Supplementary

Appendix 1 Custom-designed gene panel

Table S1 Genes and associated diseases in the custom-designed gene panel

Category	Disease name	Gene symbol	Inheritance pattern
Small vessel disease	Autosomal dominant cerebral artery disease with subcortical infarction and leukoencephalopathy (CADASIL)	*NOTCH3*	AD
	Autosomal recessive cerebral artery disease with subcortical infarction and leukoencephalopathy (CARASIL)	*HTRA1*	AR
	Cerebral retinal microangiopathy with calcification and cyst degeneration (CRMCC)	*CTC1*	AR
	Polyarteritis nodosa (PAN) in childhood	*CECR1 (ADA2)*	AR
	Hereditary vascular disease with nephropathy, aneurysms, and	*COL4A1*	AD

	muscle cramps syndrome (HANAC)		
	Cerebrovascular disease with or without eye abnormalities (BSVD)		AD
	Pseudoxanthoma elasticum (PXE)	*ABCC6*	AR
		XYLT1	AR
		XYLT2	AR
	Fabry disease	*GLA*	XL
	Retinal vascular disease with leukodystrophy (RVCL)	*TREX1*	AD
Other blood vessels	Marfan syndrome (MFS)	*FBN1*	AD
	Arterial tortuous syndrome (ATS)	*SLC2A10*	AR
	Generalized arterial calcification of infancy type 1 (GACI1)	*ENPP1*	AR
	Generalized arterial calcification of infancy type 2 (GACI2)	*ABCC6*	AR
	Gallbladder disease type 4	*ABCG8*	–
	Morbid obesity and spermatogenesis disorders	*CEP19*	AR
	Cerebrotendinous xanthomatosis (CTX)	*CYP27A1*	AR

Supravalvular aortic stenosis (SVAS)	*ELN*	AD
Ehlers-Danlos syndrome (classic type 1)	*COL5A1*	AD
Ehlers-Danlos syndrome (classic type 2)	*COL5A2*	–
Ehlers-Danlos syndrome (cardiac-valvular type)	*COL1A2*	AR
Ehlers-Danlos syndrome (classic type)	*TNXB*	AR
Ehlers-Danlos syndrome (dermatosparaxis type)	*ADAMTS2*	AR
Diabetic microvascular complications type 1 (MVCD1)	*VEGFA*	–
Diabetic microvascular complications type 3 (MVCD3)	*ACE*	–
Diabetic microvascular complications type 4 (MVCD4)	*IL1RN*	–
Diabetic microvascular complications type 5 (MVCD5)	*PON1*	–
Diabetic microvascular complications type 6 (MVCD6)	*SOD2*	–

	Cavernous hemangioma type 1 (CCM1)	*KRIT1*	AD
	Cavernous hemangioma type 2 (CCM2)	*CCM2*	AD
	Cavernous hemangioma type 3 (CCM3)	*PDCD10*	–
	Capillary malformation-arteriovenous malformation syndrome (CM-AVM)	*RASA1*	AD
	Parkes-Weber syndrome (PKWS)		
	Sturge-Weber syndrome (SWS)	*GNAQ*	–
	Bosley-Salih-Alorainy syndrome (BSAS)	*HOXA1*	–
	Ataxia telangiectasia (AT)	*ATM*	AR
	Ataxia-like telangiectasia type 1 (ATLD1)	*MRE11A*	AR
	Ataxia telangiectasia-like disorder type 2 (ATLD2)	*PCNA*	AR
	Familial cutaneous telangiectasia and cancer syndrome (FCTCS)	*ATR*	AD

	Hereditary hemorrhagic telangiectasia type 1 (HHT1)	*ENG*	AD
	Hereditary hemorrhagic telangiectasia type 2 (HHT2)	*ACVRL1*	AD
	Hereditary hemorrhagic telangiectasia type 5 (HHT5)	*GDF2*	AD
	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (JPHT)	*SMAD4*	AD
	Hypotrichosis--lymphedema-telangiectasia syndrome (HLTS)	*SOX18*	AR
	Dextro-transposition of the great arteries-1 (D-TGA)	*MED13L*	AD
	Glomuvenous Malformations	*GLMN*	AD
	Loeys-Dietz syndrome type 1 (LDS1)	*TGFBR1*	AD
	Loeys-Dietz syndrome type 2 (LDS2)	*TGFBR2*	AD
	Loeys-Dietz syndrome type 3 (LDS3)	*SMAD3*	AD
	Loeys-Dietz syndrome type 4 (LDS4)	*TGFB2*	AD

	Loeys-Dietz syndrome type 5 (LDS5)	*TGFB3*	AD
	Familial thoracic aortic aneurysm type 4 (AAT4)	*MYH11*	AD
	Familial thoracic aortic aneurysm type 6 (AAT6)	*ACTA2*	AD
	Familial thoracic aortic aneurysm type 7 (AAT7)	*MYLK*	AD
	Familial thoracic aortic aneurysm type 8 (AAT8)	*PRKG1*	AD
	Familial thoracic aortic aneurysm type 9 (AAT9)	*MFAP5*	AD
	Familial thoracic aortic aneurysm type 10 (AAT10)	*LOX*	AD
	Microcephalic osteodysplastic primordial dwarfism type II (MOPD2)	*PCNT*	AR
	Polycystic kidney disease type 1 (PKD1)	*PKD1*	AD
	Polycystic kidney disease type 2 (PKD2)	*PKD2*	AD

	Polycystic kidney disease type 4 (with or without polycystic liver disease)	*PKHD1*	AR
	Bone fragility with contractures, arterial rupture, and deafness syndrome due to lysyl hydroxylase-3 deficiency	*PLOD3*	AR
	Moyamoya disease type 2 (MYMY2)	*RNF213*	–
	Moyamoya disease type 4 (MYMY4)	*MTCP1* *BRCC3*	XR XR
	Moyamoya disease type 5 (MYMY5)	*ACTA2*	–
	Moyamoya disease type 6 (MYMY6) (with achalasia)	*GUCY1A3*	AR
	Grange syndrome (GRNG)	*YY1AP1*	AR
	Behcet's disease	*HLA-B*	–
	Adenosine deaminase 2 (ADA2) deficiency	*ADA2*	AR
	Early-onset STING-associated vasculopathy (SAV) with onset in infancy and early childhood	*TMEM173*	AD

Granulomatosis with polyangiitis (GPA)	*HLA-DPB1*	–
Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis	*HLA-DPB1*	–
APP-related cerebral amyloid angiopathy (CAA)	*APP*	AD
GSN-related cerebral amyloid angiopathy (CAA)	*GSN*	AD
CST3-related cerebral amyloid angiopathy (CAA)	*CST3*	AD
ITM2B-related cerebral amyloid angiopathy (CAA)	*ITM2B*	AD
PRNP-related cerebral amyloid angiopathy (CAA)	*PRNP*	AD
Hereditary transthyretin-associated amyloidosis (ATTR)	*TTR*	AD
Diabetic microvascular complications type 1 (MVCD1)	*VEGFA*	–
Diabetic microvascular complications type 3 (MVCD3)	*ACE*	–
Diabetic microvascular complications type 4 (MVCD4)	*IL1RN*	–

