1303350887	686090778	289.28	325.36	270.27	99.6	99.5	99.7	97.7	98.9	97.1	94.4	98	92.5	86.2	94.4	82
V1.05	1641523000	1195222257	637282471	268.63	298.28	253.01	99.7	99.5	99.7	97.6	98.9	97	93.8	97.9	91.7	84.3	93.2	79.7
V1.06	2100703400	1579542394	853771624	360.02	398.63	339.67	99.6	99.3	99.8	98.1	98.9	97.6	95.7	98.2	94.4	89.9	96	86.7
V1.07	2869433600	2167359316	1072784699	452.21	503.56	425.16	99.7	99.4	99.8	98.5	99	98.2	96.9	98.6	96	93.2	97.5	90.9
V1.08	2550773800	1933898916	1026048161	432.66	472.66	411.58	99.6	99.4	99.7	98.1	98.9	97.7	95.9	98.3	94.7	90.7	96.3	87.8
V1.09	2354231600	1774468518	909271752	383.38	425.66	361.1	99.7	99.4	99.8	98.2	99	97.9	96.2	98.5	94.9	90.9	96.6	87.9
V1.10	1713496800	1283336880	691905675	291.67	321.11	276.16	99.7	99.5	99.8	97.6	99	96.9	93.9	97.9	91.8	85.2	93.8	80.7
V1.11	2530456400	1906056269	1009463211	425.6	476.94	398.54	99.7	99.5	99.8	98.5	99.1	98.1	96.7	98.6	95.6	92.2	97.2	89.6
V1.12	2486134200	1883955509	1032670398	435.41	491.12	406.05	99.7	99.5	99.8	98.4	99.1	98.1	96.7	98.7	95.7	92.5	97.3	89.9
V1.13	2182365400	1613504161	835260345	352.15	390.72	331.83	99.7	99.5	99.8	98.1	99	97.6	95.4	98.3	93.8	88.9	95.8	85.3
V1.14	2284365400	1691327624	866816596	365.33	407.21	343.26	99.7	99.5	99.8	98.3	99.1	97.8	95.9	98.5	94.6	90.2	96.5	86.8
V1.15	2281142800	1687807698	912197621	384.7	423.73	364.13	99.5	99.3	99.6	97.7	98.7	97.2	95.2	97.9	93.8	89.5	95.3	86.4
V1.16	1250639000	944935101	538571957	227.08	251.73	214.1	99.6	99.4	99.7	97.2	98.7	96.4	92.5	97.1	90	81.1	90.9	76
Mean	2191983413	1650096290	864927577	364.67	404.04	343.92	99.64	99.44	99.74	97.98	98.94	97.48	95.31	98.18	93.81	88.93	95.49	85.48

<sup>o</sup>targeted regions = baited regions + 15 bp on either side, \*includes only reads with MQ > 30, Diag. = Diagnostic, Disc. = Discovery

