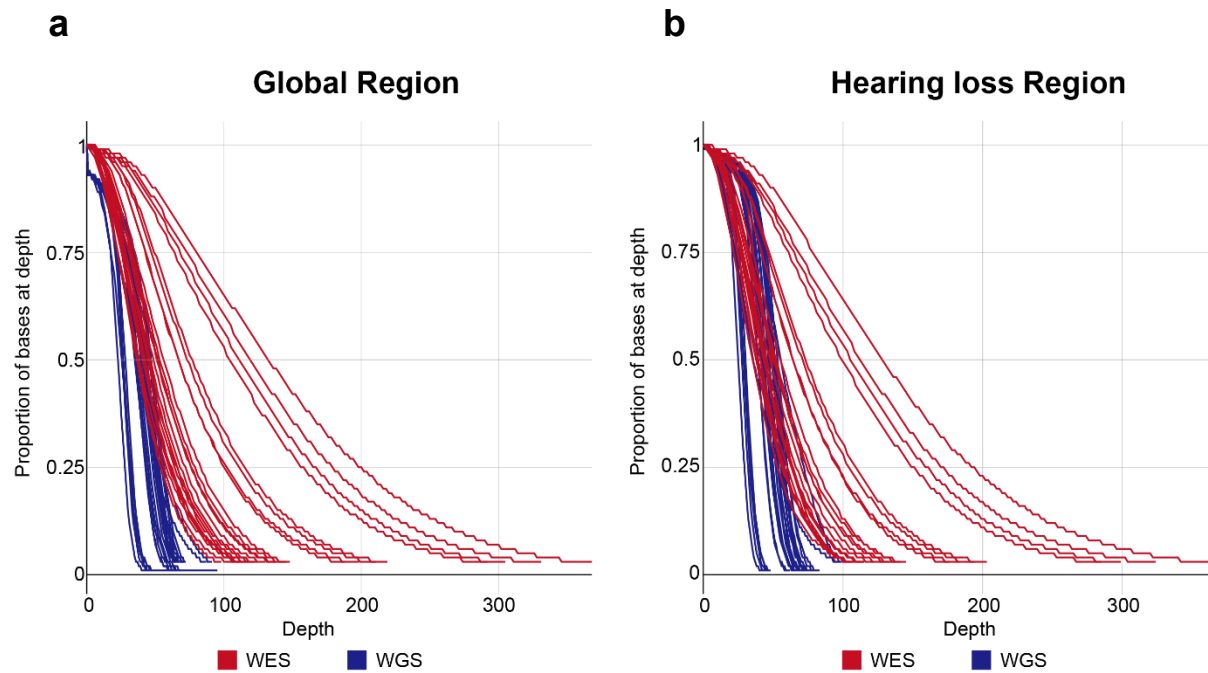
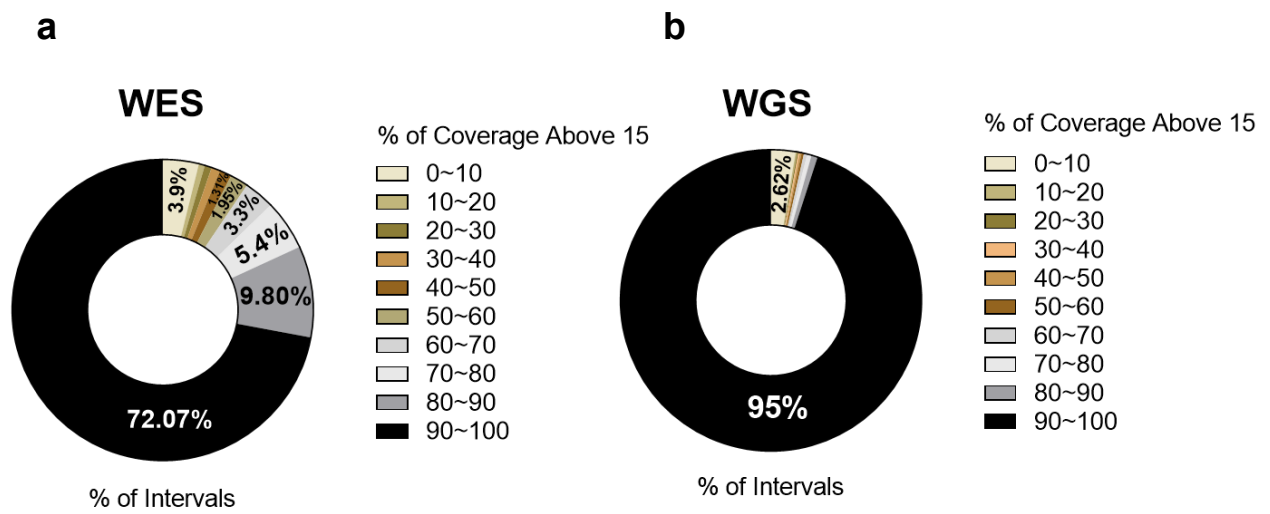




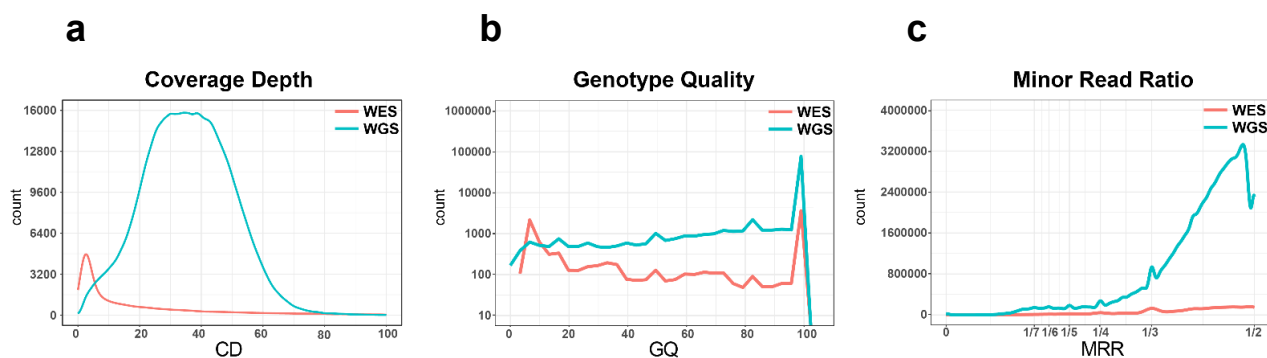
Supplementary Fig. 1. Sequencing depth of samples both screened by WES and WGS

a Sequencing depth of samples screened by WES and WGS over entire genomic region and **b** genomic regions associated with hearing loss. As of WES, an Agilent SureSelect V5 enrichment capture bed was given as interval options and the depth of corresponding regions was calculated, blue; WGS, red; WES