	Diabetic microvascular complications type 5 (MVCD5)	*PON1*	–
	Diabetic microvascular complications type 6 (MVCD6)	*SOD2*	–
	Genetic susceptibility to Behcet syndrome	*ERAP1*	-
	MalaCards integrated aliases for Cerebral cavernous Malformations:	*FLT1*	AD
	Kawasaki disease	*ITPKC*	-
	Vasculitis	*PRTN3*	-
	Moyamoya disease	*GUCY1A1*	AR
	Fibromuscular dysplasia	*OBSCN*	AD
Coagulation dysfunction	Sickle cell disease	*HBB*	AR
	Familial polycythemia type 1 (ECYT1)	*EPOR*	AD
	Familial polycythemia type 2 (ECYT2)	*VHL*	AR
	Familial polycythemia 3 (ECYT3)	*EGLN1*	AD
	Familial polycythemia type 4 (ECYT4)	*EPAS1*	–

	Familial polycythemia type 5 (ECYT5)	*EPO*	AD
	Hereditary antithrombin III deficiency	*SERPINC1*	AD/AR
	Heparin cofactor II deficiency (HCII)	*SERPIND1*	AD
	Glycosylphosphatidylinositol deficiency (GPID)	*PIGM*	AR
	Essential thrombocythemia (THCYT)	*THPO*	AD
	Thrombomodulin deficiency thrombosis	*THBD*	–
	Autosomal dominant protein C Defective thrombosis (THPH3)	*PROC*	AD
	Tissue plasminogen reduction thrombosis	*PLAT*	–
	Familial thrombotic thrombocytopenic purpura (TTP)	*ADAMTS13*	AR
	Thrombocythemia-2 (THCYT2)	*MPL*	AD
	Thrombocythemia-3 (THCYT3)	*JAK2*	AD

Autosomal dominant thrombophilia due to protein S deficiency (THPH5)	*PROS1*	AD
Autosomal recessive thrombophilia tendency due to protein S deficiency (THPH6)		AR
Prothrombin deficiency	*F2*	AR
Factor III deficiency	*F3*	–
Factor V deficiency	*F5*	AD
Factor VII deficiency	*F7*	AR
Factor X deficiency	*F10*	AR
Factor XI deficiency	*F11*	AD/AR
Factor XII deficiency	*F12*	AR
Factor VIIIA deficiency	*F13A1*	AR
Factor VIIIB deficiency	*F13B*	AR
Hereditary combined vitamin K–dependent clotting factors deficiency (VKCFD) type 1	*GGCX*	AR
Hereditary combined vitamin K–dependent clotting factors deficiency type 2	*VKORC1*	–
Hemophilia A (HEMA)	*F8*	XR
Von Willebrand disease (VWD)	*VWF*	AD/AR

Congenital afibrinogenemia	*FGB*	AR
	FGA	AR
	FGG	AR
Platelet bleeding disorder type 16 (BDPLT16)	*ITGA2B*	AD
	ITGB3	AD
Platelet bleeding disorder type 17 (BDPLT17)	*GFI1B*	AD/AR
Quebec platelet disease (QPD)	*PLAU*	AD
X-linked thrombocytopenia	*WAS*	XR
Thrombocytopenia with absent radii (TAR) syndrome	*RBM8A*	AR
Giant platelet syndrome type A1 (BSSA1)	*GP1BA*	AD
Thrombocytopenia type 4 (THC4)	*CYCS*	AD
Thrombocytopenia type 5 (THC5)	*ETV6*	AD
Thrombocytopenia type 6 (THC6)	*SRC*	AD
Platelet bleeding disorder type 8 (BDPLT8)	*P2RY12*	AR
Platelet bleeding disorder type 11 (BDPLT11)	*GP6*	AR

	Platelet bleeding disorder type 13 (BDPLT13)	*TBXA2R*	AD
	Plasminogen activator inhibitor 1 deficiency	*SERPINE1*	AD/AR
	Sebastian syndrome (SBS)	*MYH9*	AD
	Stormorken syndrome (STRMK)	*STIM1*	AD
	Thrombocytopenia	*IL1A*	-
	Platelet-type bleeding disorder 9	*ITGA2*	AD
	Thrombocythemia, somatic	*CALR*	-
	Erythrocytosis, somatic	*SH2B3*	-
	Sticky platelet syndrome	*GAS6*	-
	Hutchinson-Gilford progeria syndrome	*NAT10*	AR/AD
	Thrombophilia	*PROCR*	-
Metabolic disease	Hyperlipoproteinemia type III	*APOE*	–
	Familial partial lipodystrophy type 2	*LMNA*	AD
	Familial partial lipodystrophy type 3	*PPARG*	AD
	Familial partial lipodystrophy type 4	*PLIN1*	AD

Familial partial lipodystrophy type 5	*CIDEC*	AR
Familial partial lipodystrophy type 6	*LIPE*	AR
Dysplasia with lipodystrophy type A	*LMNA*	AD
Dysplasia with lipodystrophy type B	*ZMPSTE24*	AR
Cholesteryl ester storage disease	*LIPA*	AR
Abetalipoproteinemia (ABL)	*MTTP*	AR
Hyperalphalipoproteinemia (HALP)	*CETP*	AD
Liver lipase deficiency	*LIPC*	AR
Congenital leptin deficiency (LEPD)	*LEP*	AR
Familial HDL deficiency	*APOA1*	AD
Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy (MDPL) syndrome	*POLD1*	AD
Familial hypercholesterolemia	*APOA2*	AD
	ITIH4	AD
	GHR	AD

	PPP1R17	AD
	EPHX2	AD
	ABCA1	AD
	LDLR	AD
	APOB	AD
	PCSK9	–
	LDLRAP1	AR
Sitosterolemia	*ABCG8*	AR
	ABCG5	AR
Mixed hyperlipidemia	*USF1*	AR
	LPL	AD
Familial hypertriglyceridemia	*APOA5*	AD
	LIPI	AD
Familial lecithin cholesterol acyltransferase deficiency (Norum disease)	*LCAT*	AR
Congenital glycosylation disorder type Ia	*PMM2*	AR
Congenital glycosylation disorder type Ib	*MPI*	AR
Congenital glycosylation disorder type Ic	*ALG6*	AR

