SUPPLEMENTAL MATERIAL

Genetic testing methodology

Targeted HCM genetic testing

For the panel testing performed by Partners Laboratory for Molecular Medicine, all regions in the assays were either covered by array probes (for CardioChip assays) or a minimum depth of 20x for NGS-based assays. Any base that did not meet the coverage requirements above were sequenced via Sanger sequencing.

WGS

Sequencing reads were aligned to the NCBI reference sequence (GRCh37) using the Burrows-Wheeler Aligner 0.6.1-r104. The aligned reads were sorted and PCR duplicates removed using samtools 0.1.18. Local indel realignment, base quality recalibration, and variant calling were performed with UnifiedGenotyper using Genome Analysis ToolKit (GATK) 2.2.5 and the recommended best practices by the GATK development team at the Broad Institute.

Supplemental table. Carrier variants for recessive conditions

Gene	Variant (Nucleotide)	Variant (Protein)	Disease	Classification
ABCB4	c.959C>T	p.Ser320Phe	Familial progressive intrahepatic cholestasis	Uncertain significance - Favor Pathogenic
ACOX1	c.1851delT	p.Gly618AlafsX24	Peroxisomal acyl-CoA oxidase deficiency	Likely Pathogenic
ASPA	c.854A>C	p.Glu285Ala	Canavan disease	Pathogenic
ATP7B	c.383delG	p.Gly128GlufsX25	Wilson disease	Pathogenic
AURKC	c.94_101dup	p.Met35AlafsX40	Spermatogenic failure 5	Pathogenic
BTD	c.1330G>C	p.Asp444His	Biotinidase deficiency	Pathogenic
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C2	c.841_849+19del		C2 deficiency	Likely Pathogenic
CBS	c.833T>C	p.Ile278Thr	Homocystinuria	Pathogenic
CFTR	c.1521_1523delCTT	p.Phe508del	Cystic fibrosis	Pathogenic
CFTR	c.1521_1523delCTT	p.Phe508del	Cystic fibrosis	Pathogenic
CRTAP	c.471+2C>A		Osteogenesis imperfecta type II	Pathogenic
DNAH11	c.7508_7509insTTG	p.Lys2504X	Primary ciliary dyskinesia	Pathogenic
ESCO2	c.294_297del	p.Arg99SerfsX2	Roberts syndrome	Pathogenic
EYS	c.6416G>A	p.Cys2139Tyr	Retinitis pigmentosa	Uncertain significance - Favor Pathogenic
GJB2	c.109G>A	p.Val37Ile	Hearing loss	Pathogenic
GJB2	c.167del	p.Leu56ArgfsX	Nonsyndromic hearing loss	Pathogenic
GJB2	c.109G>A	p.Val37Ile	Nonsyndromic hearing loss	Pathogenic
GPR56	c.10C>T	p.Gln4X	Bilateral frontoparietal polymicrogyria	Pathogenic
HEXA	c.745C>T	p.Arg249Trp	HEXA pseudodeficiency	Pseudodeficiency allele
HFE	c.845G>A	p.Cys282Tyr	Hereditary hemochromatosis	Pathogenic
HFE	c.187C>G	p.His63Asp	Hereditary Hemochromatosis	Pathogenic
HFE	c.187C>G	p.His63Asp	Hereditary hemochromatosis	Pathogenic
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HFE	c.187C>G	p.His63Asp	Hereditary hemochromatosis	Pathogenic
HFE2	c.959G>T	p.Gly320Val	Hemochromatosis type 2	Pathogenic
IFT172	c.112C>T	p.Arg38X	Short-rib thoracic dysplasia	Likely Pathogenic
LAMA2	c.5563-2A>G		Congenital muscular dystrophy type 1A	Likely Pathogenic
LIFR	c.2074C>T	p.Arg692X	Stuve-Wiedemann syndrome	Likely Pathogenic
LIPA	c.253C>T	p.Gln85X	Lysosomal acid lipase A deficiency	Pathogenic
LOXHD1	c.4714C>T	p.Arg1572X	Nonsyndromic hearing loss	Pathogenic
LOXHD1	c.4480C>T	p.Arg1494X	Hearing loss	Pathogenic
LTBP4	c.254delT	p.Leu85ArgfsX15	Cutis laxa, autosomal recessive, type IC	Pathogenic
MMAB	c.700C>T	p.Gln234X	Methylmalonic acidemia	Likely Pathogenic
MUTYH	c.536A>G	p.Tyr179Cys	MUTYH-associated polyposis	Pathogenic
MUTYH	c.934-2A>G		MUTYH-associated polyposis	Likely Pathogenic
MYH2	c.3002delA	p.Glu1001GlyfsX26	Myopathy with external ophthalmoplegia	Likely Pathogenic
MYO7A	c.5648G>A	p.Arg1883Gln	Usher syndrome type I	Likely Pathogenic
NPHS2	c.868G>A	p.Val290Met	Idiopathic steroid-resistant nephrotic syndrome,	Likely Pathogenic
PAH	c.842+5G>A	p.(?)	Phenylketonuria (PKU)	Likely Pathogenic
PARK2	c.1289G>A	p.Gly430Asp	Parkinson disease	Likely Pathogenic
PHYH	c.766_767delGT	p.Val256PhefsX14	Refsum disease	Likely Pathogenic