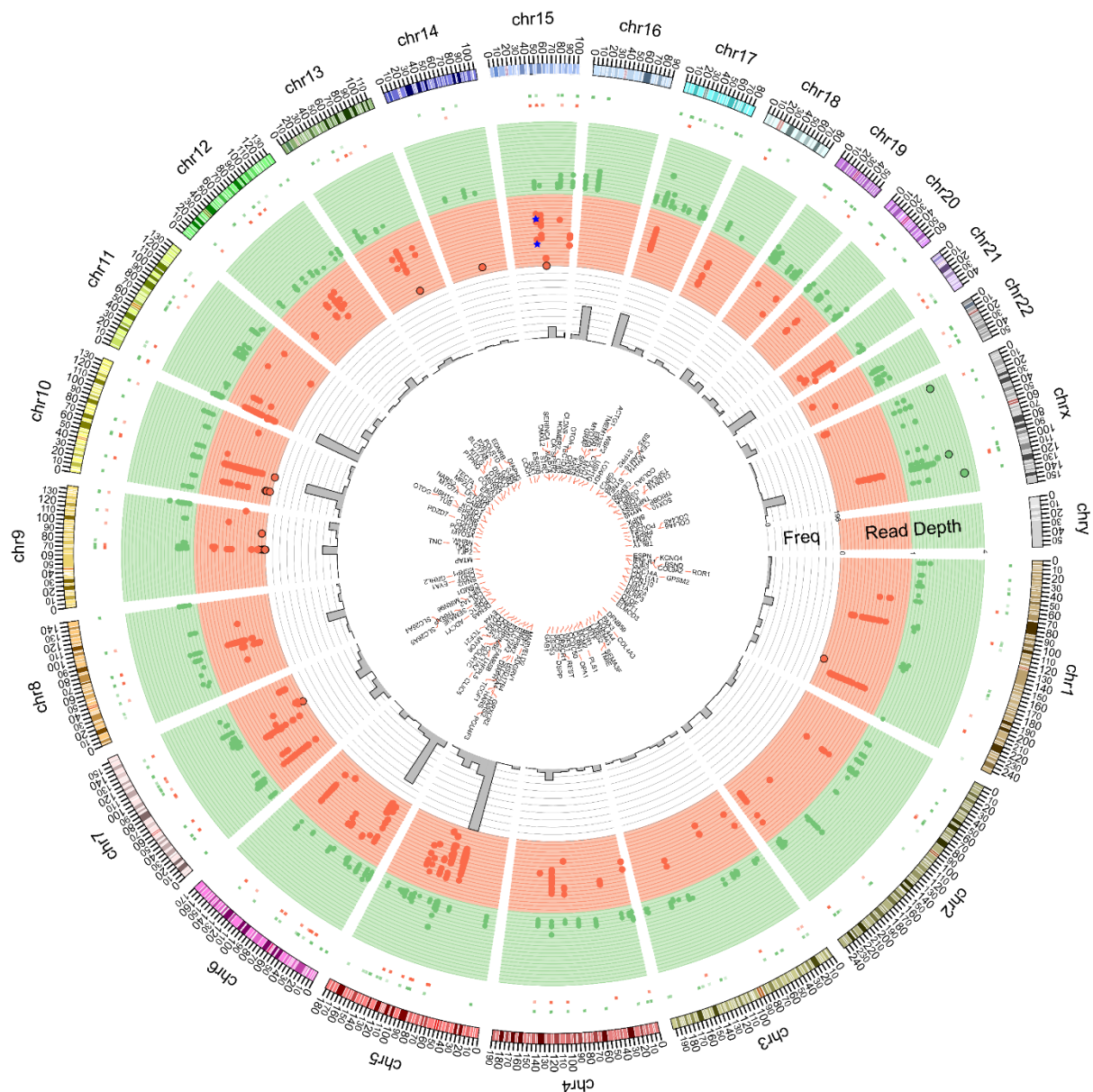
Supplementary Fig. 2. Coverage of genes associated with hearing loss in WES and WGS

A pie plot representing the distribution of percentage of intervals corresponding to certain coverage by WES (**a**) and WGS (**b**) over regions associated with hearing loss. Detailed methods of coverage calculations are described in the method section.



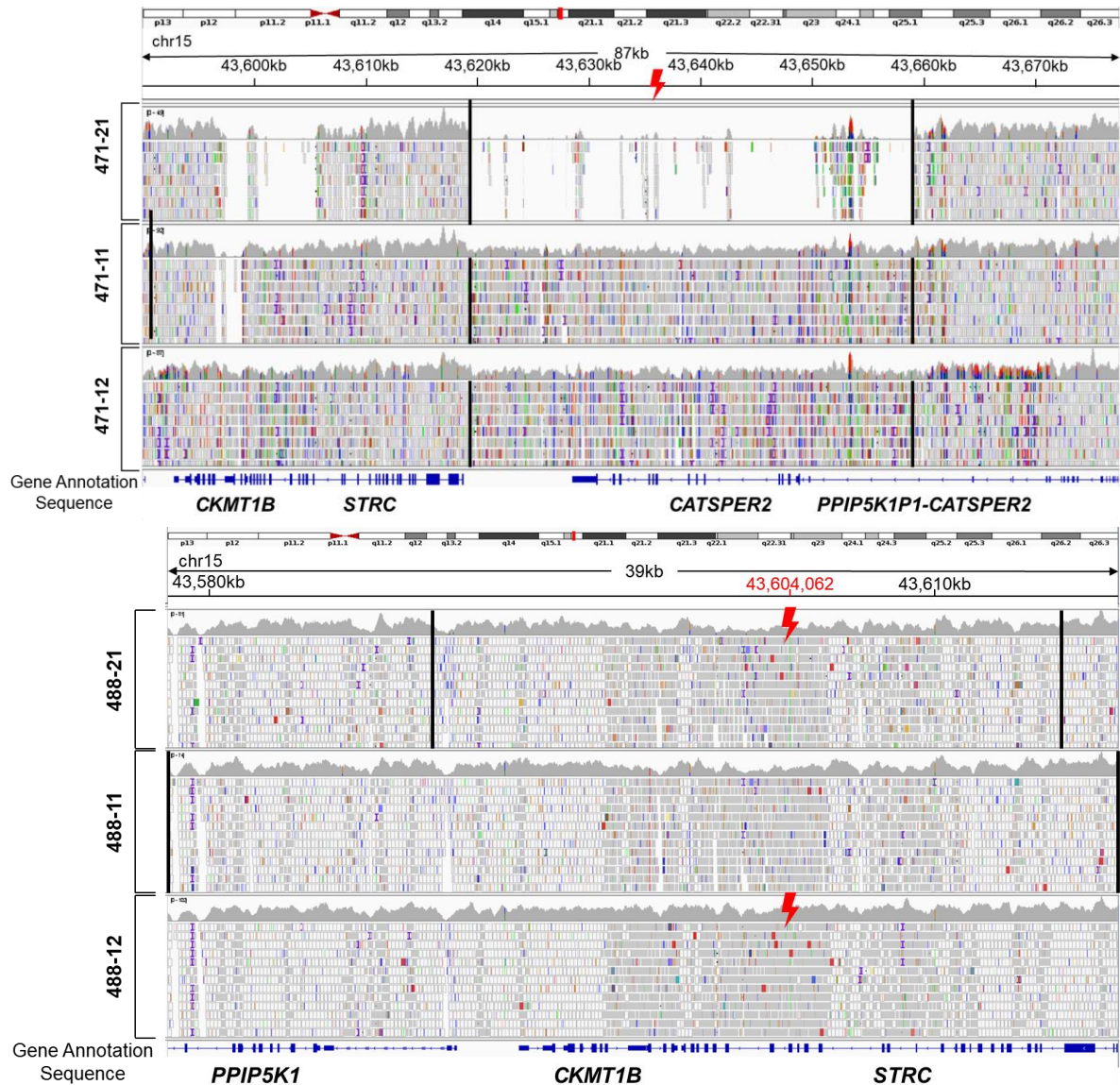
Supplementary Fig. 3. Distribution of the three main quality parameters for the variants detected by WES or WGS in genes associated with hearing loss

