

## SUPPLEMENTARY FILES

The p.(Cys150Tyr) variant in *CSRP3* is associated with late-onset hypertrophic cardiomyopathy in heterozygous individuals

### Contents:

<b>Supplementary Table 1: Genes related to inherited cardiovascular disorders included in the library.....</b>	<b>2</b>
<b>Supplementary Table 2: Other genetic variants identified in index cases.....</b>	<b>8</b>
<b>Supplementary Table 3. Bioinformatic predictors.....</b>	<b>8</b>
<b>Supplementary Figure 1: Pedigrees.....</b>	<b>9</b>

**Supplementary Table 1:** Genes related to inherited cardiovascular disorders included in the library

<b>Gene</b>	<b>Protein name</b>
<b>AARS2</b>	Alanine-tRNA ligase, mitochondrial
<b>ABCC9</b>	ATP-binding cassette, sub-family C (CFTR/MRP), member 9
<b>ACAD9</b>	Acyl-CoA dehydrogenase family member 9, mitochondrial
<b>ACADVL</b>	Very long-chain specific acyl-CoA dehydrogenase, mitochondrial
<b>ACTA1</b>	Actin, alfa 1, skeletal muscle
<b>ACTC1</b>	Actin, alpha cardiac muscle 1
<b>ACTN2</b>	Alpha-actinin-2
<b>AGK</b>	Acylglycerol kinase, mitochondrial
<b>AGL</b>	Glycogen debranching enzyme
<b>AGPAT2</b>	1-acyl-sn-glycerol-3-phosphate acyltransferase beta
<b>AKAP9</b>	A-kinase anchor protein 9
<b>ALMS1</b>	Alstrom syndrome protein 1
<b>ANK2</b>	Ankyrin 2
<b>ANK3</b>	Ankyrin-3
<b>ANKRD1</b>	Ankyrin repeat domain-containing protein 1
<b>ANO5</b>	Anoctamin-5
<b>ATP5F1E</b>	ATP synthase subunit epsilon, mitochondrial
<b>ATPAF2</b>	ATP synthase mitochondrial F1 complex assembly factor 2
<b>BAG3</b>	BAG family molecular chaperone regulator 3
<b>BRAF</b>	Serine/threonine-protein kinase B-raf
<b>BSCL2</b>	Seipin
<b>CACNA1C</b>	Voltage-dependent L-type calcium channel subunit alpha-1C
<b>CACNA1D</b>	Voltage-dependent L-type calcium channel subunit alpha-1D
<b>CACNA2D1</b>	Voltage-dependent calcium channel subunit alpha-2/delta-1
<b>CACNB2</b>	Voltage-dependent L-type calcium channel subunit beta-2
<b>CALM1</b>	Calmodulin
<b>CALM2</b>	Calmodulin
<b>CALM3</b>	Calmodulin
<b>CALR3</b>	Calreticulin 3
<b>CAPN3</b>	Calpain-3
<b>CASQ2</b>	Calsequestrin-2
<b>CAV3</b>	Caveolin 3
<b>CAVIN1</b>	Polymerase I and transcript release factor
<b>CAVIN4</b>	Caveolae-associated protein 4
<b>CHRM2</b>	muscarinic acetylcholine receptor M2
<b>COA5</b>	cytochrome c oxidase assembly factor 5