**Supplementary Table 5. Regions with an average per sample coverage <20X in v1.0 of the panel**

Chr	Region Start	Region End	%GC	Region Length	Average Coverage Per Individual	Gene	Position
<i>Diagnostic sub-panel</i>							
7	74150814	74151053	42.26%	239	0	<i>GTF2I</i>	exon18
7	74163577	74163816	45.61%	239	0	<i>GTF2I</i>	exon26
7	74168150	74168389	48.54%	239	0	<i>GTF2I</i>	exon30
X	153786686	153786925	61.51%	239	0	<i>IKBK</i>	exon4
X	153788578	153788817	73.22%	239	0	<i>IKBK</i>	exon5
X	153789831	153790070	59.41%	239	0	<i>IKBK</i>	exon6
X	153790977	153791216	62.76%	239	0	<i>IKBK</i>	exon7
X	153791725	153791964	63.18%	239	0	<i>IKBK</i>	exon8
X	153792115	153792294	63.13%	179	0	<i>IKBK</i>	exon9
7	74163305	74163484	37.99%	179	0.033170391	<i>GTF2I</i>	exon25
7	74165631	74165810	39.11%	179	0.065293296	<i>GTF2I</i>	exon27
7	74169765	74169944	32.96%	179	0.065293296	<i>GTF2I</i>	exon31
X	153792485	153792724	64.02%	239	0.132583682	<i>IKBK</i>	exon10/3'UTR
7	74143059	74143298	47.28%	239	0.484309623	<i>GTF2I</i>	exon13
7	74144510	74144689	35.75%	179	0.689944134	<i>GTF2I</i>	exon14
18	59992470	59992709	83.68%	239	0.966788703	<i>TNFRSF11A</i>	5'UTR/exon1
4	2819914	2820153	85.36%	239	1.021705021	<i>SH3BP2</i>	5'UTR/exon1
4	5713075	5713314	82.43%	239	2.111140167	<i>EVC</i>	5'UTR/exon1
11	68080108	68080347	82.01%	239	3.053870293	<i>LRP5</i>	5'UTR/exon1
17	17713200	17713379	73.74%	179	7.438896648	<i>RAI1</i>	exon6/3'UTR
9	137533968	137534207	82.01%	239	10.91082636	<i>COL5A1</i>	5'UTR/exon1
2	220417548	220417787	75.73%	239	13.43122385	<i>OBSL1</i>	exon17
1	110612916	110613275	78.33%	359	19.7992688	<i>ALX3</i>	5'UTR/exon1
<i>Discovery sub-panel</i>							
9	140513401	140513580	87.15%	179	0.061103352	<i>EHMT1</i>	5'UTR/exon1
14	105634635	105634814	86.59%	179	0.274790503	<i>JAG2</i>	5'UTR/exon1
8	42995507	42995806	81.27%	299	0.327759197	<i>HGSNAT</i>	5'UTR/exon1
1	15250815	15251114	83.61%	299	0.35451505	<i>KAZN</i>	5'UTR/exon1
18	72923762	72923941	82.12%	179	0.423882682	<i>TSHZ1</i>	intron1
9	139440118	139440297	78.21%	179	0.468924581	<i>NOTCH1</i>	5'UTR
9	101867416	101867655	84.10%	239	0.486401674	<i>TGFBR1</i>	5'UTR/exon1
X	153784336	153784635	62.54%	299	0.525710702	<i>IKBK</i>	exon3
12	112856833	112857012	77.10%	179	0.808659218	<i>PTPN11</i>	5'UTR/exon1
7	150760182	150760361	75.42%	179	0.992667598	<i>SLC4A2</i>	5'UTR/exon1
5	177027147	177027326	81.56%	179	1.301326816	<i>B4GALT7</i>	5'UTR/exon1
9	132428096	132428455	82.73%	359	1.313022284	<i>PRRX2</i>	5'UTR/exon1
9	140353399	140353638	81.17%	239	1.360355649	<i>NSMF</i>	5'UTR/exon1
1	3310967	3311146	69.83%	179	1.392458101	<i>PRDM16</i>	intron4
21	38119940	38120419	81.42%	479	1.4375	<i>SIM2</i>	exon11/3'UTR
3	38495750	38495929	81.56%	179	1.516061453	<i>ACVR2B</i>	5'UTR/exon1
1	22469257	22469496	82.01%	239	1.531380753	<i>WNT4</i>	5'UTR/exon1
9	96717167	96717466	78.60%	299	1.567934783	<i>BARX1</i>	5'UTR/exon1
1	110453575	110453754	83.80%	179	1.930865922	<i>CSF1</i>	5'UTR/exon1
5	134369367	134369606	76.99%	239	1.947437238	<i>PITX1</i>	5'UTR/exon1
6	44225052	44225231	78.77%	179	2.208100559	<i>SLC35B2</i>	5'UTR/exon1
18	10454568	10454747	78.77%	179	2.311452514	<i>APCDD1</i>	5'UTR
1	120534005	120534184	41.90%	179	2.470670391	<i>NOTCH2</i>	intron4