	Congenital glycosylation disorder type Id	*ALG3*	AR
	Congenital glycosylation disorder type Ie	*DPM1*	AR
	Congenital glycosylation disorder type If	*MPDU1*	AR
	Congenital glycosylation disorder type Ig	*ALG12*	–
	Congenital glycosylation disorder type Ih	*ALG8*	AR
	Congenital glycosylation disorder type Ii	*ALG2*	AR
	Congenital glycosylation disorder type Ij	*DPAGT1*	AR
	Congenital glycosylation disorder type Ik	*ALG1*	AR
	Congenital glycosylation disorder type Im	*DOLK*	AR
	Congenital glycosylation disorder type In	*RFT1*	AR
	Congenital glycosylation disorder type Io	*DPM3*	–

	Congenital glycosylation disorder type Ip	*ALG11*	AR
	Congenital glycosylation disorder type Iq	*SRD5A3*	AR
	Congenital glycosylation disorder type Ir	*DDOST*	AR
	Congenital glycosylation disorder type Is	*ALG13*	XD
	Congenital glycosylation disorder type Iu	*DPM2*	AR
	Congenital glycosylation disorder type II	*ALG9*	–
	Congenital glycosylation disorder-type IIa	*MGAT2*	AR
	Congenital glycosylation disorder type IIb	*MOGS*	AR
	Congenital glycosylation disorder type IIc	*SLC35C1*	AR
	Congenital glycosylation disorder type IId	*B4GALT1*	AR
	Congenital glycosylation disorder type IIe	*COG7*	–

	Congenital glycosylation disorder type IIf	*SLC35A1*	AR
	Congenital glycosylation disorder type IIg	*COG1*	–
	Congenital glycosylation disorder type IIh	*COG8*	–
	Congenital glycosylation disorder type IIi	*COG5*	–
	Congenital glycosylation disorder type IIj	*COG4*	AR
	Congenital glycosylation disorder type IIk	*TMEM165*	AR
	Congenital glycosylation disorder type IIl	*COG6*	AR
	Thrombotic homocysteinemia	*CBS*	AR
	Transfer cobalamin II deficiency	*TCN2*	AR
	MTHFR-deficient homocysteinemia	*MTHFR*	AR
	Methylmalonic aciduria with homocysteinemia type cblC	*MMACHC*	AR
	Methylmalonic aciduria with homocysteinemia type cblD	*MMADHC*	AR

	Methylmalonic aciduria with homocysteinemia type cblF	*LMBRD1*	AR
	Methylmalonic aciduria with homocysteinemia type cblJ	*ABCD4*	AR
	Homocystinuria-megaloblastic anemia type cblE	*MTRR*	AR
	Homocystinuria-megaloblastic anemia type cblG	*MTR*	AR
	Menkes disease (MD)	*ATP7A*	XR
	Galactosialidosis (GSL)	*CTSA*	AR
	Sialic aciduria	*GNE*	AD
	Carnitine palmitoyltransferase IA deficiency	*CPT1A*	AR
	Carnitine palmitoyltransferase II deficiency	*CPT2*	AR
	Acyl-CoA dehydrogenase 9-deficient mitochondrial complex I deficiency	*ACAD9*	AR
	Purine nucleoside Phosphorylase deficiency (PNPD)	*PNP*	AR
	Hypermethioninemia due to adenosine kinase deficiency	*ADK*	AR

	11β-hydroxylase-deficient congenital adrenal hyperplasia (CAH)	*CYP11B1*	AR
	Hyperaldosteronism (GRA)		AD
	Histidine-rich glycoprotein deficiency (THPH11)	*HRG*	AD
	Liddle syndrome	*SCNN1G*	AD
	Hypertension with brachydactyly syndrome	*PDE3A*	AD
	Thiamine-responsive megaloblastic anemia syndrome	*SLC19A2*	AR
	Nephrotic syndrome type 1	*NPHS1*	AR
	Abdominal obesity with metabolic syndrome type 3	*DYRK1B*	AD
	Niemann-Pick disease type C1/D	*NPC11*	AR
	Combined oxidative phosphorylation deficiency type 1	*GFM1*	AR
	3-methylglutaric aciduria type VIII	*HTRA2*	AR
	Glycogen storage disease type II (Pompe disease)	*GAA*	AR

	Mitochondrial DNA depletion syndrome type 4A (Alpers type)	*POLG*	AR
	Mitochondrial DNA exhaustion syndrome type 4B (MNGIE type)		
	Mitochondrial DNA exhaustion syndrome type 12A (cardiomyopathy type)	*SLC25A4*	AD
	Hereditary folic acid malabsorption disorder (HFM)	*SLC46A1*	AR
	Very long chain acyl-CoA dehydrogenase deficiency	*ACADVL2*	AR
	Glycine N-methyltransferase deficiency	*GNMT*	AR
	Susceptibility to hypertension	*AGT*	Mu
	Essential hypertension	*AGTR1*	Mu
	Myopathy due to myoadenylate deaminase deficiency	*AMPD1*	AR
	Modifier of coronary artery disease	*CCL2*	-
	Atypical hemolytic uremic syndrome	*CFH*	AD, AR

	Atypical hemolytic uremic syndrome	*CFHR1*	AD, AR
	Atypical hemolytic uremic syndrome	*CFHR3*	AD, AR
	High-density lipoprotein cholesterol level quantitative trait locus (QTL) 7	*EDN1*	-
	Fasting plasma glucose level QTL 5	*GCKR*	-
	Low-density lipoprotein cholesterol level QTL 3	*HMGCR*	-
	Susceptibility to diabetes	*IL6*	-
	Susceptibility to diabetes	*PTPN22*	AR
	Mitochondrial complex II deficiency	*SDHAF1*	AR
	Genetic susceptibility to diabetic angiopathy	*AGER*	-
	MalaCards integrated aliases for tumoral calcinosis, Hyperphosphatemic, familial, 1:	*ZC3HC1*	AR
	susceptibility to lupus nephritis	*FCGR2A*	AD
	behcet syndrome	*KLRC4*	-

Congenital heart disease	Visceral ectopic-4 type (HTX4)	*ACVR2B*	–
	Visceral heterotaxy type 5 (HTX5)	*NODAL*	AD
	Visceral heterotaxy type 6 (HTX6)	*CFAP53*	AR
	3MC syndrome type 1 (3MC1)	*MASP1*	AR
	3MC syndrome type 2 (3MC2)	*COLEC11*	AR
	Ventricular septal defect type 1 (VSD1)	*GATA4*	AD
	Atrial septal defect type 2 (ASD2)		AD
	Atrial septal defect type 4 (ASD4)	*TBX20*	–
	Atrial septal defect type 6 (ASD6)	*TLL1*	AD
	Atrial septal defect type 7 (ASD7) (with or without atrioventricular block)	*NKX2-5*	AD
	Atrial septal defect type 9 (ASD9)	*GATA6*	AD
	Atrioventricular septal defect type 2 (AVSD2)	*CRELD1*	AD