<b>Gene</b>	<b>Protein name</b>
<b>COA6</b>	cytochrome c oxidase assembly factor 6 homolog
<b>COL7A1</b>	collagen alpha-1(VII) chain
<b>COQ2</b>	4-hydroxybenzoate polyprenyltransferase, mitochondrial
<b>COX15</b>	Cytochrome c oxidase assembly protein COX15 homolog
<b>COX6B1</b>	Cytochrome c oxidase subunit 6B1
<b>CRYAB</b>	Alpha-crystallin B chain
<b>CSRP3</b>	Cysteine and glycine-rich protein 3
<b>CTNNA3</b>	catenin alpha-3
<b>CTNNB1</b>	catenin beta-1
<b>DES</b>	Desmin
<b>DLD</b>	Dihydrolipoyl dehydrogenase, mitochondrial
<b>DMD</b>	Dystrophin
<b>DNAJC19</b>	Mitochondrial import inner membrane translocase subunit TIM14
<b>DNM1L</b>	Dynamin-1-like protein
<b>DOLK</b>	Dolichol kinase
<b>DSC2</b>	Desmocollin 2
<b>DSG2</b>	Desmoglein 2
<b>DSP</b>	Desmoplakin
<b>DTNA</b>	Dystrobrevin alpha
<b>ELAC2</b>	Zinc phosphodiesterase ELAC protein 2
<b>EMD</b>	Emerin
<b>EYA4</b>	Eyes absent homolog 4
<b>FAH</b>	Fumarylacetoacetase
<b>FGF12</b>	Fibroblast growth factor 12
<b>FHL1</b>	Four and a half LIM domains protein 1
<b>FHL2</b>	Four and a half LIM domains 2 (FHL-2)
<b>FHOD3</b>	FH1/FH2 domain-containing protein 3
<b>FKRP</b>	Fukutin-related protein
<b>FKTN</b>	Fukutin
<b>FLNC</b>	Filamin-C
<b>FOXD4</b>	Forkhead box protein D4
<b>FOXRED1</b>	FAD-dependent oxidoreductase domain-containing protein 1
<b>FXN</b>	Frataxin, mitochondrial
<b>GAA</b>	Lysosomal alpha-glucosidase
<b>GATA4</b>	Transcription factor GATA-4
<b>GATA5</b>	Transcription factor GATA-5
<b>GATA6</b>	Transcription factor GATA-6
<b>GATAD1</b>	GATA zinc finger domain-containing protein 1
<b>GFM1</b>	Elongation factor G, mitochondrial
<b>GJA1</b>	Gap junction alpha-1 protein

<b>Gene</b>	<b>Protein name</b>
<b>GJA5</b>	Gap junction alpha-5 protein
<b>GLA</b>	Alpha galactosidase A
<b>GLB1</b>	Beta-galactosidase
<b>GNPTAB</b>	N-acetylglucosamine-1-phosphotransferase subunits alpha/beta
<b>GPD1L</b>	Glycerol-3-phosphate dehydrogenase 1-like protein
<b>GREM2</b>	Gremlin-2
<b>GUSB</b>	Beta-glucuronidase
<b>HCN4</b>	Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4
<b>HFE</b>	Hereditary hemochromatosis protein
<b>HRAS</b>	GTPase HRas
<b>IDH2</b>	isocitrate dehydrogenase [NADP], mitochondrial
<b>ILK</b>	Integrin-linked protein kinase
<b>IRX3</b>	iroquois-class homeodomain protein IRX-3
<b>JPH2</b>	Junctophilin 2
<b>JUP</b>	Junction plakoglobin
<b>KCNA5</b>	Potassium voltage-gated channel subfamily A member 5
<b>KCND2</b>	Potassium voltage-gated channel subfamily D member 2
<b>KCND3</b>	Potassium voltage-gated channel subfamily D member 3
<b>KCNE1</b>	Potassium voltage-gated channel subfamily E member 1
<b>KCNE2</b>	Potassium voltage-gated channel subfamily E member 2
<b>KCNE3</b>	Potassium voltage-gated channel subfamily E member 3
<b>KCNE5</b>	Potassium voltage-gated channel subfamily E member 1-like protein
<b>KCNH2</b>	Potassium voltage-gated channel subfamily H member 2
<b>KCNJ2</b>	Inward rectifier potassium channel 2
<b>KCNJ5</b>	G protein-activated inward rectifier potassium channel 4
<b>KCNJ8</b>	ATP-sensitive inward rectifier potassium channel 8
<b>KCNK17</b>	Potassium channel subfamily K member 17
<b>KCNK3</b>	potassium channel subfamily K member 3
<b>KCNQ1</b>	Potassium voltage-gated channel subfamily KQT member 1
<b>KLF10</b>	Krueppel-like factor 10
<b>KRAS</b>	GTPase KRas
<b>LAMA2</b>	Laminin subunit alpha-2
<b>LAMA4</b>	Laminin subunit alpha-4
<b>LAMP2</b>	Lysosome-associated membrane glycoprotein 2
<b>LDB3</b>	LIM domain-binding protein 3
<b>LDLR</b>	Low density lipoprotein receptor
<b>LIAS</b>	Lipoyl synthase, mitochondrial
<b>LMNA</b>	Prelamin-A/C
<b>LZTR1</b>	Leucine-zipper-like transcriptional regulator 1