Chr	Region Start	Region End	%GC	Region Length	Average Coverage Per Individual	Gene	Position
17	78193949	78194188	77.82%	239	2.544979079	<i>SGSH</i>	5'UTR/exon1
6	132272190	132272369	79.33%	179	2.602304469	<i>CTGF</i>	5'UTR
20	10654018	10654257	77.41%	239	2.612186192	<i>JAG1</i>	5'UTR/exon1
4	980832	981071	79.50%	239	2.720188285	<i>IDUA</i>	5'UTR/exon1
11	130029795	130030034	78.66%	239	2.83289749	<i>ST14</i>	5'UTR/exon1
17	80009329	80009688	81.34%	359	2.934192201	<i>RFNG</i>	5'UTR/exon1
5	178772140	178772379	80.75%	239	2.951621339	<i>ADAMTS2</i>	5'UTR/exon1
11	46939815	46939994	78.21%	179	2.981494413	<i>LRP4</i>	5'UTR/exon2
19	7293733	7293972	78.66%	239	2.993723849	<i>INSR</i>	5'UTR/exon1
X	128674346	128674525	76.54%	179	3.069832402	<i>OCRL</i>	5'UTR/exon1
5	179248469	179248648	70.95%	179	3.455656425	<i>SQSTM1</i>	intron1
19	5229449	5229748	80.27%	299	3.777801003	<i>PTPRS</i>	exon15
X	20284626	20284805	77.65%	179	4.146997207	<i>RPS6KA3</i>	5'UTR
6	10412805	10413044	74.48%	239	4.197960251	<i>TFAP2A</i>	intron1
7	558517	558696	75.98%	179	4.499301676	<i>PDGFA</i>	5'UTR/exon1
17	73749801	73750100	78.93%	299	4.509824415	<i>ITGB4</i>	exon33
20	60941973	60942332	78.27%	359	4.547179666	<i>LAMA5</i>	5'UTR/exon1
19	15311541	15311780	80.33%	239	4.950052301	<i>NOTCH3</i>	5'UTR/exon1
7	74162283	74162522	35.98%	239	4.967573222	<i>GTF2I</i>	exon24
3	184098061	184098300	79.50%	239	5.02248954	<i>CHRD</i>	5'UTR/exon1
7	559571	559870	77.59%	299	5.138586957	-	upstream
15	68724290	68724469	76.54%	179	5.259078212	<i>ITGA11</i>	5'UTR/exon1
7	140624315	140624554	77.41%	239	5.379445607	<i>BRAF</i>	5'UTR/exon1
9	124990858	124991097	77.82%	239	5.442730126	<i>LHX6</i>	5'UTR/exon1
22	17565931	17566170	77.82%	239	5.686453975	<i>IL17RA</i>	5'UTR/exon1
17	40688242	40688721	79.12%	479	6.322286013	<i>NAGLU</i>	5'UTR/exon1
20	30946517	30946696	76.54%	179	6.405726257	<i>ASXL1</i>	5'UTR/exon1
19	41836916	41837155	74.06%	239	6.517259414	<i>TGFB1</i>	5'UTR/exon1
3	110790825	110791064	73.64%	239	6.552824268	<i>PVRL3</i>	5'UTR/exon1
13	31774167	31774346	77.65%	179	6.819832402	<i>B3GALTL</i>	5'UTR/exon1
7	74157704	74157943	34.73%	239	6.993200837	<i>GTF2I</i>	exon20
14	95235965	95236384	76.85%	419	7.16900358	<i>GSC</i>	5'UTR/exon1
5	1294845	1295144	79.60%	299	7.27132107	<i>TERT</i>	5'UTR/exon1
16	18900651	18900950	40.13%	299	7.477842809	<i>SMG1</i>	exon6
16	68771253	68771432	76.54%	179	7.535963687	<i>CDH1</i>	5'UTR/exon1
2	172291031	172291270	78.66%	239	7.769089958	<i>DCAF17</i>	5'UTR/exon1
2	174829087	174829326	73.22%	239	8.390167364	<i>SP3</i>	exon2
10	134000497	134000676	77.65%	179	8.491620112	<i>DPYSL4</i>	5'UTR/exon1
10	31608103	31608282	68.72%	179	8.50349162	<i>ZEB1</i>	5'UTR/exon1
6	132271871	132272170	74.58%	299	8.639423077	<i>CTGF</i>	exon2
2	174828430	174828669	76.99%	239	8.67834728	<i>SP3</i>	exon3
19	4123707	4123946	77.41%	239	8.754445607	<i>MAP2K2</i>	5'UTR/exon1
7	100860381	100860620	74.90%	239	8.780857741	<i>PLOD3</i>	5'UTR/exon1
11	65381392	65381571	73.18%	179	9.057960894	<i>MAP3K11</i>	5'UTR
19	8649739	8649978	72.38%	239	9.0666841	<i>ADAMTS10</i>	exon25
9	124989604	124989843	73.22%	239	9.203713389	<i>LHX6</i>	exon2
3	38070924	38071103	73.74%	179	9.818435754	<i>PLCD1</i>	5'UTR/exon1
20	60884342	60884581	69.87%	239	9.882060669	<i>LAMA5</i>	exon80
16	88923106	88923345	76.99%	239	9.935669456	<i>GALNS</i>	5'UTR/exon1
7	557977	558216	75.73%	239	10.41082636	<i>PDGFA</i>	intron1