PINK1	c.620del	p.Arg207Glnfs*14	Parkinson disease	Likely Pathogenic
POLG	c.2209G>C	p.Gly737Arg	POLG-related mitochondrial disorder	Uncertain significance: Favor pathogenic
PRX	c.2289delT	p.Asp765ThrfsX10	Charcot-Marie-Tooth disease type 4F	Likely Pathogenic
RAPSN	c.264C>A	p.Asn88Lys	Congenital myasthenic syndrome	Pathogenic
SERAC1	c.262_265dupCATG	p.Gly89AlafsX32	3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome	Likely Pathogenic
SERPINA1	c.1096G>A	p.Glu366Lys	Alpha-1 Antitrypsin Deficiency Disorder	Pathogenic
SGCG	c.525delT	p.Leu85ArgfsX15	Limb girdle muscular dystrophy type 2C	Pathogenic
SLC12A3	c.2221G>A	p.Gly741Arg	Gitelman syndrome	Uncertain significance: Favor pathogenic
SLC26A4	c.1003T>C	p.Phe335Leu	DFNB4/Pendred syndrome	Likely Pathogenic
SLC35C1	c.464_466del	p.Phe155del	Congenital disorder of glycosylation, type Iic	Likely Pathogenic
SLC52A2	c.916G>A	p.Gly306Arg	Brown-Vialetto-Van Laere syndrome	Pathogenic
SPG11	c.1951C>T	p.Arg651X	Spastic paraplegia	Pathogenic
TALDO1	c.516dupC	p.Ala173ArgfsX23	Transaldolase deficiency	Pathogenic
TCIRG1	c.1674-1G>A		Infantile malignant osteopetrosis	Pathogenic
TCTN2	c.1877T>A	p.Leu626X	Joubert syndrome	Pathogenic
TMCO1	c.240_243delGGTT	p.Val81ThrfsX9	Cerebrofaciothoracic dysplasia	Pathogenic
TMEM5	c.1018C>T	p.Arg340X	Congenital muscular dystrophy-dystrophoglycanopathy with brain and eye anomalies	Pathogenic
TRDN	c.613C>T	p.Gln205X	Catecholaminergic polymorphic ventricular tachychardia	Likely Pathogenic
TREX1	c.341G>A	p.Arg114His	Aicardi-Goutieres syndrome	Pathogenic
TSHR	c.545+2_545+3del		Hypothyroidism	Likely Pathogenic
TTC8	c.489G>A	p.Thr163Thr	Bardet Biedl syndrome	Uncertain significance: Favor pathogenic
TYR	c.1118C>A	p.Thr373Lys	Oculocutaneous albinism type 1	Pathogenic
TYRP1	c.1057_1060del	p.Asn353ValfsX31	Oculocutaneous albinism	Pathogenic

			type III	
USH2A	c.1214delA	p.Asn405fs	Usher syndrome type II	Pathogenic
VWF	c.2561G>A	p.Arg854Gln	von Willebrand disease type 2 N	Pathogenic

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