Table S9: Genomic profile of each patient

Patients	Gene [a]	Variant	Reason for gene selection	Type	Human
HD09C	***CCT2***	**NC_000012.11:g.69993654G>A**	**Seed**	***De novo* CDS**	**BBS syndrome. HSCR is a secondary feature sometimes associated with BBS. Leber Congenital Amaurosis (hereditary eye disease)**
	VRK2	**NG_029717.2:g.186911A>G**	**Seed + Homo in patient HK164-**	**Maternally inherited**	**ND**
	VASH1	NC_000014.8:g.77242233A>G	Seed	*De novo CDS*	ND
	FOCAD	NC_000009.11:g.[20990242G>A];[20990242G>A]	Seed	Homo	ND
	BRD4	NC_000019.9:g.[15391074C>T];[15349596C>A]	Seed	CH	Translocation breakpoints in 2 patients with t(15;19)(q13;p13.1) carcinomas
	FGFRL1	NC_000004.11:g.[1018102G>A];[1018242G>A]	Seed	CH	Wolf–Hirschhorn syndrome (WHS)
	MAGI3	NC_000001.10:g.[114216074A>G];[114133195T>C]	Seed	CH	ND
	SSH2	NC_000017.10:g.[27958079C>T];[27958200G>A]	Seed	CH	ND
	TFR2	NC_000007.13:g.[100238661G>A];[100225717T>C]	Seed	CH	Hemochromatosis, Type 3
	RET	NG_007489.1:g.39340G>A	ENS candidate; Table S3	Paternally inherited	HSCR; MEN
	CDC14A	NG_051602.1:g.159358C>G	Seed + CH in patient HK164-	Paternally inherited	Nonsyndromic Deafness (AR)
	FRAS1	NG_015812.1:g.228865_228866insT	Seed + CH in patient HK164-	Maternally inherited	Cryptophthalmos, cutaneous syndactyly and genitourinary anomalies (AR)
	CUL7	NG_016205.1:g.18757A>G	Seed + CH in patients HK180 and VH105-	Paternally inherited	3M syndrome (AR), Dubowitz's syndrome
	ADRA1A	exonic deletion	Genetic interaction with *SSH2* and *FOCAD*	Maternally inherited	Horner's Syndrome and Prostatic Hypertrophy

[a] Co-existing mutated interacting genes according to the STRING database v.10.0 are bold and highlighted in grey

Patients	Gene [a]	Variant	Reason for gene selection	Type	Human
HK164C	*BRD1*	NC_000022.10:g.[50191485G>A];[50191485G>A]	Seed	Homo	Associated with schizophrenia
	C5orf42	NG_032772.1:g.[84908G>A];[84908G>A]	Seed	Homo	Joubert syndrome 17 (AR) ALSO HSCR features
	GINS4	NC_000008.10:g.[41399354G>A];[41399354G>A]	Seed	Homo	ND
	GLRX3	NC_000010.10:g.[131977636A>G];[131977636A>G]	Seed	Homo	ND
	HK2	NC_000002.11:g.[75105837G>A];[75105837G>A]	Seed	Homo	Diabetes Mellitus, Insulin-Dependent, 2
	ITGB5	**NC_000003.11:g.[124578170G>C];[124578170G>C]**	**Seed**	**Homo**	**ND**
	COL6A3	**NG_008676.1:g.50512C>A**	**Interacting partner of *ITGB5***	**Maternally inherited**	**Ullrich Congenital Muscular Dystrophy 1. Bethlem Myopathy 1. Dystonia 27**
	LAMB2	**NG_008094.1:g.5528C>A**	**Interacting partner of *ITGB5***	**Maternally inherited**	**Pierson syndrome (AR); Congenital nephrotic syndrome**
	ITGA2	**NG_008330.1:g.76609G>A**	**Interacting partner of *ITGB5***	**Maternally inherited**	**Bleeding Disorder, Platelet-Type, 9**
	COL1A2	**NG_007405.1:g.36442C>A**	**Interacting partner of *ITGB5***	**Maternally inherited**	**Ehlers-Danlos Syndrome, Type VII (AD). Osteogenesis Imperfecta**
	SORBS1	**NG_034041.1:g.133941C>T**	**Interacting partner of *ITGB5***	**Paternally inherited**	**ND**
	COL6A2	**NG_008675.1:g.36331G>C**	**Interacting partner of *ITGB5***	**Paternally inherited**	**Ullrich Congenital Muscular Dystrophy 1. Bethlem Myopathy 1. Myosclerosis (AR)**
	ZEB2	NC_000002.11:g.145137510C>T	Seed + ENS-candidate; Table S3	*De novo* NCDS	Mowat-Wilson Syndrome (AD)
	NEK1	NG_027982.1:g.[109891G>A];[109891G>A]	Seed	Homo	**Short-rib thoracic dysplasia. Associated with ALS, Polycystic kidney disease (PKD) and amyotrophic lateral sclerosis**
	NRG1	NG_012005.2:g.92222G>T	Seed + ENS- candidate; Table S3	*De novo* NCDS	Associated with HSCR and schizophrenia
	PLAT	NG_023264.1:g.[33661T>C];[33661T>C]	Seed	Homo	Familial thrombophilia
	PPP2R3A	NG_029234.1:g.[142637A>G];[142637A>G]	Seed	Homo	ND
	RRP7A	NC_000022.10:g.[42912117G>A];[42912117G>A]	Seed	Homo	ND