<b>Chr</b>	<b>Region Start</b>	<b>Region End</b>	<b>%GC</b>	<b>Region Length</b>	<b>Average Coverage Per Individual</b>	<b>Gene</b>	<b>Position</b>
2	121103719	121104258	75.88%	539	10.43552876	<i>INHBB</i>	5'UTR/exon1
11	69589473	69589892	77.57%	419	10.58412888	<i>FGF4</i>	5'UTR/exon1
16	68679476	68679715	69.87%	239	10.76281381	<i>CDH3</i>	exon2
2	178129192	178129371	74.86%	179	10.77513966	<i>NFE2L2</i>	5'UTR/exon1
5	78280706	78281125	76.37%	419	10.91139618	<i>ARSB</i>	5'UTR/exon1
22	20791835	20792074	79.92%	239	11.20737448	<i>SCARF2</i>	5'UTR/exon1
2	219724681	219724920	76.15%	239	11.67651674	<i>WNT6</i>	5'UTR/exon1
16	53468439	53468738	73.91%	299	12.00585284	<i>RBL2</i>	5'UTR/exon1
22	20779637	20780596	76.12%	959	12.44584202	<i>SCARF2</i>	exon11/3'UTR
3	129159104	129159283	65.36%	179	13.49965084	<i>IFT122</i>	5'UTR/exon1
7	128828948	128829367	77.33%	419	13.60739857	<i>SMO</i>	5'UTR/exon1
20	60897644	60897883	69.87%	239	13.80334728	<i>LAMA5</i>	exon46
X	153991159	153991338	72.07%	179	13.82087989	<i>DKC1</i>	5'UTR/exon1
20	62680481	62680900	77.33%	419	14.07741647	<i>SOX18</i>	5'UTR/exon1
7	556959	557198	74.48%	239	14.16971757	<i>PDGFA</i>	exon2
4	996476	997004	78.03%	528	14.34824811	<i>IDUA</i>	exon9/10
22	46367956	46368195	75.31%	239	14.42024059	<i>WNT7B</i>	intron1
20	62679467	62680366	75.97%	899	15.1881257	<i>SOX18</i>	exon2/3'UTR
X	54521532	54521891	73.61%	359	17.47423398	<i>FGD1</i>	5'UTR/exon1
17	78187524	78187763	70.29%	239	17.77301255	<i>SGSH</i>	exon6
1	11994755	11994994	74.48%	239	17.78242678	<i>PLOD1</i>	5'UTR/exon1
18	10454840	10455079	75.00%	239	17.79550209	<i>APCDD1</i>	5'UTR/exon1
2	42275299	42276018	77.78%	719	17.81389082	<i>PKDCC</i>	5'UTR/exon1
5	52776544	52776783	72.50%	239	18.40115063	<i>FST</i>	5'UTR/exon1
19	5250930	5251109	58.89%	179	18.53840782	<i>PTPRS</i>	intron 9
1	2985752	2985931	70.00%	179	18.89385475	<i>PRDM16</i>	5'UTR/exon1
11	2905860	2906759	77.44%	899	18.92575083	<i>CDKN1C</i>	5'UTR/exon1
19	3366560	3366739	72.22%	179	19.40851955	<i>NFIC</i>	5'UTR/exon1
11	65374713	65375012	73.33%	299	19.76066054	<i>MAP3K11</i>	exon5