	Atrioventricular septal defect type 4 (AVSD4)	*GATA4*	AD
	Atrioventricular septal defect-type 5 (AVSD5)	*GATA6*	AD
	Patent ductus arteriosus type 2 (PTA2)	*TFAP2B*	AD
	Patent ductus arteriosus type 3 (PTA3)	*PRDM6*	AD
	Leopard syndrome type 1 (LPRD1)	*PTPN11*	AD
	Leopard syndrome type 2 (LPRD2)	*RAF1*	–
	Leopard syndrome type 3 (LPRD3)	*BRAF*	AD
	Multiple congenital heart defects type 1 (CHTD1)	*ZIC3*	XR
	A variety of congenital heart defects type 6 (CHTD6)	*GDF1*	AD
	Autosomal dominant coronary heart disease with myocardial infarction type 1 (ADCAD1)	*MEF2A*	AD

Autosomal dominant coronary heart disease with myocardial infarction type 2 (ADCAD2)	*LRP6*	AD
LADD syndrome	*FGFR2*	AD
	FGFR3	AD
	FGF10	AD
Mayer-Rokitansky-Küster-Hauser syndrome type 2	*SHOX*	AD
Costello syndrome	*HRAS*	AD
Alagille syndrome type 1	*JAG1*	AD
Left heart hypoplasia syndrome (HLHS)	*GJA1*	AR
	NKX2-5	AD
Heart-hand syndrome (Holt-Oram syndrome)	*TBX5*	AD
Cardiofacial skin syndrome Type 1 (CFC1)	*BRAF*	AD
Cardiofacial skin syndrome type 3 (CFC3)	*MAP2K1*	–
Cardiofacial skin syndrome type 4 (CFC4)	*MAP2K2*	–
Hajdu-Cheney syndrome (HJCYS)	*NOTCH2*	AD

	Wolff-Parkinson-White syndrome (WPW)	*PRKAG2*	AD
	Noonan syndrome type 1	*PTPN11*	AD
	Noonan syndrome type 3	*KRAS*	AD
	Noonan syndrome type 4	*SOS1*	AD
	Noonan syndrome type 5	*RAF1*	AD
	Noonan-like syndrome with or without juvenile myelomonocytic leukemia	*CBL*	AD
	Noonan-like syndrome with loose hair	*SHOC2*	AD
	X-linked Emery-Dreifuss muscular dystrophy type 1 (EDMD1)	*EMD*	XR
	Shprintzen-Goldberg syndrome	*SKI*	AD
	Congenital contractural arachnodactyly (CCA; Beals syndrome)	*FBN2*	AD
	Aortic valve disease type 1 (AOVD1)	*NOTCH1*	AD
	Aortic valve disease type 2 (AOVD2)	*SMAD6*	AD

	Cardiac conus artery malformation	*NKX2-6*	–
	Pancreatic hypoplasia with congenital heart defects	*GATA6*	AD
	Cardiac septal defect	*TLL1*	AD
		NKX2-5	AD
		CITED2	AD
		GATA4	AD
		MYH6	–
		TMEM87B	–
		COMT	AD
		PRKAR1A	AD
	Tetralogy of Fallot (TOF)	*NKX2-5*	AD
		GATA4	AD
		ZFPM2	AD
		GATA6	AD
		GDF1	AD
		JAG1	AD
		TBX1	AD
	Noonan syndrome	*LZTR1*	AD
Hereditary cardiomyopathy	Familial hypertrophic cardiomyopathy type 1 (CMH1)	*MYH7*	AD

Familial hypertrophic cardiomyopathy type 2 (CMH2)	*TNNT2*	AD
Familial hypertrophic cardiomyopathy type 3 (CMH3)	*TPM1*	AD
Familial hypertrophic cardiomyopathy type 4 (CMH4)	*MYBPC3*	AD
Familial hypertrophic cardiomyopathy type 6 (CMH6)	*PRKAG2*	AD
Familial hypertrophic cardiomyopathy type 7 (CMH7)	*TNNI3*	AD
Familial hypertrophic cardiomyopathy type 8 (CMH8)	*MYL3*	AD
Familial hypertrophic cardiomyopathy type 9 (CMH9)	*TTN*	AD
Familial hypertrophic cardiomyopathy type 10 (CMH10)	*MYL2*	AD
Familial hypertrophic cardiomyopathy type 11 (CMH11)	*ACTC1*	AD
Familial hypertrophic cardiomyopathy type 12 (CMH12)	*CSRP3*	AD

	Familial hypertrophic cardiomyopathy type 13 (CMH13)	*TNNC1*	AD
	Familial hypertrophic cardiomyopathy type 14 (CMH14)	*MYH6*	AD
	Familial hypertrophic cardiomyopathy type 15 (CMH15)	*VCL*	AD
	Familial hypertrophic cardiomyopathy type 16 (CMH16)	*MYOZ2*	AD
	Familial hypertrophic cardiomyopathy type 17 (CMH17)	*JPH2*	AD
	Familial hypertrophic cardiomyopathy type 18 (CMH18)	*PLN*	AD
	Familial hypertrophic cardiomyopathy type 19 (CMH19)	*CALR3*	AD

	Familial hypertrophic cardiomyopathy type 20 (CMH20)	*NEXN*	AD
	Familial hypertrophic cardiomyopathy type 23 (CMH23) (with or without LVNC)	*ACTN2*	AD
	Familial hypertrophic cardiomyopathy type 25 (CMH25)	*TCAP*	AD
	Familial hypertrophic cardiomyopathy type 26 (CMH26)	*FLNC*	AD
	Hypertrophic cardiomyopathy (CMH)	*MYLK2*	AD
		CAV3	AD
	NDUFAF1-related mitochondrial hypertrophic cardiomyopathy	*NDUFAF1*	AD
	TSFM-related mitochondrial hypertrophic cardiomyopathy (COXPD3)	*TSFM*	AR