<b>Gene</b>	<b>Protein name</b>
<b>MAP2K1</b>	Dual specificity mitogen-activated protein kinase kinase 1
<b>MAP2K2</b>	Dual specificity mitogen-activated protein kinase kinase 2
<b>MIB1</b>	E3 ubiquitin-protein ligase MIB1
<b>MLYCD</b>	Malonyl-CoA decarboxylase, mitochondrial
<b>MRPL3</b>	39S ribosomal protein L3, mitochondrial
<b>MRPL44</b>	39S ribosomal protein L44, mitochondrial
<b>MRPS22</b>	28S ribosomal protein S22, mitochondrial
<b>MTO1</b>	Protein MTO1 homolog, mitochondrial
<b>MYBPC3</b>	Myosin-binding protein C, cardiac-type
<b>MYH11</b>	Myosin-11
<b>MYH6</b>	Myosin-6
<b>MYH7</b>	Myosin-7
<b>MYL2</b>	Myosin regulatory light chain 2, ventricular/cardiac muscle isoform
<b>MYL3</b>	Myosin light chain 3
<b>MYLK2</b>	Myosin light chain kinase 2, skeletal/cardiac muscle
<b>MYOM1</b>	Myomesin-1
<b>MYOT</b>	Myotilin
<b>MYOZ2</b>	Myozenin-2
<b>MYPN</b>	Myopalladin
<b>NEBL</b>	Nebulette
<b>NEXN</b>	Nexilin
<b>NF1</b>	Neurofibromin
<b>NKX2-5</b>	Homeobox protein Nkx-2.5
<b>NKX2-6</b>	Homeobox protein Nkx-2.6
<b>NNT</b>	NAD(P) transhydrogenase, mitochondrial
<b>NOS1AP</b>	Carboxyl-terminal PDZ ligand of neuronal nitric oxide synthase protein
<b>NOTCH1</b>	Neurogenic locus notch homolog protein 1
<b>NPPA</b>	Atrial natriuretic factor
<b>NRAS</b>	GTPase NRas
<b>OBSCN</b>	Obscurin
<b>OBSL1</b>	Obscurin-like protein 1
<b>OPA3</b>	optic atrophy 3 protein
<b>PDHA1</b>	Pyruvate dehydrogenase E1 component subunit alpha, somatic form, mitochondrial
<b>PDLIM3</b>	PDZ and LIM domain protein 3
<b>PERP</b>	p53 apoptosis effector related to PMP-22
<b>PHKA1</b>	Phosphorylase b kinase regulatory subunit alpha, skeletal muscle isoform
<b>PITX2</b>	Pituitary homeobox 2
<b>PKP2</b>	Plakophilin 2
<b>PKP4</b>	Plakophilin 4