Distribution of the three main quality parameters for the variants in hearing loss associated regions detected by WES or WGS. **(a)** Coverage depth (CD), **(b)** genotype quality (GQ) score, and **(c)** minor-read ratio (MRR). Coverage depth (CD), corresponding to the number of aligned reads covering a single position; and genotype quality (GQ), indicates accuracy of genotype calls. The minor-read ratio (MRR) is defined as the ratio of reads for the less covered allele (reference or variant allele) over the total number of reads covering the position at which the variant was called. For each of the three parameters, the average of samples both undergone WES (red) and the six WGS (turquoise) were plotted.



Supplementary Fig. 4. Genome-wide circos plot of total detected CNVs of WGS samples

A circos plot of human whole genome with total detected copy number variants (CNVs) in the study. The innermost part of the circle represents genes associated with hearing loss. Scatter plot and heatmap represent read depth of total detected CNVs from the analysis. Green color represents duplication and red color represents deletion, respectively. Putative pathogenic homozygous deletion of YUHL471-21 and heterozygous deletion of YUHL488-21 in *STRC* region are plotted as blue star. A histogram represents the number of patients harboring variants present in a region when the chromosome is divided into 2,000kbp bins.



Supplementary Fig. 5. Visualization of detected gross copy number deletions in YUHL 471 and YUHL 488 trios

Integrative Genomics Viewer images of the copy number deletions in *STRC* gene regions of YUHL471 and YUHL488 trios. The sequencing coverage (top) and sequencing reads (bottom) are shown. The called regions are bordered by two black lines, -21; proband, -11; father, -12; mother

Supplementary Table 1. Demographics of patients screened by WES and WGS

Clinical characteristics		WGS	WES
Age of Onset	Pre	57/140 (40.7%)	85/437 (19.4%)
	Post	83/140 (59.3%)	347/437 (79.4%)
	Unknown	0/140 (0%)	5/437 (1.1%)
Mode of Inheritance	AD XL	47/140 (33.6%)	196/437 (44.9%)
	AR	93/140 (66.4%)	240/437 (54.9%)
	Unknown	0/140 (0%)	1/437 (0.2%)
Simplex/Multiplex	Simplex	58/140 (41.4%)	152/437 (34.8%)
	Multiplex	82/140 (58.6%)	285/437 (65.2%)
Syndromic Feature	SHL	5/140 (3.6%)	16/437 (3.7%)
	NSHL	135/140 (96.4%)	417/437 (95.4%)
	Unknown	0/140 (0%)	4/437 (0.9%)
Severity	Mild	11/140 (7.9%)	47/437 (10.8%)
	Moderate	52/140 (37.1%)	236/437 (54%)
	Severe	22/140 (15.7%)	61/437 (14%)
	Profound	55/140 (39.3%)	91/437 (20.8%)
	Unknown	0/140 (0%)	2/437 (0.5%)
Vertigo	Yes	31/140 (22.1%)	109/437 (24.9%)
	No	109/140 (77.9%)	310/437 (70.9%)
	Unknown	0/140 (0%)	18/437 (4.1%)

Supplementary Table 2. Variants information of diagnosed patients by WGS.