	AARS2-related mitochondrial hypertrophic cardiomyopathy (COXPD8)	*AARS2*	AR
	MRPL3-related mitochondrial hypertrophic cardiomyopathy (COXPD9)	*MRPL3*	AR
	MTO1-related mitochondrial hypertrophic cardiomyopathy (COXPD10)	*MTO1*	AR
	MRPL44-related mitochondrial hypertrophic cardiomyopathy (COXPD16)	*MRPL44*	AR
	Hypertrophic cardiomyopathy associated with myocardial anchoring repeat protein	*ANKRD1*	AD
	Fatal infantile cardio-encephalomyopathy type1 with cytochrome c oxidase deficiency	*SCO2*	AR
	Fatal infantile cardio-encephalomyopathy type 2 with cytochrome c oxidase deficiency	*COX15*	AR
	Fatal infantile cardio-encephalomyopathy due to	*COA5*	AR

cytochrome c oxidase deficiency type 3		
Fatal infantile cardioencephalomyopathy due to cytochrome c oxidase deficiency type 4	*COA6*	AR
Danon disease	*LAMP2*	XD
Dilated cardiomyopathy type 1A (CMD1A)	*LMNA*	AD
Dilated cardiomyopathy type 1AA (CMD1AA)	*ACTN2*	AD
Dilated cardiomyopathy type 1C (CMD1C)	*LDB3*	AD
Dilated cardiomyopathy type 1CC (CMD1CC)	*NEXN*	AD
Dilated cardiomyopathy type 1D (CMD1D)	*TNNT2*	AD
Dilated cardiomyopathy type 1DD (CMD1DD)	*RBM20*	AD
Dilated cardiomyopathy type 1E (CMD1E)	*SCN5A*	AD
Dilated cardiomyopathy type 1EE (CMD1EE)	*MYH6*	–

	Dilated cardiomyopathy type 1G (CMD1G)	*TTN*	–
	Dilated cardiomyopathy type 1GG (CMD1GG)	*SDHA*	–
	Dilated cardiomyopathy type 1HH (CMD1HH)	*BAG3*	AD
	Dilated cardiomyopathy type 1I (CMD1I)	*DES*	AD
	Dilated cardiomyopathy type 1J (CMD1J)	*EYA4*	AD
	Dilated cardiomyopathy type 1JJ (CMD1JJ)	*LAMA4*	AD
	Dilated cardiomyopathy type 1KK (CMD1KK)	*MYPN*	AD
	Dilated cardiomyopathy type 1L (CMD1L)	*SGCD*	–
	Dilated cardiomyopathy type 1LL (CMD1LL)	*PRDM16*	AD
	Dilated cardiomyopathy type 1M (CMD1M)	*CSRP3*	AD
	Dilated cardiomyopathy type 1MM (CMD1MM)	*MYBPC3*	AD

	Dilated cardiomyopathy type 1N (CMD1N)	*TCAP*	AD
	Dilated cardiomyopathy type 1O (CMD1O)	*ABCC9*	AD
	Dilated cardiomyopathy type 1P (CMD1P)	*PLN*	AD
	Dilated cardiomyopathy type 1R (CMD1R)	*ACTC1*	AD
	Dilated cardiomyopathy type 1S (CMD1S)	*MYH7*	AD
	Dilated cardiomyopathy type 1T (CMD1T)	*TMPO*	AD
	Dilated cardiomyopathy type 1U (CMD1U)	*PSEN2*	AD
	Dilated cardiomyopathy type 1W (CMD1W)	*VCL*	AD
	Dilated cardiomyopathy type 1X (CMD1X)	*FKTN*	AR
	Dilated cardiomyopathy type 1Y (CMD1Y)	*TPM1*	AD
	Dilated cardiomyopathy type 1Z (CMD1Z)	*TNNC1*	–

	Dilated cardiomyopathy type 1II (CMD1II)	*CRYAB*	AD
	Dilated cardiomyopathy type 2A (CMD2A)	*TNNI3*	AD
	Dilated cardiomyopathy type 2B (CMD2B)	*GATAD1*	AR
	Dilated cardiomyopathy type 3B (CMD3B)	*DMD*	XR
	Integrin-linked kinase-related dilated cardiomyopathy	*ILK*	AD
	Myocardial anchoring repeat protein-related dilated cardiomyopathy	*ANKRD1*	AD
	Nesprin-1–related dilated cardiomyopathy	*SYNE1*	AD
	MURC-related dilated cardiomyopathy	*MURC*	AD
	DOLK-related dilated cardiomyopathy (CDG1M)	*DOLK*	AR
	Barth syndrome	*TAZ*	XR
	Familial restrictive cardiomyopathy type 1 (RCM1)	*TNNI3*	AD

	Familial restrictive cardiomyopathy type 3 (RCM3)	*TNNT2*	AD
	Familial restrictive cardiomyopathy type 4 (RCM4)	*MYPN*	AD
	Familial restrictive cardiomyopathy type 5 (RCM5)	*FLNC*	AD
	Insufficiency of left ventricular muscle type 1	*DTNA*	AD
	Insufficiency of left ventricular muscle 7 type	*MIB1*	AD
	Insufficiency of left ventricular muscle type 8	*PRDM16*	AD
	X-linked heart valve dysplasia	*FLNA*	XR
Arrhythmia	Arrhythmogenic right ventricular dysplasia type 1	*TGFB3*	AD
	Arrhythmogenic right ventricular dysplasia type 2	*RYR2*	AD
	Arrhythmogenic right ventricular dysplasia type 5	*TMEM43*	AD
	Arrhythmogenic right ventricular dysplasia type 8	*DSP*	AD
	Arrhythmogenic right ventricular dysplasia type 9	*PKP2*	AD

Arrhythmogenic right ventricular dysplasia type 10	*DSG2*	AD
Arrhythmogenic right ventricular dysplasia type 11	*DSC2*	AD/AR
Arrhythmogenic right ventricular dysplasia type 12	*JUP*	AD
Arrhythmogenic right ventricular dysplasia type 13	*CTNNA3*	AD
Autosomal dominant catecholamine sensitivity polymorphic ventricular tachycardia (CPTV)	*RYR2*	AD
Autosomal recessive catecholamine sensitive polymorphic ventricular tachycardia (CPTV)	*CASQ2*	AR
	TECRL	AR
	CALM1	AR
	TRDN	AR
Familial ventricular tachycardia	*GNAI2*	AD
Naxos disease	*JUP*	AR
Long QT syndrome type 1	*KCNQ1*	AD
Long QT syndrome type 2	*KCNH2*	AD
Long QT syndrome type 3	*SCN5A*	AD
Long QT syndrome type 4	*ANK2*	AD
Long QT syndrome-type 5	*KCNE1*	AD

Long QT syndrome type 6	*KCNE2*	AD
Long QT syndrome type 7	*KCNJ2*	AD
Long QT syndrome type 8	*CACNA1C*	AD
Long QT syndrome type-9	*CAV3*	AD
Long QT syndrome type-10	*SCN4B*	AD
Long QT syndrome type-11	*AKAP9*	AD
Long QT syndrome type-12	*SNTA1*	AD
Long QT syndrome type-13	*KCNJ5*	AD
Long QT syndrome type-14	*CALM1*	AD
Long QT syndrome type-15	*CALM2*	AD
Short QT syndrome type-1	*KCNH2*	–
Short QT syndrome type-2	*KCNQ1*	AD
Short QT syndrome type-3	*KCNJ2*	–
Jervell and Lange-Nielsen cardiac auditory syndrome (JLNS)	*KCNQ1*	AD
	KCNE2	AD
Familial atrial fibrillation type 3	*KCNQ1*	AD
Familial atrial fibrillation type 4	*KCNE2*	AD
Familial atrial fibrillation type 6	*NPPA*	AD
Familial atrial fibrillation type 7	*KCNA5*	AD
Familial atrial fibrillation type 9	*KCNJ2*	AD
Familial atrial fibrillation type 11	*GJA5*	AD