Patients	Gene [a]	Variant	Reason for gene selection	Type	Human
HK164C (continued)	*STXBP5L*	NC_000003.11:g.[120977910G>A];[120977910G>A]	Seed	Homo	ND
	USP42	NC_000007.13:g.[6196402A>G];[6196402A>G]	Seed	Homo	ND
	VRK2	NG_029717.2:g.[256898G>A];[256898G>A]	Seed	Homo	ND
	CDC14A	NG_051602.1:g.[159238G>A];[84272C>A]	Seed	CH	Nonsyndromic Deafness (AR)
	DOCK8	**NG_017007.1:g.[176505C>G;253791C>G];[208237C>T]**	**Seed**	**CH**	**Hyper-Ige Recurrent Infection Syndrome, Autosomal Recessive and Autosomal Dominant Non-Syndromic Intellectual Disability**
	KANK1	**NG_016331.2:g.246747_246748insAGCTGT**	**Interacting partner of *DOCK8***	**Paternally inherited**	**Cerebral Palsy Spastic Quadriplegic 2 (CPSQ2)**
	FRAS1	NG_015812.1:g.[454891A>G];[388680A>C]	Seed	CH	Cryptophthalmos, cutaneous syndactyly and genitourinary anomalies (AR)
	SLC24A1	NG_031968.2:g.[39211A>G];[19238G>A]	Seed	CH	Congenital stationary night blindness (AR)
	GLI2	NG_009030.1:g.195951G>A	ENS candidate; Table S3	Maternally inherited	Holoprosencephaly. Culler-Jones Syndrome (AD)
HK180C	*XRN2*	NC_000020.10:g.[21327108G>A];[21327108G>A]	Seed	Homo	ND
	ACOX2	NC_000003.11:g.[58510169C>T];[58512313C>T]	Seed	CH	ND
	ARFGEF3	NC_000006.11:g.[138531086G>T];[138607972G>C]	Seed	CH	ND
	DCC	NG_013341.2:g.651331G>A	Seed + ENS-candidate; Table S3	De *novo* NCDS	Mirror Movements 1 and Colorectal Cancer
	NACAD	NC_000007.13:g.[45121368G>C];[45124560C>T]	Seed	CH	ND
	CUL7	**NG_016205.1:g.[21037C>G];[10418C>T]**	**Seed**	**CH**	**3M syndrome (AR). Dubowitz's syndrome**
	ANAPC2	**NC_000009.11:g.140079485C>A**	**Interacting partner of *CUL7***	**Maternally inherited**	**ND**
	RET	NG_007489.1:g.30277G>A	ENS-candidate; Table S3	Paternally inherited	HSCR; MEN