<b>Gene</b>	<b>Protein name</b>
<b>PLN</b>	Cardiac phospholamban
<b>PMM2</b>	Phosphomannomutase 2
<b>PPP1R13L</b>	relA-associated inhibitor
<b>PRDM16</b>	PR domain zinc finger protein 16
<b>PRKAG2</b>	5'-AMP-activated protein kinase subunit gamma-2
<b>PSEN1</b>	Presenilin-1
<b>PSEN2</b>	Presenilin-2
<b>PTPN11</b>	Tyrosine-protein phosphatase non-receptor type 11
<b>RAF1</b>	RAF proto-oncogene serine/threonine-protein kinase
<b>RANGRF</b>	Ran guanine nucleotide release factor
<b>RASA2</b>	ras GTPase-activating protein 2
<b>RBM20</b>	Probable RNA-binding protein 20
<b>RIT1</b>	GTP-binding protein Rit1
<b>RRAS</b>	ras-related protein R-Ras
<b>RYR2</b>	Ryanodine receptor 2
<b>SCN10A</b>	sodium channel protein type 10 subunit alpha
<b>SCN1B</b>	Sodium channel subunit beta-1
<b>SCN2B</b>	Sodium channel subunit beta-2
<b>SCN3B</b>	Sodium channel subunit beta-3
<b>SCN4B</b>	Sodium channel subunit beta-4
<b>SCN5A</b>	Sodium channel protein type 5 subunit alpha
<b>SCO2</b>	Protein SCO2 homolog, mitochondrial
<b>SDHA</b>	Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial
<b>SGCA</b>	Alpha-sarcoglycan
<b>SGCB</b>	Beta-sarcoglycan
<b>SGCD</b>	Delta-sarcoglycan
<b>SHOC2</b>	Leucine-rich repeat protein SHOC-2
<b>SLC22A5</b>	Solute carrier family 22 member 5
<b>SLC25A3</b>	phosphate carrier protein, mitochondrial
<b>SLC25A4</b>	ADP/ATP translocase 1
<b>SLMAP</b>	Sarcolemmal membrane-associated protein
<b>SNTA1</b>	Alpha-1-syntrophin
<b>SOS1</b>	Son of sevenless homolog 1
<b>SOS2</b>	Son of sevenless homolog 2
<b>SPEG</b>	Striated muscle preferentially expressed protein kinase
<b>SPRED1</b>	Sprouty-related, EVH1 domain-containing protein 1
<b>SRY</b>	Sex-determining region Y protein
<b>SURF1</b>	Surfeit locus protein 1
<b>SYNE1</b>	Nesprin-1
<b>SYNE2</b>	Nesprin-2
<b>TAZ</b>	Tafazzin

<b>Gene</b>	<b>Protein name</b>
<b>TBX20</b>	T-box transcription factor TBX20
<b>TBX5</b>	T-box transcription factor TBX5
<b>TCAP</b>	Telethonin
<b>TGFB3</b>	Transforming growth factor, beta 3
<b>TMEM43</b>	Transmembrane protein 43
<b>TMEM70</b>	Transmembrane protein 70, mitochondrial
<b>TMPO</b>	Thymopoietin
<b>TNNC1</b>	Troponin C, slow skeletal and cardiac muscles
<b>TNNI3</b>	Troponin I, cardiac muscle
<b>TNNI3K</b>	Serine/threonine-protein kinase TNNI3K
<b>TNNT2</b>	Troponin T, cardiac muscle
<b>TOR1AIP1</b>	torsin-1A-interacting protein 1
<b>TPM1</b>	Tropomyosin alpha-1 chain
<b>TRDN</b>	Triadin
<b>TRIM63</b>	E3 ubiquitin-protein ligase TRIM63
<b>TRPM4</b>	Transient receptor potential cation channel subfamily M member 4
<b>TSFM</b>	Elongation factor Ts, mitochondria
<b>TTN</b>	Titin
<b>TTR</b>	Transthyretin
<b>TXNRD2</b>	Thioredoxin reductase 2, mitochondrial
<b>VCL</b>	Vinculin
<b>XK</b>	Membrane transport protein XK
<b>ZFH3</b>	Zinc finger homeobox protein 3
<b>ZFPM2</b>	Zinc finger homeobox protein 3