**Supplementary Table 6. Variant detection statistics in samples V1.01-V1.16 with v1.0 of the gene panel**

ID	Number of variants identified	Number of SNPs	Number of INDELS	Number of filtered* variants with allele frequency < 1% in dbSNP137, 1000G, EVS and in-house database	Number of filtered variants annotated as missense	Number of filtered variants annotated as frameshift	Number of filtered variants annotate as nonsense	Number of filtered variants annotated as splice mutations
V1.01	2547	2138	409	74	22	0	1	1
V1.02	2572	2127	445	64	16	3	0	0
V1.03	3059	2560	499	180	40	1	0	0
V1.04	2704	2260	444	68	19	0	1	1
V1.05	3077	2582	495	189	31	3	0	0
V1.06	2671	2225	446	79	28	0	0	0
V1.07	2553	2134	419	77	13	1	0	1
V1.08	2553	2144	409	72	20	0	0	1
V1.09	2622	2186	436	70	13	0	1	0
V1.10	2441	2018	423	69	22	0	0	0
V1.11	2701	2263	438	81	21	1	1	0
V1.12	2563	2130	433	69	16	0	0	0
V1.13	2581	2149	432	90	22	0	0	0
V1.14	2538	2091	447	76	18	0	1	0
V1.15	2588	2158	430	59	15	0	0	0
V1.16	2599	2188	411	72	14	0	1	0
<b>Mean</b>	<b>2648.06</b>	<b>2209.56</b>	<b>438.50</b>	<b>86.81</b>	<b>20.63</b>	<b>0.56</b>	<b>0.38</b>	<b>0.25</b>

\* filtered: variants that passed the following criteria: allele frequency < 1% in dbSNP137, 1000 genomes, Exome Variant Server, and in-house database; °includes only reads with MQ > 30



**Supplementary Table 7. Sequencing statistics for patients v2.01-v2.95 sequenced with v2.0 of the gene panel**

ID	Total sequenced nucleotides	Total passed filter aligned nucleotides	Total passed filter aligned nucleotides in targeted regions	Mean coverage	% bases ≥ 1X°	% bases ≥ 20X°	% bases ≥ 50X°	# variants	# SNP	# Indel	# filtered* variants	# filtered mis-sense	# filtered frame-shift	# filtered nonsense	# filtered splice
					Total	Total	Total								
V2.01	848050800	736028984	277592817	107.8	99.8	96	81.5	2780	2262	518	70	13	0	0	1
V2.02	960169200	860522137	327213166	127.05	99.8	96.4	85	2876	2364	512	83	14	3	0	0
V2.03	747160000	667348632	261857870	101.64	99.8	95.1	78.5	2642	2167	475	65	11	1	0	1
V2.04	800411200	725089453	282525424	109.54	99.8	95.4	80.3	2869	2349	520	74	11	0	0	0
V2.05	746819200	684586911	269867229	104.51	99.8	94.2	77.3	2670	2215	455	110	23	3	0	0