Patient ^a	Gene	hg38	Accession	cDNA	Amino acid	Conservation	dbSNP ^b	Zygosity	gnomAD MAF ^c	gnomAD EAS ^d	gnomAD D KOR ^e	Mutation Taster ^f	PP2 ^g	SIFT ^h	CAD ⁱ	DV ^j	Clinvar ^k	ACMG Classification ^l
YUHL9 5-21	MYO1 5A	chr17:18119700_T/-	NM_01623 9.4	c.900delT	p.P301Rfs*143	-	rs21422242 418	Het	0.0000006 211	0.000022 31	-	-	-	-	-	-	-	LP (PVS1,PM2)
		chr17:18119978_-/C		c.1179dupC	p.E396Rfs*35	-	rs7725365 99	Het	0.0000322 5	0.000245 6	0.00131 0	-	-	-	-	P	P	LP (PVS1,PM2)
YUHL2 31-21	MYO1 5A	chr17:18157832_C/T	NM_01623 9.4	c.C889T	p.R2967*	-	rs9444870 15	Het	0.0000037 71	0	0	A (0.81)	-	-	35	VUS	-	LP (PVS1,PM2)
		chr17:18172203_C/G		c.C10263G	p.I342M	<i>Danio rerio</i>	rs7482464 42	Het	0.0000390 3	0.001381	0.00131 0	DC (0.488)	Dam (0.62 1)	Del (0.01)	23.6	LP	-	VUS (PM2_Supporting)
YUHL7 28-21	MYO1 5A	chr17:18119978_-/C	NM_01623 9.4	c.1179dupC	p.E396Rfs*35	-	rs7725365 99	Hom	0.0000322 5	0.000245 6	0.00131 0	-	-	-	-	P	P	LP (PVS1,PM2)
YUHL 748-21	MYO1 5A	chr17:18172203_C/G	NM_01623 9.4	c.C10263G	p.I342M	<i>Danio rerio</i>	rs7482464 42	Het	0.0000390 3	0.001381	0.00131 0	DC (0.488)	Dam (0.62 1)	Del (0.01)	23.6	LP	-	VUS (PM2_Supporting)
		chr17:18172292_T/G		c.10350+2T >G	-	-	rs7601484 86	Het	0.0000006 195	0.000022 28	0.00026 19	-	-	-	24.5	VUS	-	LP (PVS1,PM2)
YUHL 488-21	STRC	chr15:43604062_G/A	NM_15370 0.2	c.C4309T	p.Q1437*	-	rs7692461 94	Hemi	0.0000049 59-	0	0	A (1)	-	-	335	-	VUS	LP (PVS1,PM2)
YUHL 85-21	CDH23	chr10:71570884_C/T	NM_02212 4.6	c. C719T	p.P240L	<i>Danio rerio</i>	rs1219083 54	Het	0.0000334 6	0.001203	0.00235 7	A (1)	Dam (0.98)	Tol (0.05)	24.6	P	P	VUS (PM2_Supporting)
		chr10:71805818_CGCT CCAA/-		c.7887_789 4del	p.S2630Vfs *10	-	-	Het	-	-	-	-	-	-	-	-	-	LP (PVS1,PM2)
YUHL 1118-21	CDH2 3	chr10:71807606_C/T	NM_02212 4.6	c.C8399T	p.S2800F	<i>Danio rerio</i>	-	Het	-	-	-	DC (0.81)	Dam (0.77 4)	Del (0.47 7)	25.5	-	-	VUS (PM2)
		chr10:71803233_C/T		c.C7685T	p.S2562L	<i>Xenopus tropicalis</i>	rs5384357 11	Het	0.0000262 0	0.000045 09	0.00028 69	DC (0.81)	Ben (0.15 4)	Del (0.50 6)	28.3	VUS	VUS	VUS (PM2_Supporting, BP4)

YUHL 844-21	<i>USH2A</i>	chr1:215674796- 215674799_ATTT/ -	NM_206933.4	c.13112_13115p.Q4371Rfs* del 19	-	-	rs7681613He	0.0000061	0.000089	0.00078	-	-	-	33	P/LP	P	LP (PVS1,PM2)
		chr1:216086749_ G/A		c.C4957T	p.R1653*	-	rs7547688He	0.0000117	0.000066	0	A (1)	-	-	33	P/LP	P	LP (PVS1,PM2)
YUHL 1133- 21	<i>USH2A</i>	chr1:215877882_T /C	NM_206933.4	c.8559-2A>G	-	-	rs3975180He	0.0000099	0.000334	0.00078	-	-	-	34	P	P	VUS (PVS1_Moderate,PM2_Supp orting)
		chr1:216246592_ A/C		c.T2802G	p.C934W	<i>Danio rerio</i>	rs2015276He	0.0000904	0.002564	0.00368	DC (1)	Dam (0.99 9)	Del (0)	25. 5	P/LP	VU S	VUS (PP3,BS1_Supporting)
YUHL 603-21	<i>ILDR1</i>	chr3:122001823_ C/G	NM_00119979 9.2	c.G421C	p.G141R	<i>Danio rerio</i>	rs7651368He	0.0000173	0.000623	0.00052	DC (1)	Dam (0.99 9)	Del (0)	26. 4	-	P	VUS (BS1_Supporting)
		chr3:121725861_ G/T		c.C206A	p.P69H	<i>Danio rerio</i>	rs7544925He	0.0000074	0.000245	0.00026	DC (1)	Dam (0.99 8)	Del (0)	26. 8	-	P	VUS (PM2_Supporting,PP3)
YUHL 239-21	<i>TRIOB P</i>	chr22:37726245_ C/T	NM_00103914 1.3	c.C3689T	p.P390L	<i>Mus muscul us</i>	rs2006658He	0.0000508	0.001761	0.00157	DC (0.9 9)	Dam (0.98 9)	Del (0)	27. 6	-	VU S	VUS (PM2_Supporting)
		chr22:37759248_ C/T		c.C6308T	p.P2103L	<i>Mus muscul us</i>	rs2002500He	0.0000905	0.001805	0.00157	DC (0.9 6)	Ben (0.24)	Tol (0.1 2)	27. 6	VUS	-	VUS (PM2_Supporting,BP4)
YUHL 438-21	<i>TWNK</i>	chr10:100989382_ G/A	NM_021830.5	c.G1172A	p.R391H	<i>Mus muscul us</i>	rs5564456He	0.0000285	0.000289	0.00052	DC (0.6 8)	Dam (0.83 6)	Del (0.0 4)	23. 4	P/VUS/ LB	VU S	VUS (PM1,PM2_Supporting,PP3)
		chr10:100989406_ A/G		c.A1196G	p.N399S	<i>Danio rerio</i>	rs8632239He	0.0000074	0.000022	0	DC (0.9 9)	Dam (0.89 6)	Tol (0.0 7)	21. 9	P/LP/V US	P	VUS (PM1,PM2)
YUHL 742-21	<i>LOXH D1</i>	chr18:46534334_ C/T	NM_144612	c.4212+1G>A	-	-	rs8891109He	0.0000238	0.000708	0.00267	-	-	-	24. 2	-	P	VUS (PVS1_Moderate, PM2_Supporting)
		chr18:46579680_ G/A		c.C1759T	p.R587W	<i>Danio rerio</i>	rs5401006He	0.0000715	0.000122	0	DC (0.9 3)	Dam (0.99 9)	Del (0)	33	VUS	LP	VUS (PM2)
YUHL2 0-21	<i>CHD7</i>	chr8:60860946_ /C	NM_017780	c.7652dupC	p.P2553Tfs* 22	-	-	He t	-	-	-	-	-	33	P	P	LP (PVS1,PM2)