**Supplementary Table 2.** Other rare exonic genetic variants (MAF<0.001) identified in index cases.

<b>Family</b>	<b>Case</b>	<b>Gene</b>	<b>Genomic position</b>	<b>Protein change</b>	<b>gnomAD count</b>	<b>ClinVar</b>
F1	II:2	<i>TTN</i>	g.179545020C>T	p.(Val10810Ile)	2/247184	-
F2	II:4	-	-	-	-	-
F3	II:3	<i>HRAS</i>	g.532746C>T	p.(Asp154Asn)	7/247850	2 VUS
F4	II:6	-	-	-	-	-
F5	II:2	<i>DMD</i>	g.31222109A>G	p.(Ile3259Thr)	-	-
F6	II:3	<i>FKTN</i>	g.108397539_10839740insA	p.(Tyr461fs)	5/251356	1 VUS
F7	II:1	<i>LAMA4</i>	g.112575200G>T	p.(Ser51Arg)	-	-
F8	II:3	<i>COQ2</i>	g.84193317delA	p.(Leu234Argfs*14)	1/241316	-
F9	II:3	-	-	-	-	-
F10	II:2	-	-	-	-	-
F11	II:2	-	-	-	-	-

gnomAD: genome aggregation database; MAF: minor allele frequency; VUS: Variant of unknown significance

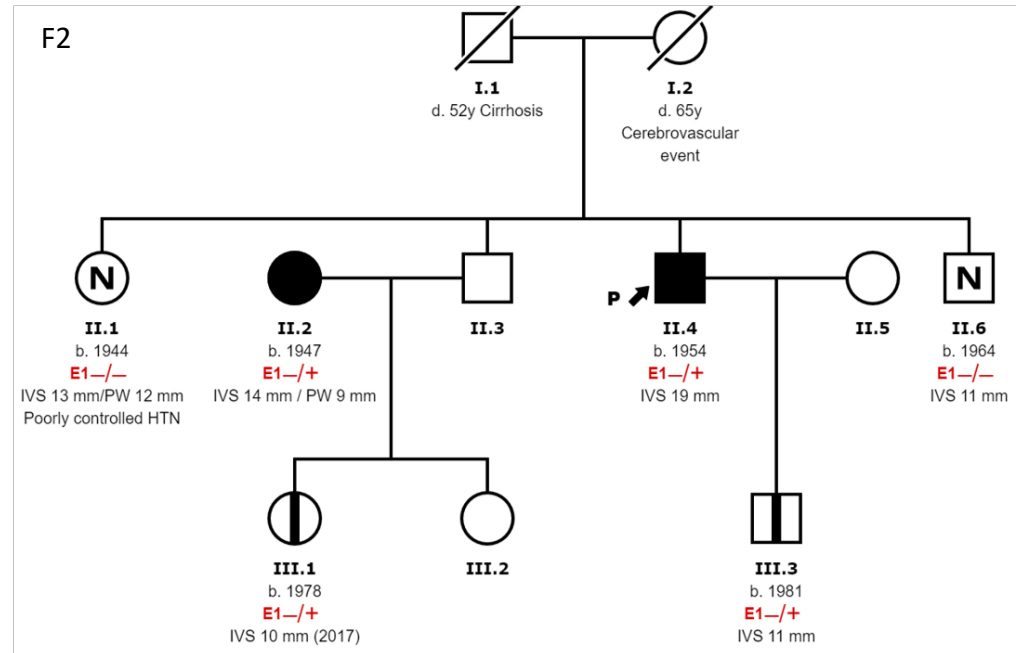
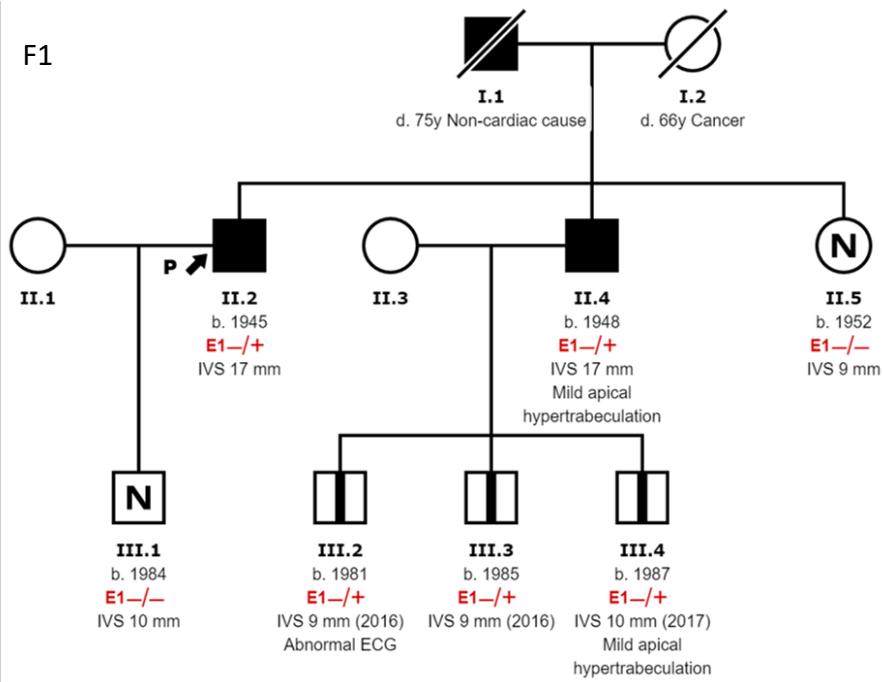
**Supplementary Table 3.** Bioinformatic predictors