Familial atrial fibrillation type 14	*SCN2B*	AD
Familial atrial fibrillation type 15	*NUP155*	AR
Familial atrial fibrillation type 16	*SCN3B*	AD
Familial atrial fibrillation type 17	*SCN4B*	AD
Familial atrial fibrillation type 18	*MYL4*	AD
Progressive familial heart block type 1A	*SCN5A*	AD
Progressive familial heart block type 1B	*TRPM4*	AD
Familial conduction defect	*AKAP10*	AD
Familial paroxysmal ventricular fibrillation type 2	*DPP6*	AD
Brugada syndrome type 1	*SCN5A*	AD
Brugada syndrome type 2	*GPD1L*	–
Brugada syndrome type 3	*CACNA1C*	–
Brugada syndrome type 4	*CACNB2*	–
Brugada syndrome type 5	*SCN1B*	–
Brugada syndrome type 6	*KCNE3*	–

	Brugada syndrome type 7	*SCN3B*	AD
	Brugada syndrome type 8	*HCN4*	–
	Brugada syndrome type 9	*KCND3*	AD
	Autosomal dominant sick sinus syndrome (SSS)	*HCN4*	AD
	Autosomal recessive sick sinus syndrome (SSS)	*SCN5A*	AR
	Romano-Ward syndrome	*KCNQ1*	AR
		KCNH2	AD
		KCNE2	AD
		SCN5A	AD
Other illnesses	Paraganglioma type 1 (PGL1) (with or without deafness)	*SDHD*	AD
	Paraganglioma type 2 (PGL2)	*SDHAF2*	AD
	Paraganglioma type 3 (PGL3)	*SDHC*	AD
	Paraganglioma type 4 (PGL4)	*SDHB*	AD
	Neurofibromatosis type 1 (NF1)	*NF13*	AD
	Neurofibroma type 2 (NF2)	*NF23*	AD
	Pheochromocytoma (PHEO)	*MAX*	AD
		KIF1B	AD
		SDHB	AD
		VHL	AD
		GDNF	AD

	RET	AD
	SDHD	AD
	TMEM127	AD
Bannayan-Riley-Ruvalcaba syndrome (BRR)	*PTEN*	AD
Von Hippel-Lindau syndrome (VHL)	*VHL*	AD
	CCND1	AD
Leukemia with ataxia (LKPAT)	*CLCN2*	AR
Hereditary diffuse leukoencephalopathy with axonal degeneration (HDLS)	*CSF1R*	AD
Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL)	*DARS2*	AR
Aicardi-Goutieres syndrome type 1 (AGS1)	*TREX1*	AD/AR
Aicardi-Goutieres syndrome type 2 (AGS2)	*RNASEH2B*	AR
Aicardi-Goutieres syndrome type 3 (AGS3)	*RNASEH2C*	AR
Aicardi-Goutieres syndrome type 4 (AGS4)	*RNASEH2A*	AR

	Aicardi-Goutieres syndrome type 5 (AGS5)	*SAMHD1*	AR
	Aicardi-Goutieres syndrome type 6 (AGS6)	*ADAR*	AR
	Aicardi-Goutieres syndrome type 7 (AGS7)	*IFIH1*	AD
	Leukemia with dystonia and motor neuropathy (LKDMN)	*SCP2*	AR
	White matter ablative leukoencephalopathy (VWM)	*EIF2B1*	AR
		EIF2B2	AR
		EIF2B3	AR
		EIF2B4	AR
		EIF2B5	AR
	Familial Alzheimer's disease type 1 (AD)	*APP*	AD
	Familial Alzheimer's disease type 2 (AD)	*APOE*	AD
	Familial Alzheimer's disease Type 3 (AD)	*PSEN1*	AD
	Familial Alzheimer's disease type 4 (AD)	*PSEN2*	AD
	Autoimmune lymphoid tissue syndrome type IA	*FAS*	AD

	Autoimmune lymphoid tissue syndrome type IB	*FASLG*	AD
	Autoimmune polyendocrine syndrome type I (with or without reversible metaphyseal dysplasia)	*AIRE*	AD/AR
	Early-onset hemophagocytic lymphohistiocytosis (HLH)	*FHL2*	–
	Sex-linked immunodeficiency with high IgM	*CD40LG*	XR
	Mitochondrial complex V deficiency karyotype 2	*TMEM70*	AR
	Axenfeld-Rieger syndrome type 1	*PITX2*	AD
	Axenfeld-Rieger syndrome type 3	*FOXC1*	AD
	Werner syndrome	*WRN*	AR
	Coffin-Lowry syndrome	*RPS6KA3*	XD
	Testicular dysplasia with sudden infant death syndrome	*TSPYL1*	AR
	Dwarf-facial telangiectasia syndrome (Bloom syndrome)	*BLM*	AR

	Primary pulmonary hypertension	*BMPR2*	AD
	Diastolic hypertension	*KCNMB1*	AD
	Heme oxygenase 1 deficiency (HMOX1D)	*HMOX1*	–
	Porencephaly type 1 (POREN1)	*COL4A1*	–
	Porencephaly type 2 (POREN2)	*COL4A2*	AD
	Hemorrhagic destruction of the brain, subependymal calcification, and cataracts (HDBSCC)	*JAM3*	AR
	Susceptibility to stroke	*ALOX5AP*	Mu
	Acatalasemia	*CAT*	-
	Melanoma and neural system tumor syndrome	*CDKN2A*	AD
	WHIM syndrome	*CXCR4*	-
	Susceptibility to myocardial infarction	*ESR1*	-
	Susceptibility to malaria	*ICAM1*	-
	Protection against graft-versus-host disease	*IL10*	-
	Early infantile epileptic encephalopathy (EIEE) type 70	*PHACTR1*	AD

	Platelet-activating factor acetylhydrolase deficiency	*PLA2G7*	-
	Susceptibility to hyperapobetalipoproteinemia	*PPARA*	-
	Susceptibility to cerebral infarction	*PRKCH*	Mu
	Susceptibility to vascular dementia	*TNF*	
	Mental retardation, autosomal recessive 7	*TUSC3*	AR
	Genetic susceptibility to cardiovascular disease	*ADORA1*	-
	Genetic susceptibility to Klippel-Trenaunay-Weber syndrome	*AGGF1*	-
	Familial Mediterranean fever	*CASP1*	AR
	Genetic susceptibility to central nervous system malignant neoplasms	*CASP3*	-
	Genetic susceptibility to ischemia	*CASP9*	-
	Genetic susceptibility to melanoma	*CBX7*	-

	Genetic susceptibility to ischemia	*HIF1A*	-
	Genetic susceptibility to cardiovascular disease	*IL18*	-
	Genetic susceptibility to stroke	*PSORS1C2*	-

AR: autosomal recessive inheritance; AD: autosomal dominant inheritance; XR: X-linked recessive inheritance.