YUH L 67-21	<i>CHD7</i>	chr8:60742366_C/T	NM_017780	c.C934T	p.R312*	-	-	He t	-	-	-	A (1)	-	-	37	P	P	LP (PVS1,PM2)
YUH L 199-21	<i>CHD7</i>	chr8:60853179_C/T	NM_017780	c.C6454T	p.Q2152*	-	-	He t	-	-	-	A (1)	-	-	40	P	P	LP (PVS1,PM2)
YUH L 477-21	<i>TECTA</i>	chr11:121109260_C/T	NM_005422	c.C248T	p.T83M	<i>Danio rerio</i>	rs145898158	He t	0.00009789	0.0001114	0.0002621	DC (1)	Dam (0.899)	Del (0.518)	27.1	P/VUS/LB	LP	VUS (PM2)
YUH L 749-21	<i>TECTA</i>	chr11:121113638_C/T	NM_005422	c.C710T	p.T237I	<i>Danio rerio</i>	-	He t	-	-	-	DC (0.99)	Dam (0.999)	Del (0)	25.8	-	P	VUS (PM2, PP3)
YUH L 1113-21	<i>KCNQ4</i>	chr1:40784233_T/C	NM_004700	c.T140C	p.L47P	<i>Danio rerio</i>	rs1271250198	He t	0.00002544	0.001156	-	DC (0.81)	Ben (0.093)	Tol (0.365)	16.52	P	P	VUS (PM2)
YUH L 1119-21	<i>KCNQ4</i>	chr1:40784233_T/C	NM_004700	c.T140C	p.L47P	<i>Danio rerio</i>	rs1271250198	He t	0.00002544	0.001156	-	DC (0.81)	Ben (0.093)	Tol (0.365)	16.52	P	P	VUS (PM2)
YUH L 464-21	<i>POU4F3</i>	chr5:146339986_C/G	NM_002700.3	c.C559G	p.L187V	<i>Danio rerio</i>	rs1200909411	He t	0.000001860	0.00006685	0	DC (1)	Dam (0.999)	Del (0)	26.5	-	VUS	VUS (PM2, PP3)
YUH L 1136-21	<i>POU4F3</i>	chr5:146340390_G/C	NM_002700.3	c.G963C	p.W321C	<i>Danio rerio</i>	-	He t	-	-	-	DC (1)	Dam (1)	Del (0)	32	-	-	VUS (PM2, PP3)
YUH L 1143-21	<i>WFS1</i>	chr4:6301752_C/T	NM_006005.3	c.C1957T	p.R653C	<i>Xenopus tropicalis</i>	rs201064551	He t	0.0002832	0.0008468	0.001048	DC (1)	Dam (0.953)	Del (0.007)	33	LP/VUS/LB	LP	VUS (PP3, BS1)
YUH L 187-21	<i>GRHL2</i>	chr8:102643941_A/G	NM_024915.4	c.A1334G	p.Q445R	<i>Xenopus tropicalis</i>	rs145717789	He t	0.00003224	0.001137	0.0005311	N (0.7)	Ben (0)	Tol (0.62)	17.64	-	LP	VUS (BP4)
YUH L 975-21	<i>MYO7A</i>	chr11:77156018_C/G	NM_000260.4	c.C397G	p.H133D	<i>Danio rerio</i>	rs111033403	He t	0.0000006196	0	0	DC (1)	Dam (0.998)	Del (0.04)	27.3	VUS	P	VUS (PM2, PM5, PP3)
YUH L 1107-21	<i>MYH9</i>	chr22:36285744_G/A	NM_002473.6	c.C5188T	p.R1730C	<i>Danio rerio</i>	rs201021615	He t	0.00007197	0.001205	0.0005297	DC (1)	Dam (0.952)	Del (0)	32	VUS	P	VUS (PP3, BS1)

YUH L 1153- 21	MYH14	chr19:50292309_C/T	NM_001145809. 2	c.C5176T	p.R1726 W	Danio rerio	rs372062358	He t	0.00002252	0.0002036	0.000563 1	DC (0.96)	Dam (0.989)	Del (0)	33	VUS	P	VUS (-)
YUH L 301- 21	DIAPH1	chr5:141576797_A/T	NM_005219.5	c.T1355A	p.F452Y	Xenopus tropicalis	rs757579900	He t	0.000000619 6	0.0000222 8	0.000261 9	DC (0.99)	Dam (0.855)	Del (0)	28.1	-	VUS S	VUS (PM2, PP3)
YUH L 174- 21	LMX1A	chr1:165249528_C/T	NM_001174069. 2	c.G376A	p.E126K	Gallus gallus	rs376042184	He t	0.000004956	0.0001114	0.000261 9	DC (0.99)	Dam (0.713)	Tol (0.13)	24.9	-	VUS S	VUS (PM2)
YUH L 609- 21	SEMA3 E	chr7:83490113_C/T	NM_001178129. 2	c.96+1G> A	-	-	-	He t	-	-	-	-	-	-	33	-	-	VUS (PM2)

A, automated; AD, autosomal dominant; AR, autosomal recessive; Ben, benign; Dam, probably damaging; Del, deleterious; DC, disease-causing; Het, heterozygous in the affected individual; Hom, homozygous in the affected individual; **Hemi, hemizygous in the affected individual**; LP, likely pathogenic; P, pathogenic; Tol, tolerated; VUS, variant of unknown significance;

^aIndividual indicate affected patients in whom variants were found, comprising one case cohort.

^bdbSNP database (<http://www.ncbi.nlm.nih.gov/SNP>).

^{c,d,e}Population frequency of variants in gnomAD, EAS(East Asian) and KOR(Korean) database (<https://gnomad.broadinstitute.org/>).

^fMutationTaster (<http://www.mutationtaster.org/>).

^gPolyPhen-2 HumVar prediction score (<http://genetics.bwh.harvard.edu/pph2/>).

^hSIFT Sorting Intolerant from Tolerant (<http://sift.jcvi.org/>).

ⁱphred-like scores (scaled C-scores) on the Combined Annotation-Dependent Depletion (<http://cadd.gs.washington.edu/home/>).

^jDVD, Deafness variation database. (<https://deafnessvariationdatabase.org/>)

^kClinvar, public archive with free access to reports on the relationships between human variations and phenotypes, with supporting evidence. (<https://www.ncbi.nlm.nih.gov/clinvar/>).

^lClassifications of variants are based on VIP-HL (<http://hearing.genetics.bgi.com/>), an online platform for classifying variants according to the ACMG guidelines adapted for hearing loss.

Supplementary Table 3. Splice-altering variant candidates detected in WGS.