V2.06	692747000	634750100	264984723	102.61	99.7	93.5	75.7	2874	2357	517	128	19	5	1	0
V2.07	887134800	756202602	284776259	110.64	99.8	95.7	81.5	2726	2208	518	71	12	3	0	2
V2.08	922939800	823410379	320339971	124.17	99.8	96.2	83.5	2789	2284	505	86	12	0	0	0
V2.09	776923600	651158111	299181653	115.81	99.8	96	83.1	2741	2227	514	73	6	3	1	1
V2.10	644774400	545336576	262728853	101.82	99.7	95	79.1	2769	2278	491	72	15	0	0	2
V2.11	757023200	659217579	313145842	121.23	99.8	96.4	84.7	2790	2280	510	78	13	0	0	1
V2.12	855912600	779255895	359977159	139.45	99.9	96.9	87.4	2823	2316	507	41	2	0	0	1
V2.13	1502519800	1282612834	528188469	204.98	99.9	98.2	94	2846	2328	518	82	18	3	0	2
V2.14	1149269200	1015333953	438537896	169.99	99.8	97.8	91.6	2738	2234	504	77	15	0	0	2
V2.15	1004121800	895602006	407007571	157.78	99.9	97.6	90.3	2766	2265	501	71	13	3	0	1
V2.16	958794200	806152575	341959344	132.41	99.8	96.5	85.4	2759	2260	499	90	23	2	0	1
V2.17	2123494400	1875903407	809214774	313.75	99.9	98.9	96.4	3745	3122	623	128	26	0	0	2
V2.18	1048638000	926159642	403679470	156.47	99.9	97.5	89.4	2766	2271	495	70	19	0	1	0
V2.19	1059056800	945324906	402670360	156.13	99.8	97.1	88.6	2889	2366	523	71	14	0	0	1
V2.20	895689600	814345529	372856997	144.44	99.8	97.2	88.7	2802	2296	506	64	13	4	1	1
V2.21	2664350600	2397448572	1007063992	390.46	99.9	99.1	97.4	3725	3090	635	169	34	3	1	1
V2.22	1935887200	1685866367	758461285	293.93	99.9	98.9	96.7	3641	3018	623	101	17	2	0	1
V2.23	1188179000	1077109416	459677384	178.31	99.9	97.5	90.7	2792	2278	514	66	10	3	0	1
V2.24	1398400200	1213462486	510731305	198.47	99.9	98.3	94.2	2801	2288	513	87	19	3	0	1
V2.25	1495761200	1364107809	591255764	229.51	99.9	98.4	94.9	2722	2204	518	85	9	0	0	1
V2.26	988928400	870596072	399228912	154.73	99.9	97.5	89.6	2805	2286	519	73	9	0	1	3
V2.27	568525800	457626650	227965737	88.22	99.8	93.9	74.1	2673	2194	479	68	10	0	0	1
V2.28	1046138800	946606434	446714024	172.78	99.9	97.9	91.7	2781	2273	508	78	10	3	1	3
V2.29	574351000	513661968	244780596	94.79	99.8	95.2	78	2744	2251	493	70	11	3	0	1
V2.30	2313111600	2007376602	880783599	340.92	100	99	97	3792	3153	639	173	38	0	1	2
V2.31	773530600	681983651	334742156	129.78	99.8	97.1	88.2	2824	2294	530	56	8	0	0	1