<b>SIFT</b>	<b>Polyphen-2</b>	<b>MutationTaster</b>	<b>CADD</b>	<b>DANN</b>	<b>FATHMM</b>
0 Damaging	1 Probably damaging	1 Disease-causing	6.880	0.998	0.995

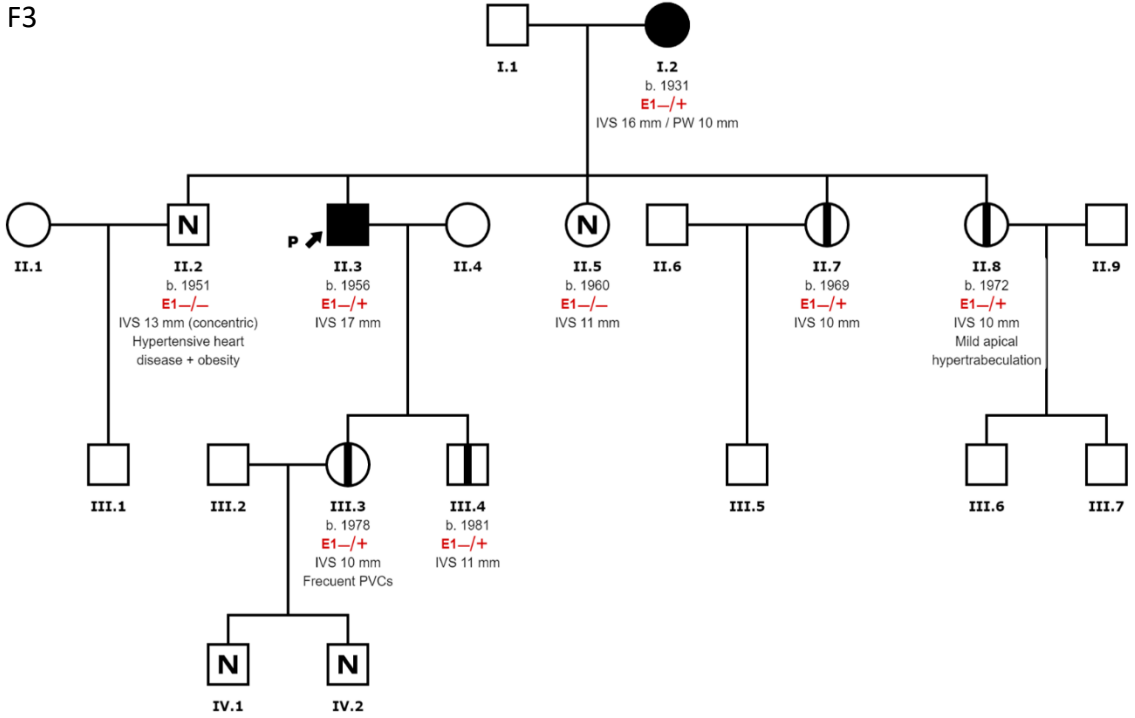
CADD: Combined Annotation Dependent Depletion; DANN: Deleterious Annotation of genetic variants using Neural Networks; FATHMM: Functional Analysis through Hidden Markov Models; Polyphen: Polymorphism Phenotyping