Patient ^a	Gene	Position (hg38)	cDNA position	SpliceAI Delta Score ^b				SpliceAI Delta Position ^c			
				Accept or Gain	Accept or Loss	Donor Gain	Donor Loss	Accept or Gain	Accept or Loss	Donor Gain	Donor Loss
YUHL121-21	<i>EYA1</i>	chr8:71299239_A/T	c.640-6T>A	0.98	0.63	0	0	-2	-6	-1	-36
YUHL704-21	<i>CDH23</i>	chr10:71791123_G/A	c.6050-9G>A	0.99	0.83	0	0	2	9	8	24
		chr10:71790959_G/A	c.6050-173G>A	0	0	0.63	0	-3	13	1	13
YUHL34-21	<i>TECTA</i>	chr11:121137419_A/G	c.2942-2A>G	0.16	0.88	0	0	10	2	17	2
YUHL183-21	<i>LMX1A</i>	chr1:165353091_T/C	c.248A>G	0	0	0.91	0.1	-1	13	0	-15
YUHL209-21	<i>MYO15A</i>	chr17:18136900_G/C	c.4779+214G>C	0.15	0	0	0	-34	0	-36	0
YUHL615-21	<i>OTOA</i>	chr16:21700868_C/A	c.841-20C>A	0.28	0.11	0	0	2	20	20	28
YUHL1049-21	<i>OTOG</i>	chr11:17556178_A/G	c.695+281A>G	0	0	0.32	0	-46	-22	-1	41
		chr11:17593310_G/T	c.3160G>T	0	0	0	0.28	17	-46	-2	17
YUHL1123-21	<i>CDH23</i>	chr10:71702283_G/A	c.2587+72G>A	0	0	0.26	0	-31	49	1	-16
		chr10:71489118_G/A	c.146-20964G>A	0.21	0	0	0	2	4	2	-38
YUHL1156-21	<i>MYO7A</i>	chr11:77213610_G/T	c.4779+214G>C	0.12	0	0.02	0	10	1	9	-5
YUHL1157-21	<i>OTOF</i>	chr2:26486603_G/A	c.1046-1970C>T	0.23	0	0.1	0	-14	45	-45	45
		chr2:26465009_C/T	c.4820G>A	0.59	0	0	0	-2	20	-2	-47

^aIndividual indicate affected patients in whom variants were found, comprising one case cohort.

^b Delta score of a variant, defined as the maximum of (DS_AG, DS_AL, DS_DG, DS_DL), ranges from 0 to 1 and can be interpreted as the probability of the variant being splice-altering.

^c Delta position conveys information about the location where splicing changes relative to the variant position (positive values are downstream of the variant, negative values are upstream).

Supplementary Table 4. Mitochondrial variant candidates detected in WGS.

Patient ^a	Gene	Position	DVD ^b	gnomAD ^c		Mitomap ^d				
				homoplasmic AF	heteroplasmic AF	Count	Coverage	status	GBCNT	GBFREQ
YUHL390-21						4572	4572			
YUHL681-21	<i>MT-RNR1</i>	chrM:1555_A/G	P	0.001117	0.000195	2022	2022	Cfrm	80	0.14
YUHL847-21						1346	1347			
YUHL58-21	<i>MT-CO1</i>	chrM:7444_G/A	B	0.005353	0.0001772	2714	2716	Reported	194	0.34
YUHL1112-21	<i>MT-ND1</i>	chrM:3396_T/C	LB	0.01508	0.0001241	2363	2363	Reported	420	0.74
YUHL972-21	<i>MT-RNR1</i>	chrM:1310_C/T	LB	0.0003367	0	8657	8660	Reported	38	0.07
YUHL560-21						2439	2459			
YUHL1137-21	<i>MT-TW</i>	chrM:5558_A/G	-	0.002375	0.0007089	3126	3127	Reported	106	0.19
YUHL1137-21	<i>MT-TC</i>	chrM:5821_G/A	-	0.002588	0.0001063	2894	2898	Reported	339	0.60
YUHL1148-21	<i>MT-TR</i>	chrM:10454_T/C	-	0.003987	0.00001772	1853	1853	Reported	190	0.33
YUHL1168-21						2236	2236			
YUHL1173-21	<i>MT-ND5</i>	chrM:13528_A/G	-	0.002091	0.00005317	2478	2481	Reported	72	0.18
YUHL188-21						740	742			
YUHL566-21	<i>MT-TE1</i>	chrM:14693_A/G	-	0.001932	0.00007089	4563	4564	Reported	329	0.58
YUHL681-21						1776	1776			
YUHL1174-21	<i>MT-TT</i>	chrM:15901_A/G	-	0.00005316	0	1667	1667	Reported	9	0.02

GBCNT; Count of allele count of control data from GenBank; GBFREQ; GBFREQ; allele frequency from GenBank

^aIndividual indicate affected patients in whom variants were found, comprising one case cohort.

^bDVD, Deafness variation database. (<https://deafnessvariationdatabase.org/>)

^cPopulation frequency of variants in gnomAD database (<https://gnomad.broadinstitute.org/>).

^dMitomap, a human mitochondrial genome database (<https://www.mitomap.org/MITOMAP>).

Supplementary Table 5. Clinical characteristics of patients harboring the m.1555A>G & m.7444G>A mutation

Patient ^a	Inheritance	Onset	Sideness	Severity	Progressiveness	PTA(dBHL)		Pattern	Exposure to Aminoglycoside	Additional history
						Right	Left			
YUHL390-21	Familial	Congenital	both	profound	stable	107.5	120	flat	No	-
YUHL681-21	Familial	Mid 20s	both	moderate	progressive	46.25	46.25	ski-sloping	No	Hearing loss of mother initiated after antibiotics administration
YUHL847-21	Familial	Late 40s	both	profound (Rt) / mild (Lt)	progressive	118.75	25	flat	No	
YUHL58-21	Familial	Early 0s	both	moderate	progressive	47.5	48.75	flat	No	-

PTA; Pure Tone Audiometry

^aIndividual indicate affected patients in whom variants were found, comprising one case cohort.

Supplementary Table 6. Copy number variant candidates detected in WGS.