Patients	Gene [a]	Variant	Reason for gene selection	Type	Human
HK180C (continued)	*PLXNB1*	NC_000003.11:g.48453691G>T	ENS-candidate; Table S3	Paternally inherited	Associated with schizophrenia
HK96C	*BICD2*	NG_033908.1:g.[50349C>T];[50349C>T]	Seed	Homo	Spinal muscular atrophy, lower extremity-predominant 2.
	ELAVL4	NC_000001.10:g.50572019T>G	ENS-candidate; Table S3	Paternally inherited	Paraneoplastic neurologic disorders
	SERPINI1	NG_008217.1:g.59951A>G	ENS-candidate; Table S3	Paternally inherited	Familial encephalopathy with neuroserpin inclusion bodies (FENIB)
	CTNNAL1	NC_000009.11:g.111775677_111775705del29	ENS-candidate; Table S3	Maternally inherited	ND
	IKBKAP	NC_000009.11:g.111688824G>T	ENS-candidate; Table S3	Maternally inherited	Hereditary Sensory and Autonomic, Type III (Familial dysautonomia)
	LAMA5	**NG_050626.1:g.44336C>T**	**Seed + CH in patient HK9C-**	**Maternally inherited**	**ND**
	ITGA6	**NG_008853.1:g.81617_81618insA**	**Interacting partner of *LAMA5***	**Paternally inherited**	**Amelogenesis imperfecta (AR)**
	ITGA2B	**NG_008331.1:g.13600G>A**	**Interacting partner of *LAMA5***	**Paternally inherited**	**Bleeding Disorder, Platelet-Type, 16. Glanzmann Thrombasthenia (AR)**
HK97C	*NEK1*	NG_027982.1:g.55474A>G	Seed + Homo in patient HK164-	Maternally inherited	Short-rib thoracic dysplasia. Associated with ALS, Polycystic kidney disease (PKD) and amyotrophic lateral sclerosis
	PFKL	**NG_034033.1:g.18977A>G**	**ENS-candidate; Table S3**	**Paternally inherited**	**ND**
	PCNT	**NG_008961.1:g.82476C>T**	**Interacting partner of *PFKL***	**Maternally inherited**	**Microcephalic osteodysplastic primordial dwarfism type 2. Primary microcephaly type 6 (AR). Seckel syndrome type 4**
	PCNT	**NG_008961.1:g.92767C>T**	**Interacting partner of *PFKL***	**Maternally inherited**	**Microcephalic osteodysplastic primordial dwarfism type 2. Primary microcephaly type 6 (AR). Seckel syndrome type 4**
	SLC24A1	NG_031968.2:g.19346C>G	Seed + CH in patient HK164-	Paternally inherited	Congenital stationary night blindness (AR)
	SMO	NG_023340.1:g.19566G>A	ENS-candidate; Table S3	Paternally inherited	Curry-Jones syndrome
	VRK2	NG_029717.2:g.237075A>C	Seed + CH in patient HK164-	Maternally inherited	ND
	ZEB2	NG_016431.1:g.125370A>C	ENS-candidate; Table S3	Paternally inherited	Mowat-Wilson Syndrome (AD)
HK9C	*CYP26A1*	NG_008067.1:g.7481A>G	Seed	*De novo* CDS	Diffuse idiopathic skeletal hyperostosis

Patients	Gene [a]	Variant	Reason for gene selection	Type	Human
HK9C (continued)	***LAMA5***	**NG_050626.1:g.[53760G>A];[57239G>A]**	**Seed**	**CH**	**ND**
	CD44	**NG_008937.1:g.81028A>G**	**Interacting partner of *LAMA5***	**Paternally inherited**	**ND**
	LAMA1	**NG_034251.1:g.171893T>C**	**Interacting partner of *LAMA5***	**Paternally inherited**	**Poretti-Boltshauser syndrome (PTBHS), AR**
	RADIL	NC_000007.13:g.[4874645C>T];[4876173A>G]	Seed	CH	ND
	RET	NG_007489.1:g.52819C>T	ENS-candidate; Table S3	Maternally inherited	HSCR; MEN
	GLI3	NG_008434.1:g.196497T>A	ENS-candidate; Table S3	Maternally inherited	Greig cephalopolysyndactyly syndrome. Postaxial polydactyly types a1 and b. Preaxial polydactyly type 4. Pallister-hall syndrome
VH105C	*PLEKHA4*	NC_000019.9:g.[49348658C>T];[49348658C>T]	Seed	Homo	ND
	ZSWIM4	NC_000019.9:g.[13915803C>T];[13919738G>T]	Seed	CH	ND
	CUL7	**NG_016205.1:g.[12938C>G];[20980G>A]**	**Seed**	**CH**	**3M syndrome (AR). Dubowitz's syndrome**
	FBXW11	**NG_009275.1:g.111834G>A**	**Interacting partner of *GLI2* and *CUL7***	**Paternally inherited**	**Deafness, neurosensory deafness (AR)**
	GLI2	**NG_009030.1:g.5166G>A**	**ENS-candidate; Table S3**	**Paternally inherited**	**Holoprosencephaly. Culler-Jones Syndrome (AD)**
VH106C	*SYNE1*	NC_000006.11:g.[152730698G>A];[152631870G>A]	Seed	CH	SYNE1-Related Autosomal Recessive Cerebellar Ataxia. Emery-Dreifuss muscular dystrophy 4, autosomal dominant (AD)
	ERBB4	**NG_011805.1:g.835055_835059delAAACA**	**Seed + ENS-candidate; Table S3**	***De novo* NCDS**	**Erbb4-Related Amyotrophic Lateral Sclerosis**
	NRG1	**NG_012005.2:g.667454G>C**	**Seed + ENS-candidate; Table S3**	***De novo* NCDS**	**Associated with HSCR and schizophrenia**
	NOTCH1	**NG_007458.1:g.44235G>A**	**ENS-candidate; Table S3**	**Paternally inherited**	**Adams-Oliver syndrome**
	ACOX2	NC_000003.11:g.58520147C>T	Seed + CH in patient HK180-	Maternally inherited	ND
	FGFRL1	NC_000004.11:g.1016203G>C	Seed + CH in patient HD9-	Paternally inherited	Wolf-Hirschhorn Syndrome