Appendix 2 Sanger sequencing of novel variants

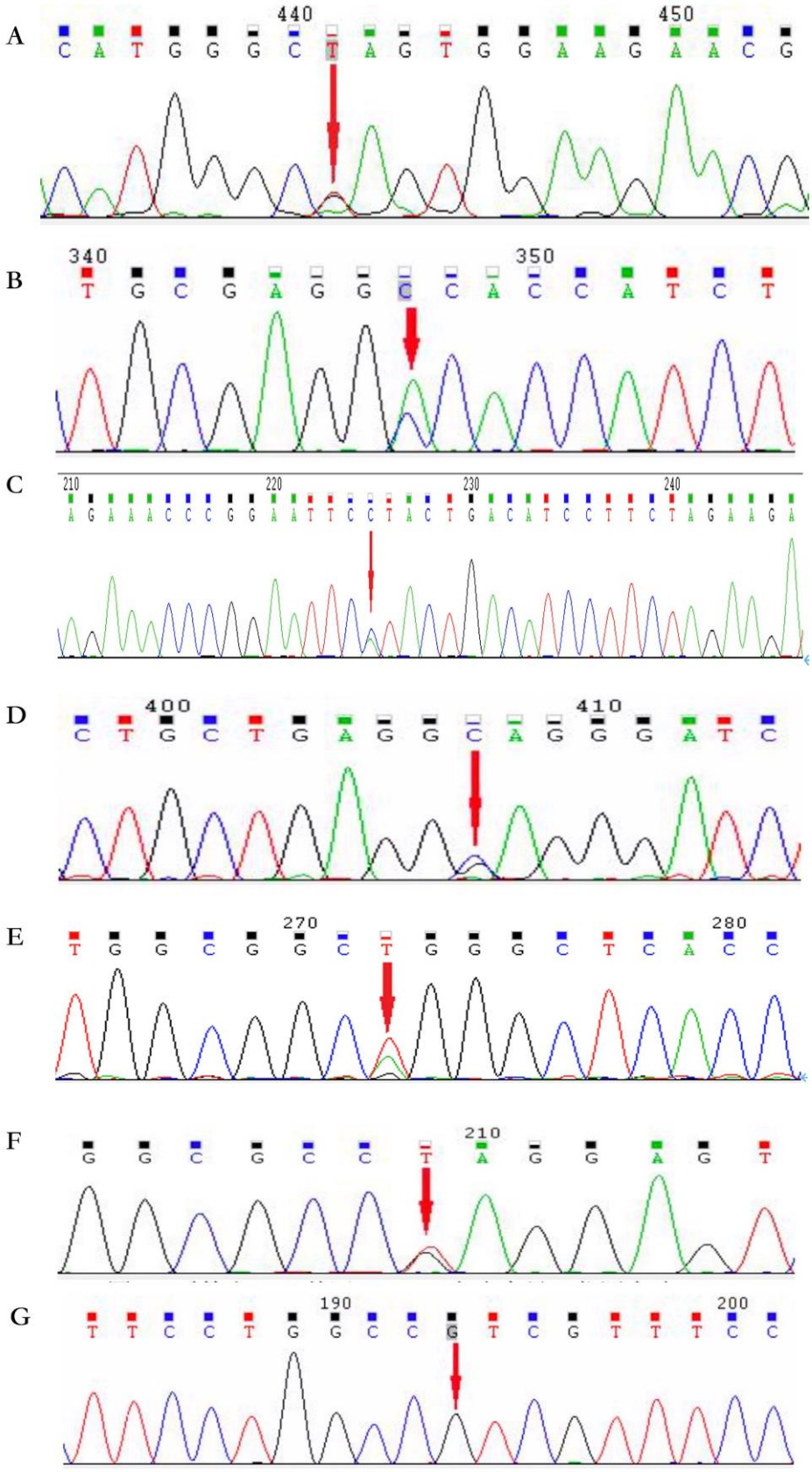
A
440
450
C A T G G G C T A G T G G A A G A A C G
B
340
350
T G C G A G G C C A C C A T C T
C
210
220
230
240
A G A A A C C C G G A A T T C C T A C T G A C A T C C T T C T A G A A G A
D
400
410
C T G C T G A G G C A G G G A T C
E
270
280
T G G C G G C T G G G C T C A C C
F
210
G G C G C C T A G G A G T
G
190
200
T T C C T G G C C G T C G T T T C C

Figure S1. Novel variants were confirmed by Sanger sequencing.

(A) The *JPH2* c.G880T in patient 7. (B) The *RYR2* c.A12584C in Patient 30. (C) The *TTN* c.T54027G in patient 44. (D) The *NOTCH3* c.C368G in patient 12. (E) The *NOTCH3* c.A502T in patient 14. (F) The *VHL* c.G106T in patient 25. (G) The *GLA* c.C61G in patient 10.

Appendix 3 Results in the control group

Table S2 The gene variants in the control group

Sex	Age	Gene symbol	Inheritance	Mutation	Status	Acmg criteria	Snp id	Frequency	Disease abbreviation	Categories
M	29	*TTN*	AD	.	Reported	Uncertain significance	rs138192315	0.0149502	Dilated cardiomyopathy	Hereditary cardiomyopathy
F	38	*TTN*	AD	Missense	Reported	Uncertain significance	rs117097948	0.00332226	Dilated cardiomyopathy	Hereditary cardiomyopathy
M	36	*BAG3*	AD	Missense	Reported	Uncertain significance	rs117671123	0.0199336	CMD1HH	Hereditary cardiomyopathy
		DSP	AD	Missense	Reported	Uncertain significance	rs116888866	0.0116279	Arrhythmogenic right ventricular dysplasia type 8	Arrhythmia
		AKAP9	AD	Missense	Reported	Uncertain significance	rs77447750	0.00996678	Long QT syndrome type 11	Arrhythmia
F	41	*THBD*	AD	.	Reported	Uncertain significance	rs16984852	0.00664452	Thrombomodulin deficiency Thrombosis	Coagulation dysfunction
		F5	AD	Missense	Reported	Uncertain significance	rs182566496	0.0149502	Factor V deficiency	Coagulation dysfunction
		POLG	AD	Missense	Reported	Uncertain significance	rs201477273	0.013289	Mitochondrial DNA depletion Syndrome-4A (Alpers type)	Metabolic disease
M	48	*TRPM4*	AD	.	Reported	Uncertain significance	rs112085495	0	Progressive familial heart block type 1B	Arrhythmia
M	55	*TTN*	AD	.	Reported	Uncertain significance	rs138192315	0.0149502	Dilated cardiomyopathy	Hereditary cardiomyopathy