ID	Total sequenced nucleotides	Total passed filter aligned nucleotides	Total passed filter aligned nucleotides in targeted regions	Mean coverage	% bases $\geq 1X^\circ$	% bases $\geq 20X^\circ$	% bases $\geq 50X^\circ$	# variants	# SNP	# Indel	# filtered* variants	# filtered mis-sense	# filtered frame-shift	# filtered nonsense	# filtered splice
V2.32	1107243800	952873442	432500622	167.53	99.8	97.7	91.3	2773	2251	522	78	15	3	0	2
V2.33	1262394400	1126406753	433938620	168.63	99.9	97.6	90.8	2868	2357	511	76	20	3	0	1
V2.34	729711600	644240049	262838572	102.14	99.8	95	78.8	2770	2256	514	77	21	0	0	1
V2.35	1088653800	995478858	399149335	154.88	99.8	97.2	89.1	2660	2153	507	66	14	1	0	1
V2.36	1402971000	1257523339	482424435	187.65	99.9	98	92.4	2942	2410	532	114	22	4	0	1
V2.37	1432402000	1286637761	483808260	188.06	99.8	97.9	92.5	2753	2249	504	78	13	3	0	1
V2.38	1185778400	1072343725	422060643	163.82	99.8	97.5	90.4	2842	2339	503	84	8	0	2	1
V2.39	798479800	710469922	311345177	120.66	99.9	96.3	83.8	2763	2267	496	65	11	1	0	1
V2.40	1501506200	1374930437	542011393	210.45	99.9	98.2	93.8	2825	2289	536	74	7	0	0	1
V2.41	755312000	668403887	283829802	110.19	99.7	94.9	80.1	2803	2277	526	76	15	0	1	1
V2.42	955305400	817563816	354413159	137.59	99.8	97.2	88.1	2894	2359	535	74	10	1	0	1
V2.43	960359000	871557783	371634147	144.17	99.8	97.1	88.1	2725	2243	482	63	9	0	0	1
V2.44	1504276200	1303262139	515070393	200.06	99.9	98.2	93.2	2772	2268	504	77	13	3	0	2
V2.45	1061382400	924381441	402600639	156.27	99.8	97.5	90	2695	2181	514	80	16	0	0	1
V2.46	1040252400	925302762	380872541	148.02	99.8	97.5	89.9	2768	2261	507	74	7	4	1	2
V2.47	1291747800	1145317180	447396501	173.76	99.8	97.8	91.7	2817	2303	514	91	15	3	0	4
V2.48	1333586800	1140100684	481154521	185.91	99.8	97.7	92.1	2784	2269	515	72	15	3	1	1
V2.49	1343604200	1196406787	480490318	186	99.8	97.9	92.7	2754	2230	524	79	15	0	1	1
V2.50	1026321600	910914613	390514110	151.06	99.9	97.3	89.2	2756	2253	503	88	17	1	0	2
V2.51	1084525800	921482358	387228819	149.66	99.8	97.4	89.9	2743	2238	505	84	21	2	0	1
V2.52	893392400	766979835	339596355	131.15	99.8	96.2	85.3	2748	2289	459	69	9	0	0	3
V2.53	1397405400	1283250012	519754347	201.22	99.8	97.6	92.2	2905	2383	522	73	16	0	0	1
V2.54	1619633800	1496266236	613038295	236.97	99.9	98.4	94.9	2771	2260	511	79	18	0	0	1
V2.55	1525109600	1409329796	565809153	218.73	99.8	98	93.7	2793	2301	492	69	10	1	0	1
V2.56	1080181600	963545575	407219662	157.32	99.8	97.4	90.2	2873	2386	487	62	12	0	0	1
V2.57	1719283000	1516114039	573781112	222.16	99.8	98.2	94.2	2784	2267	517	87	16	3	0	1
V2.58	1291547200	1099723443	446787037	172.49	99.9	97.8	91.5	2691	2220	471	81	14	1	1	1
V2.59	1056774800	958828432	402546525	155.55	99.8	97.5	90.6	2665	2172	493	68	16	2	0	1
V2.60	1386210000	1231985409	485313286	187.5	99.8	97.9	92.7	3061	2524	537	111	21	0	0	0
V2.61	1434162600	1325855516	508545342	196.55	99.8	97.6	92.5	3292	2734	558	230	40	3	0	1
V2.62	1311658400	1164036368	448507877	173.73	99.8	97.8	92.2	2842	2338	504	78	12	0	0	2
V2.63	784783800	612917519	276014895	106.25	99.8	93.8	77	2662	2214	448	85	23	0	1	0
V2.64	1477661800	1260260874	548548734	211.77	99.9	97.7	92.8	2822	2330	492	108	26	2	0	1
V2.65	1507305000	1331063062	558019554	216.29	99.8	97.8	93.2	2599	2161	438	56	10	2	1	1