Patient ^a	Gene	Chromosome	Start	End	SV length	SV type	Read Depth	GT:CN	Location	gnomAD AF ^b	AnnotSV ranking ^c
YUHL471-21	<i>STRC</i>	15	43564001	43697200	-133200	DEL	0.319508	0/1:1	txStart-txEnd	0.0001381	5
YUHL488-21	<i>STRC</i>	15	43589201	43615200	-26000	DEL	0.653585	0/1:1	intron4-txEnd	-	5
YUHL488-11	<i>STRC</i>	15	43578301	43617600	-39300	DEL	0.676284	0/1:1	exon2-txEnd	-	5
YUHL58-21	<i>STRC</i>	15	43562601	43653400	-90800	DEL	0.610974	0/1:1	txStart-txEnd	0.0001381	5
YUHL284-21	<i>COL1A1</i>	17	50184401	50185600	-1200	DEL	0.335734	0/1:1	exon51-exon51	-	4
YUHL827-21	<i>CHD7</i>	8	60678601	60679800	-1200	DEL	0.124248	1/1:0	txStart-intron1	-	4
YUHL843-21	<i>PTPRQ</i>	12	80601751	80620050	-18300	DEL	0.612192	0/1:1	intron26-intron31	0.00001586	4
YUHL972-21	<i>CHD7</i>	8	60678451	60680700	-2250	DEL	0.258161	1/1:0	txStart-intron1	0.0003103	4
YUHL975-21	<i>SLC12A2</i>	5	128083351	128084400	-1050	DEL	0.372807	0/1:1	txStart-exon1	-	4
YUHL1131-21	<i>ABHD12</i>	20	25384201	25428150	-43950	DEL	0.503705	0/1:1	txStart-intron1	0.000007931	4
YUHL1113-21	<i>PTPRQ</i>	12	80464201	80479200	-15000	DEL	0.500758	0/1:1	intron6-intron8	0.000007931	3

CN, copy number; GT; zygosity, 0/1 indicates heterozygous variant and 1/1 indicates homozygous variant; SV, structural variant

^aIndividual indicate affected patients in whom variants were found, comprising one case cohort.

^bPopulation frequency of variants in gnomAD (<https://gnomad.broadinstitute.org/>).

^cA ranking score to assess SV pathogenicity by the joint consensus recommendation of ACMG and ClinGen (Riggs et al., 2020). Data are available from (<https://lbgi.fr/AnnotSV/>)

Supplementary Table 7. Transposable element insertion candidates detected in WGS.

Patient ^a	Gene	Position (hg38)	TSD	Type	Subtype	GT	AF_DISC	LCOV	RCOV
YUHL1109-21	<i>SLC17A8</i>	chr12:100371388	AAAAAAAAGTCTCTG	Alu	two_side_tprt_both	0/1	37	29.285	36.31
YUHL471-21	<i>CDH23</i>	chr10:71433771	CCCTCTCAGCTCTACTTTG	Alu	two_side_tprt_both	1/1	30	16.04	33.3
YUHL 1107-21							59	48.7	35.96
YUHL847-21	<i>EYA1</i>	chr8:71561825	CTGAAAGTTTT	Alu	two_side_tprt_both	0/1	16	18.385	23.435
YUHL239-21	<i>PAX3</i>	chr2:222255919	TTTTTTTTTTTTTTTTTTTTTTGT	Alu	two_side_tprt_both	0/1	16	31.805	26.895
YUHL1112-21	<i>PAX3</i>	chr2:222226161	AGAAAGAGAATTCGC	Alu	two_side_tprt_both	0/1	28	47.095	35.925
YUHL1148-21	<i>TMC1</i>	chr9:72584784	TTTTTTTTTTTTTTTTTTTT	Alu	two_side_tprt_both	0/1	21	34.52	31.575

AF_DISC, Number of effective discordant pairs (for estimated allele frequency); GT, zygosity and 0/1 indicates heterozygous variant; LCOV, Left focal coverage; RCOV, Right focal coverage; TSD, target site duplication; Type, type of structural variant; two_side_tprt_both, two-sided target-primed reverse transcription (TPRT);

^aIndividual indicate affected patients in whom variants were found, comprising one case cohort.

Supplementary Table 8. Cis-regulatory variant candidates detected in WGS.

Patient ^a	Gene	Position (hg38)	cDNA position	dbSNP ^b	gnomAD MAF ^c	CADD ^d	Clinvar ^e	DVD ^f	Regulatory Feature ^g
YUHL26-21	<i>CDH23</i>	chr10:71548093_C/G	c.430-18649C>G	rs1184115420	0.00001314	17.4	-	-	Distal-enhancer like signature, CTCF-bound
YUHL518-21	<i>OTOF</i>	chr2:26491893_A/G	c.898-2153T>C	-	-	4.469	-	-	Distal-enhancer like signature
YUHL470-21	<i>MYO6</i>	chr6:75842807_T/C	c.816+1429T>C	-	-	14.2	-	-	Distal-enhancer like signature
YUHL1123-21	<i>WHRN</i>	chr9:114473312_C/T	c.837+5241G>A	rs572787776	0.0001445	0.533	-	VUS	Distal-enhancer like signature, CTCF-bound
YUHL1148-21	<i>COL4A4</i>	chr2:227065324_G/C	c.1988-2726C>G	rs1444994654	0.00002627	2.03	-	VUS	Distal-enhancer like signature, CTCF-bound
YUHL1156-21	<i>CDH23</i>	chr10:71621341_T/C	c.1134+3948T>C	-	-	0.074	-	-	Distal-enhancer like signature, CTCF-bound

VUS, variant of unknown significance

^aIndividual indicate affected patients in whom variants were found, comprising one case cohort.

^bdbSNP database (<http://www.ncbi.nlm.nih.gov/SNP>).

^cPopulation frequency of variants in gnomAD database (<https://gnomad.broadinstitute.org/>).

^dphred-like scores (scaled C-scores) on the Combined Annotation-Dependent Depletion (<http://cadd.gs.washington.edu/home/>).

^eClinvar, public archive with free access to reports on the relationships between human variations and phenotypes, with supporting evidence (<https://www.ncbi.nlm.nih.gov/clinvar/>).

^fDVD, Deafness variation database. (<https://deafnessvariationdatabase.org/>)

^gRegulatory feature of cis-regulatory element retrieved from SCREEN (Search Candidate cis-Regulatory Elements by ENCODE) database (<https://screen.encodeproject.org/>)

Supplementary Table 9. Variant information of patients screened for CMV infection using WGS.

Patient ^a	Gene	hg38	Accession	cDNA	Amino acid	Conservation	dbSNP ^b	Zygosity	gnomAD MAF ^c	gnomAD EAS ^d	gnomAD KOR ^e	Mutation Taster ^f	PP2 ^g	SIFT ^h	CADD ⁱ	DVD ^j	Clinvar ^k	CMV reads	Aligned portion (%)
YUHL 742-21	LOXH D1	chr18:46534334_C/T	NM_144612	c.4212+1G>A	-	-	rs889110926	Het	0.00002389	0.0007086	0.002674	-	-	-	33	P	-	110,046	0.15% (110,046/71,524580)
		chr18:46579680_G/A		c.C1759T	p.R587W	Danio rerio	rs540100675	Het	0.00007153	0.0001222	0	D(0.933513)	D(0)	-	29.8	LP	VUS		
YUHL 1180-21	KCNQ4	chr1:40784233_C/T	NM_004700	c.T140C	p.L47P	Danio rerio	rs1271250198	Het	0.00002544	0.001156	-	D(1)	B(0.049)	D(0.02)	24.2	P	P	1,610	0.08% (1,610/1,988,346)

AD, autosomal dominant; AR, autosomal recessive; B, benign; D, probably damaging; DC, disease-causing; Del, deleterious; Het, heterozygous in the affected individual; LP, likely pathogenic; P, pathogenic; VUS, variant of unknown significance

^aIndividual indicate affected patients in whom variants were found, comprising one case cohort.