M	54	*TTN*	AD	Missense	Reported	Uncertain significance	rs2303830	0	Dilated cardiomyopathy	Hereditary cardiomyopathy
		RYR2	AD	Missense	Reported	Uncertain significance	rs373261115	0.00996678	Arrhythmogenic right ventricular dysplasia type 2	Arrhythmia

TTN: Titin; *BAG3*: BCL2-associated athanogene 3; *DSP*: desmoplakin; *AKAP9*: A-kinase anchor protein 9; *THBD*: thrombomodulin; *F5*: coagulation factor V; *POLG*: polymerase (DNA-directed), gamma; *TRPM4*: transient receptor potential cation channel, subfamily M, member 4; *RYR2*: ryanodine receptor 2; *CMD1HH*: cardiomyopathy, dilated, 1hh; AD: autosomal dominant heredity. M: male, F: female.

Note: Frequency is from 1000genomes frequency.

Appendix 4 Results in the disease group

Table S3 Phenotypes and genotypes of patients with rare variants with unknown significance in the disease group

Patient number	Sex	Age	Risk factor	Family history	MRI characters	Gene symbol	Inheritance	Refseq	Nucleotide change (protein change)	Mutation	Status	Exon id	Snp id	Frequency	Disease abbreviation	Categories
6	F	34	No	Yes	Bilateral multiple cortex infarction in posterior circulation	*AKAP9*	AD	NM_005751.4	c.733-14_733-15ins54	Frame shift mutation	Novel	Intron 7	-	-	LQTS	Arrhythmia diseases
43	M	51	No	Yes	Unilateral single subcortical infarction in anterior circulation without involvement of the internal capsule and basal ganglia region	*ABCG5*	AR	NM_022436	c.G1528T (p.H510N)	Missense	Reported	Exon 11	Rs199984328	0.0008[c], 0.0004375[e]	Sitosterolemia	Metabolism disorders
29	M	40	No	No	Unilateral single pons infarction	*LIPE*	AR	NM_005357	c.3203_3221del (p.V1068Gfs*102X)	Frame shift mutation	Novel	Exon 10	-	0.0036[e]	FPLD6	Metabolism disorders
49	M	47	No	Yes	Unilateral single subcortical infarction in anterior circulation without involvement of the internal capsule and basal ganglia region	*PROS1*	AD	NM_000313	c.T1494C (p.N498N)	Synonymous mutation	Novel	Exon 13	Rs76877671	0.002[c], 0.0010387[e]	Protein S Deficiency	Coagulation and anticoagulation imbalance
35	M	28	No	No	Unilateral single subcortical infarction in anterior circulation without involvement of the internal capsule and basal ganglia region	*F5*	AD	NM_000130	c.G4949A (p.A1650V)	Missense	Novel	Exon 14	Rs75369131 6	0.0000579[e]	Factor V Leiden Thrombophilia	Coagulation and anticoagulation imbalance
19	M	28	Hypertension	No	Unilateral single subcortical in anterior circulation without involvement of the internal capsule and basal ganglia region	*NPHS1*	AR	NM_004646	c.G1802C (p.G601A)	Missense	Reported	Exon 14	Rs11461544 9	0.0049[c], 0.0016514[e]	CNS	Metabolic disorders

						NPHS 1	AR	NM_004646	c.G2869C (p.V957L)	Missense	Reported	Exon 21	Rs11484913 9	0.0028[c], 0.001875[e]	CNS	Metabolic disorders
						HDAC 9	AR	NM_001321878	c.1508_1511del (p.v503fsx7)	Frame shift mutation and nonsense	Novel	Exon 12	-	-	Stroke Risk Gene	Miscellaneous
15	F	23	No	Yes	Unilateral single subcortical infarction in anterior circulation without involvement of the internal capsule and basal ganglia region	*TREX1*	AD	NM_033629.5	c. 915+1G>A	Splice site mutation	Novel	Intron 1	-	0.00036[e]	Vasculopathy, Retinal, With Cerebral Leukoencephalopathy and Systemic Manifestations	Miscellaneous
34	M	48	Smoking	Not	Unilateral single pons infarction in the territory of one perforating arteriole in anterior circulation with neuroimaging features of CSVD found	*HTRA 1*	AD/AR	NM_002775	c.G523A (p.V175M)	Missense	Novel	Exon 2	-	0.0000082[e]	CARASIL and CADASIL2	Small vascular disease
39	M	49	Hypertension	Not	Bilateral multiple cortex and pons infarction in posterior circulation	*TTN*	AD	NM_001256850	c.G13388A (p.S4463N)	Missense	Reported	Exon 47	Rs147879266	0.0002[c], 0.0001332[e]	Dilated Cardiomyopathy	Hereditary cardiomyopathy
21	M	26	Not	Yes	Bilateral multiple subcortical infarctions in anterior and posterior circulation	*TTN*	AD	NM_001256850	c.G13388A (p.S4463N)	Missense	Reported	Exon 47	Rs147879266	0.0002[c], 0.0001332[e]	Dilated Cardiomyopathy	Hereditary cardiomyopathy

						PLA2G7	AR/AD	NM_001168357	c.G835T (p.V279F)	Missense	Reported	Exon 9	Rs76863441	0.016 57[c], 0.004848[e]	Platelet-activating factor acetylhydrolase deficiency	Arterial diseases
32	F	25	No	No	Unilateral single pons infarction and identified aneurysm in bilateral internal carotid artery	*MYLK*	AD	NM_053025	c.G1133A (p.R378H)	Missense	Reported	Exon 10	Rs56378 658	0.00014[e]	AAT7	Arterial diseases

AKAP9: A-kinase anchoring protein 9; *ABCG5*: ATP-binding cassette subfamily G member 5; *LIPE*: lipase E; *PROS1*: protein S; *NPHS1*: nephrotic syndrome 1; *HDAC9*: histone deacetylase 9; *TREX1*: three prime repair exonuclease 1; *HTRA1*: HtrA serine peptidase 1; *TTN*: titin; *PLA2G7*: phospholipase A2 group VII; *MYLK*: myosin light chain kinase; LQTS: long QT syndrome; FPLD6: familial partial lipodystrophy-6 ; CNS: congenital nephrotic syndrome; CARASIL and CADASIL2: cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy 2; AAT7: aortic aneurysm, familial thoracic 7; AR: autosomal recessive inheritance; AD: autosomal dominant inheritance; M: male, F: female; [c]: ClinVar frequency; [e]: ExACAF frequency

https://cdn.amegroups.cn/static/public/atm-21-3843-1.pdf