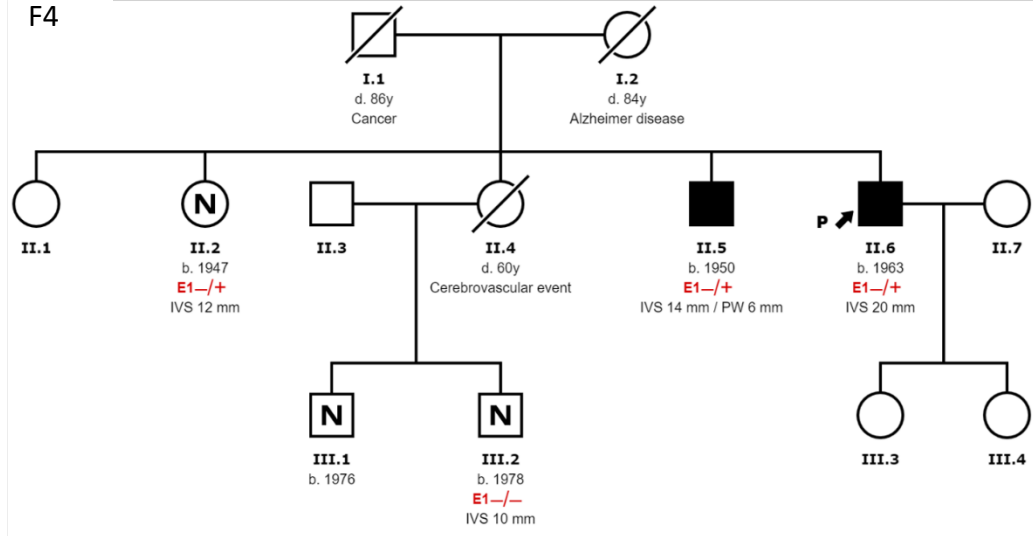
### Supplementary Figure 1. Pedigrees



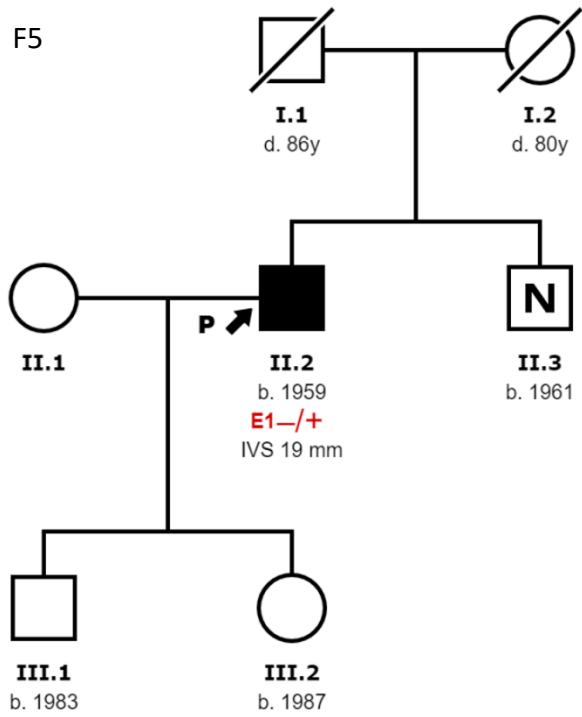
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