ID	Total sequenced nucleotides	Total passed filter aligned nucleotides	Total passed filter aligned nucleotides in targeted regions	Mean coverage	% bases $\geq 1X^{\circ}$	% bases $\geq 20X^{\circ}$	% bases $\geq 50X^{\circ}$	# variants	# SNP	# Indel	# filtered* variants	# filtered mis-sense	# filtered frame-shift	# filtered nonsense	# filtered splice
V2.66	1561032200	1301266158	553784231	213.92	99.8	97.5	92.3	2749	2285	464	42	9	2	0	1
V2.67	1845095000	1618692423	627804999	243.04	99.9	98	93.7	2801	2340	461	61	17	2	0	1
V2.68	2211562400	1953015892	735168165	285.02	99.9	98.5	95.8	2729	2229	500	55	4	3	0	1
V2.69	1365493200	1159701682	507692366	196.28	99.9	97.8	92.1	2641	2165	476	80	16	2	0	1
V2.70	2452899800	2205738567	871452465	337.39	99.9	98.3	95.7	2768	2294	474	62	9	2	1	1
V2.71	2757139800	2381482082	995840560	384.73	99.9	98.6	96.2	2808	2336	472	58	14	0	0	3
V2.72	722424400	644206852	295660531	114.65	99.8	95.3	81.4	2838	2370	468	78	18	2	0	1
V2.73	1041247000	935138556	401389849	155.98	99.8	97.2	89.4	2675	2219	456	49	12	1	0	1
V2.74	817505800	747780422	330902440	128.37	99.8	96.3	85	2667	2197	470	57	8	2	0	1
V2.75	1044084000	932546469	410852215	159.53	99.8	97	89.1	2677	2232	445	79	20	2	0	1
V2.76	1097412400	1007856644	411589046	159.73	99.8	97.4	89.6	2811	2330	481	63	14	2	0	1
V2.77	887949600	819098704	369027076	143.13	99.8	96.8	87.7	2725	2265	460	50	9	2	0	1
V2.78	1149476000	1036810860	452316293	175.16	99.8	97.4	90.9	2660	2206	454	56	14	0	0	1
V2.79	553319000	493066518	241368038	93.42	99.8	94.1	75.6	2647	2200	447	59	15	1	1	1
V2.80	1209526800	999910832	436988783	169.13	99.8	97.4	90.6	2568	2129	439	39	2	2	0	1
V2.81	848366200	739270269	340597891	132	99.8	96.9	87.2	2893	2410	483	72	15	1	2	2
V2.82	952025200	842805360	391452746	151.82	99.7	97	89.2	3263	2741	522	125	18	6	0	2
V2.83	1281135400	1159643658	485024670	188.02	99.8	97.4	91.2	2576	2143	433	49	16	3	0	1
V2.84	1642417600	1457576294	591501793	229.36	99.9	98.4	94.8	2755	2256	499	57	17	2	0	2
V2.85	1391188600	1239369834	534937296	207.52	99.8	98.1	93.9	2802	2334	468	80	11	0	0	1
V2.86	1498139000	1280633352	550946548	213.44	99.8	98	93.9	2780	2312	468	83	23	2	1	1
V2.87	2070727600	1871514233	738939121	286.94	99.9	98.6	95.9	2733	2255	478	63	13	3	1	1
V2.88	2083217200	1871302407	781453864	302.93	99.9	98.6	96.2	2825	2358	467	87	16	2	0	1
V2.89	1101851800	939454646	425625286	165.26	99.8	97.9	91.8	2835	2328	507	79	16	3	0	1
V2.90	1384881400	1233825394	538855687	208.95	99.9	98.2	93.7	2676	2220	456	68	18	2	1	2
V2.91	1933795600	1759986293	759672348	294.62	99.8	98.5	95.9	2598	2160	438	62	20	4	0	1
V2.92	1122398800	999746160	452635262	175.43	99.9	97.9	91.7	2783	2313	470	55	12	0	0	1
V2.93	901247800	798025190	378901767	146.81	99.9	97.1	88.4	2728	2259	469	64	15	3	1	1
V2.94	1181614200	1040532507	455503452	176.51	99.9	97.7	91.3	2703	2228	475	47	12	2	0	1
V2.95	1935740600	1749394743	743850497	288.45	99.9	98.6	96	2811	2317	494	52	11	0	0	1

\*filtered: variants that passed the following criteria: allele frequency < 1% in dbSNP137, 1000 genomes, Exome Variant Server, and in-house database;  $^{\circ}$ includes only reads with MQ > 30

**Supplementary Table 8. Comparison of sequence coverage of the targeted regions achieved with v2.0 of our NGS gene panel and that of the same regions achieved by whole exome sequencing in 8 random samples with a similar capture/sequencing protocol and bioinformatics pipeline**

		<b>Targeted NGS gene panel (v2.0)</b>	<b>V5</b>
Mean coverage (X)	Overall	178.90	100.84
	Diagnosis sub-panel	211.17	102.62
	Discovery sub-panel	175.35	99.97
% reads >= 20X	Overall	97.23	89.09
	Diagnosis sub-panel	99.41	89.14
	Discovery sub-panel	96.65	89.06
% reads >= 50X	Overall	89.39	70.25
	Diagnosis sub-panel	97.01	70.96
	Discovery sub-panel	87.63	69.91

Coverage calculations include only high-quality mapped reads (MQ > 30); V5: Agilent SureSelect V5 (Agilent, Santa Clara, USA)

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