^bdbSNP database (<http://www.ncbi.nlm.nih.gov/SNP>).

^{c,d,e}Population frequency of variants in gnomAD, EAS(East Asian) and KOR(Korean) database (<https://gnomad.broadinstitute.org/>).

^fMutationTaster (<http://www.mutationtaster.org/>).

^gPolyPhen-2 HumVar prediction score (<http://genetics.bwh.harvard.edu/pph2/>).

^hSIFT Sorting Intolerant from Tolerant (<http://sift.jcvi.org/>).

ⁱphred-like scores (scaled C-scores) on the Combined Annotation-Dependent Depletion (<http://cadd.gs.washington.edu/home/>).

^jDVD, Deafness variation database. (<https://deafnessvariationdatabase.org/>)

^kClinvar, public archive with free access to reports on the relationships between human variations and phenotypes, with supporting evidence. (<https://www.ncbi.nlm.nih.gov/clinvar/>).

Supplementary Table 10. Pathogenic variants detected in ACMG SF genes in WGS.

Patient ^a	Gene	hg38	Accession	cDNA	Amino acid	Conservation	dbSNP ^b	Zygosity	gnomAD MAF ^c	gnomAD EAS ^d	gnomAD KOR ^e	Mutation Taster ^f	PP2 ^g	SIFT ^h	CADD ⁱ	DVD ^j	Clinvar ^k	ACMG SF v3.2 ^l
YUHL 1049-21, YUHL 162-21	MUTYH	chr1:45332446 _G/A	NM_001350 650	c.C304T	p.R102C	Danio rerio	rs2004955 64	Het	2.79E-05	0	0.0002 62	DC (0.81)	Dam (0.875)	Del (0.912)	29.5	-	P	MUTYH-associated polyposis (AD)
YUHL 150-21		chr1:45332458 _G/A	NM_001350 650	c.C292T	p.R98W	Danio rerio	rs3412601 3	Het	2.09E-05	0.0003	0	DC (0.81)	Dam (0.971)	Del (0.912)	33	-	P/LP	
YUHL 1049-21, YUHL 1095-21, YUHL 1105-21, YUHL 1118-21, YUHL 1147-21, YUHL 1151-21, YUHL 1156-21, YUHL 1168-21,	MSH2	chr2:47414420 _T/-	NM_001258 281	c.744+2 T>	-	-	rs5877791 94	Het	0.0007	0.0023	-	-	-	-	-	-	LP	Lynch syndrome (AD)
YUHL 827-21	TTN	chr2:17853086 1_G/A	NM_003319	c.C7855 9T	p.R26187*	Danio rerio	-	Het	1.4E-05	0	-	A (0.81)	-	-	69	-	P/LP	Dilated cardiomyo pathy (truncating variants only) AD
YUHL 1153-21	DES	chr2:21942015 0_C/T	NM_001382 708	c.C634T	p.R212*	Danio rerio	rs7815905 60	Het	6.98E-06	0	0	A (0.81)	-	-	38	-	P	Dilated myopathy (AD) Myofibrillar myopathy (AD)
YUHL 827-21	BTBD	chr3:15644487 _C/T	NM_001281 723	c.C571T	p.R191C	Gallus gallus	rs3728446 36	Het	1.4E-05	0	0.0002 62	DC (0.81)	Dam (0.782)	Del (0.784)	34	P	P	Biotinidase deficiency (AR)
YUHL 464-21	BRCA2	chr13:3233287 7_A/T	NM_000059	c.A1399 T	p.K467*	Mus musculus	rs8035842 7	Het	-	-	0.0002 62	A (0.81)	-	-	35	-	P	Hereditary breast and ovarian cancer (AD)
YUHL 1127-21		chr13:3233693 6_-A	NM_000059	c.2582d upA	p.N863Kfs* 18	-	rs6062313 99	Het	6.99E-06	0	-	-	-	-	-	-	P	
YUHL 560-21		chr13:3235647 2_C/T	NM_000059	c.C7480 T	p.R2494*	Danio rerio	rs8035897 2	Het	1.4E-05	0	0.0005 24	A (0.81)	-	-	50	-	P	
YUHL 847-21	ATP7B	chr13:5195033 4_T/-	NM_001005 918	c.2027d elA	p.K676Sfs* 35	Danio rerio	rs7773620 50	Het	-	-	0.0005 24	-	-	-	-	-	LP	Wilson disease (AR)
YUHL 1107-21	TP53	chr17:7674972 _C/T	NM_001126 114	c.560- 1G>A	-	-	-	Het	6.98E-06	0.0003	-	DC (0.81)	-	-	23.6	-	P	Li- Fraumeni

YUHL 277-21	GAA	chr17:8010881 8_T/A	NM_000152	c.T1316 A	p.M439K	<i>Mus musculus</i>	rs7476100 90	Het	-	-	0.0017 69	DC (0.394)	Ben (0.342)	Del (0.721)	22.9	-	P/LP	syndrome (AD) Pompe disease (AR)
YUHL 33-21	LDLR	chr19:1111620 9_C/G	NM_001195 800	c.C1198 G	p.L400V	<i>Danio rerio</i>	-	Het	-	-	-	DC (0.588)	Dam (0.719)	Del (0.784)	24.1	-	P/LP	Familial hyperchole sterolemia (AD)

A, automated; AD, autosomal dominant; AR, autosomal recessive; Ben, benign; Dam, probably damaging; Del, deleterious; DC, disease-causing; Het, heterozygous in the affected individual; LP, likely pathogenic; P, pathogenic

^aIndividual indicate affected patients in whom variants were found, comprising one case cohort.

^bdbSNP database (<http://www.ncbi.nlm.nih.gov/SNP>).

^{c,d,e}Population frequency of variants in gnomAD, EAS(East Asian) and KOR(Korean) database (<https://gnomad.broadinstitute.org/>).

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^lACMG Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing (<https://www.ncbi.nlm.nih.gov/clinvar/docs/acmg/>)