Patients	Gene [a]	Variant	Reason for gene selection	Type	Human
VH106C (continued)	*NEK1*	NG_027982.1:g.55474A>G	Seed + Homo in patient HK164-	Paternally inherited	Short-rib thoracic dysplasia. Associated with ALS, Polycystic kidney disease (PKD) and amyotrophic lateral sclerosis
	LAMA5	**NG_050626.1:g.51487C>T**	**Seed + CH in patient HK9C-**	**Paternally inherited**	**ND**
	ITGB6	**NG_042041.1:g.78833G>A**	**Interacting partner of *LAMA5***	**Maternally inherited**	**Amelogenesis imperfecta (AR)**
	PLXNB1	**NC_000003.11:g.48453691G>T**	**ENS-candidate; Table S3**	**Maternally inherited**	**Associated with schizophrenia**
	SEMA3A	**NG_011489.1:g.210732delT**	**Seed + ENS-candidate; Table S3**	***De novo* NCDS**	**Hypogonadotropic Hypogonadism 16**
VH108C	*SEMA7A*	NG_011733.1:g.[24026G>A];[24026G>A]	Seed	Homo	Antigen JMH blood group system. Exotropia. Hemoglobinuria
	POLD3	**NC_000011.9:g.74336572A>G**	**Interacting partner of *RFC2***	**Paternally inherited**	**Involved in DNA replication and repair**
	RFC2	**NG_008102.1:g.[19397G>A];[5089C>T]**	**Seed**	**CH**	**Williams-Beuren Syndrome critical region. Infantile hypercalcemia supravalvar aortic stenosis syndrome**
	LAMA5	NG_050626.1:g.57903T>G	Seed + CH in patient HK9C-	Maternally inherited	ND
	MAPT	**NG_007398.1:g.104533C>G**	**ENS-candidate; Table S3**	**Paternally inherited**	**Frontotemporal dementia (FTD). Alzheimer Disease, Progressive Supranuclear Palsy 1 (PSNP1). Parkinson Disease**
	ATP13A2	**NG_009054.1:g.20831C>G**	**Interacting partner of *MAPT***	**Maternally inherited**	**Early-onset Parkinson disease 15 (AR). Kufor-rakeb syndrome**
	MARK1	**NC_000001.10:g.220809273C>G**	**Interacting partner of *MAPT***	**Maternally inherited**	**Alzheimer Disease. May be associated with susceptibility to autism.**
	SYK	**NG_017046.1:g.82046A>G**	**Interacting partner of *MAPT***	**Maternally inherited**	**Nasu-Hakola disease (NHD)**
	NRG1	NG_012005.2:g.146124A>G	Seed + ENS-candidate; Table S3	*De novo* NCDS	Associated with HSCR and schizophrenia
	POFUT1	NG_033906.1:g.5075C>T	ENS-candidate; Table S3	Maternally inherited	Dowling-Degos disease-2 (DDD2) (AD)