Table S2 Pathogenic/likely pathogenic/VUS mutations detected in our cohort

Case No.	Gene	Chromosome position	Nucleotide change	Protein change	Hetero-zygosity	First interpreta-tion of variants	Second interpretation of variants				
							Mutation	Evidence of mutation	Reference (PMID)	HGMD	Reported diseases
2	*RYR1*	chr19-38931428	c.89A>G	p.E30G	Het	VUS			-	-	-
	RYR1	chr19-38987554	c.6851A>G	p.N2284S	Het	VUS			-	-	-
3	*SCN5A*	chr3-38592648	c.5215C>T	p.R1739W	Het	Pathogenic	VUS	PP2; PP3	19716085	DM	Long QT syndrome
	KCNQ1	chr11-2604728	c.985G>A	p.A329T	Het	VUS			-	-	-
4	*ABCA1*	chr9-107558696	c.5131G>A	p.V1711I	Het	VUS			-	-	-
5	*NKX2-5*	chr5-172659699	c.848C>A	p.P283Q	Het	Pathogenic			21110066	DM	Ventricular septal defect
	MYH11	chr16-15932077	c.33G>T	p.E11D	Het	Likely pathogenic			30056620	DM?	Aortic dissection, acute
	MYLK	chr3-123339135	c.5287A>C	p.M1763L	Het	VUS			-	-	-
6	*APP*	chr21-27264120	c.2125G>A	p.G709S	Het	VUS			-	-	-
	PKD1	chr16-2156408	c.7480G>A	p.E2494K	Het	Likely pathogenic			27567292	DM?	Intracranial aneurysms
7	*NOTCH3*	chr19-15297982	c.1774C>T	p.R592C	Het	Pathogenic	Likely pathogenic	PS3; PM2; PP3	19488902	DM	CADASIL
8	*RNF213*	chr17-78358903	c.14387A>G	p.K4796R	Het	VUS			-	-	-
	RBM20	chr10-112544565	c.1445T>C	p.L482P	Het	VUS			-	-	-

	RBM20	chr10-112572206	c.2051G>A	p.R684K	Het	VUS			-	-	-
9	*NOTCH3*	chr19-15291543	c.3091C>T	p.R1031C	Het	Pathogenic	VUS	PM2; PP2	9388399	DM	CADASIL
10	*PKD1*	chr16-2140803	c.12010C>T	p.Q4004*	Het	Pathogenic	VUS	PVS1; PP2	16456780	DM	Polycystic kidney disease 1
	PSEN1	chr14-73664777	c.808A>T	p.M270L	Het	VUS			-	-	-
	MTHFR	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with
11	*MTHFR*	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with
12	*MYH9*	chr22-36681204	c.5446A>G	p.I1816V	Het	Pathogenic	VUS	PS3	12533692	DM	Alport syndrome with macrothrombocytopaenia
	NOTCH3	chr19-15296391	c.2051C>T	p.P684L	Het	VUS			-	-	-
13	*APOA5*	chr11-116662359	c.104G>A	p.S35N	Het	VUS			-	-	-
	MYLK	chr3-123366135	c.4555C>A	p.P1519T Het	Het	VUS			-	-	-
	RYR2	chr1-237850803	c.9066T>G	p.F3022L	Het	VUS			-	-	-
14	*MTHFR*	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with
15	*LDLR*	chr19-11217364	c.817+1G>C	splicing site	Het	Pathogenic	Likely pathogenic	PVS1; PM2	-	-	-
	MTHFR	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with

16	*COL4A2*	chr13-111080914	c.461G>A	p.G154E	Het	VUS			-	-	-
	ITGA2B	chr17-42453087	c.2602-3C>A	splicing site	Het	Pathogenic			25373348	DM	Glanzmann thrombasthenia
17	*FBN1*	chr15-48780424	c.3223C>T	p.R1075C	Het	VUS			-	-	-
	MTHFR	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with
18	*ABCC6*	chr16-16244099	c.4404-1G>A	splicing site	Het	Likely pathogenic	Likely pathogenic	PVS1; PM2	-	-	-
	NOTCH3	chr19-15292616	c.2567-4G>A	splicing site	Het	VUS			-	-	-
	MTHFR	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with
19	*PCNT*	chr21-47847639	c.7424G>A	p.R2475Q	Het	VUS			-	-	-
	PCNT	chr21-47817349	c.4387C>A	p.L1463M	Het	VUS			-	-	-
21	*VWF*	chr12-6128749	c.3835G>A	p.V1279I	Het	Likely pathogenic	VUS	PM2; PP2	8096943	DM?	Von Willebrand disease 1
	VWF	chr12-6128787	c.3797C>T	p.P1266L	Het	Pathogenic	VUS	PM2; PP2	8486782	DM	Von Willebrand disease 1
22	*APOA5*	chr11-116660852	c.1093G>A	p.D365N	Het	VUS			-	-	-
	MTHFR	chr1-11863038	c.136C>T	p.R46W	Het	Pathogenic	VUS	PS3; PP2	25736335	DM	Methylenetetrahydrofolate reductase deficiency
	MTHFR	chr1-11856378	c.665C>T	p.A222V	Het	VUS			7647779	DFP	Cardiovascular disease, association with
23	*PKD1*	chr16-2167855	c.1138C>T	p.R380C	Het	Likely pathogenic	VUS	PP2; PP3	27835667	DM?	Polycystic kidney disease 1

	MTHFR	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with
24	*KRIT1*	chr7-91855885	c.1101delT	p.H367Qfs*4	Het	Likely pathogenic	VUS	PM2	-	-	-
25	*ETV6*	chr12-12038953	c.1246T>A	p.L416M	Het	VUS			-	-	-
	MYH11	chr16-15826512	c.3560C>T	p.T1187M	Het	VUS			-	-	-
26	*MTHFR*	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with
27	*HBB*	chr11-5247993-5247996	c.126_129 delCTTT	p.F42Lfs*19	Het	Pathogenic			6826539	DM	Thalassaemia beta
	RYR2	chr1-237732463	c.3442G>T	p.G1148C	Het	VUS			-	-	-
29	*PRNP*	chr20-4680156	c.290G>A	p.S97N	Het	Pathogenic			-	DM	Dementia，HGOL
30	*MTHFR*	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with
	ABCC6	chr16-16263555	c.2943G>T	p.Q981H	Het	Pathogenic			18157818	DM	Pseudoxanthoma elasticum, autosomal recessive
31	*MTHFR*	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with
32	*GSN*	chr9-124073043	c.586C>T	p.R196C	Het	VUS			-	-	-
	MTHFR	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with
33	*COL5A1*	chr9-137710541	c.4270C>T	p.P1424S	Het	VUS			-	-	-
34	*NOS3*	chr7-150704216	c.1964G>A	p.R655Q	Het	VUS			-	-	-
	PSEN2	chr1-227069609	c.1A>G	p.0?	Het	VUS			-	-	-

	SERPIND1	chr22-21138287	c.919delA	p.M307*	Het	Likely pathogenic	VUS	PVS1; PM2	-	-	-
35	*MYLK*	chr3-123366171	c.4519C>T	p.R1507W	Het	VUS			-	-	-
	SCN5A	chr3-38592108	c.5755C>T	p.R1919C	Het	VUS			-	-	-
	MTHFR	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with
	MTHFR	chr1-11854002	c.1492G>A	p.V498M	Het	VUS			-	-	-
36	*FBN1*	chr15-48829846	c.698G>A	p.R233H	Het	Pathogenic	VUS	PP3	26272055	DM	Thoracic aortic aneurysms and dissections
37	*NOTCH3*	chr19-15299809	c.1369T>C	p.C457R	Het	VUS			-	-	-
39	*MYH11*	chr16-15808938	c.5614G>A	p.A1872T	Het	VUS			-	-	-
	MTHFR	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with
40	*PROS1*	chr3-93605275	c.1228C>A	p.P410T	Het	VUS			-	-	-
	RNF213	chr17-78358945	c.14429G>A	p.R4810K	Het	VUS			21048783	Suscepti-bility	Moyamoya disease
41	*ABCC6*	chr16-16244099	c.4404-1G>A	splicing site	Het	Likely pathogenic	Likely pathogenic	PVS1; PM2	-	-	-
	JAK2	chr9-5072559	c.1709A>G	p.Y570C	Het	VUS			-	-	-
	MTHFR	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with
42	*COL1A2*	chr7-94037528	c.673G>C	p.V225L	Het	VUS			-	-	-
	MTHFR	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with

43	*RYR1*	chr19-39039020	c.12242C>T	p.T4081M	Het	Pathogenic	VUS	PP2	16917943	DM	Malignant hyperthermia
	THBD	chr20-23029313	c.829G>T	p.G277W	Het	VUS			-	-	-
44	*RNF213*	chr17-78313166	c.4999G>A	p.G1667R	Het	VUS			-	-	-
	MTHFR	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with
45	*MTHFR*	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with
46	*MTHFR*	chr1-11856378	c.665C>T	p.A222V	Hom	VUS			7647779	DFP	Cardiovascular disease, association with
	HTRA1	chr10-124221572	c.404C>A	p.A135D	Het	VUS					

DM, disease causing mutation; DFP, disease-associated polymorphism with additional supporting functional evidence; Het, heterogeneous mutation; Hom, homogenous mutation; PM, the weight of pathogenicity criteria is moderate; PM2, absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium; PP, the weight of pathogenicity criteria is supporting; PP2, missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease; PP3, multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc.); PS, the weight of pathogenicity criteria is strong; PS3, well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product; PVS, the weight of pathogenicity criteria is very strong; PVS1, null variant (nonsense, frameshift, canonical ±1 or 2 splice sites, initiation codon, single or multiexon deletion) in a gene where LOF is a known mechanism of disease; VUS, variants of uncertain significance.