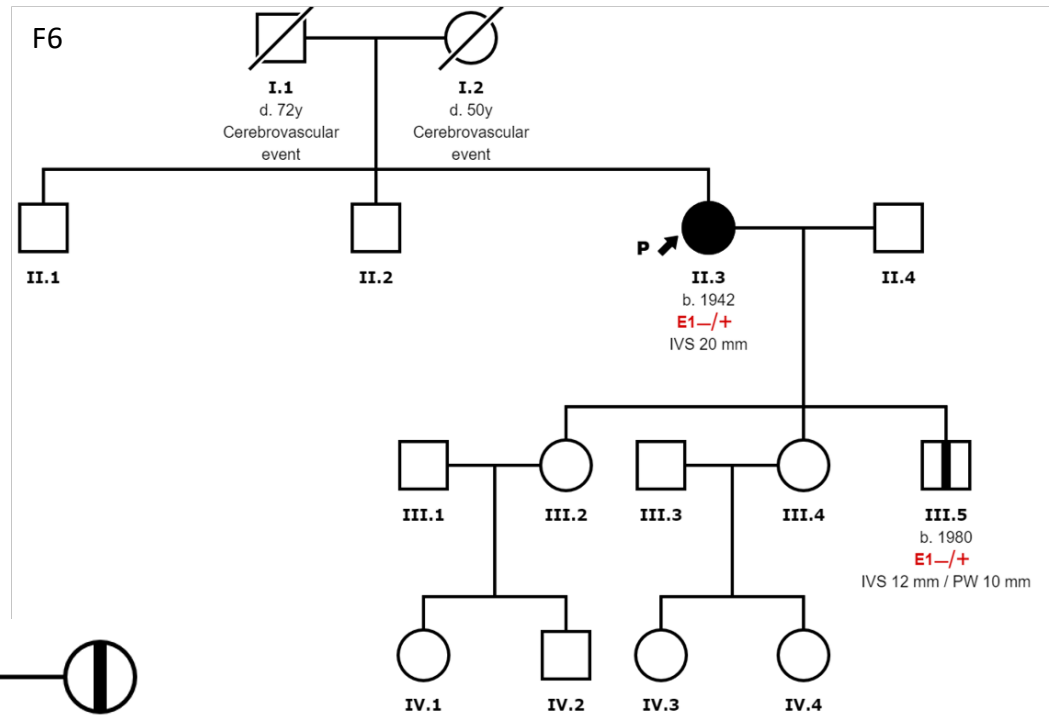
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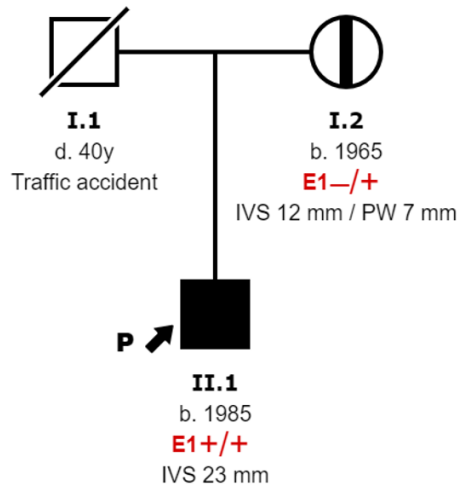
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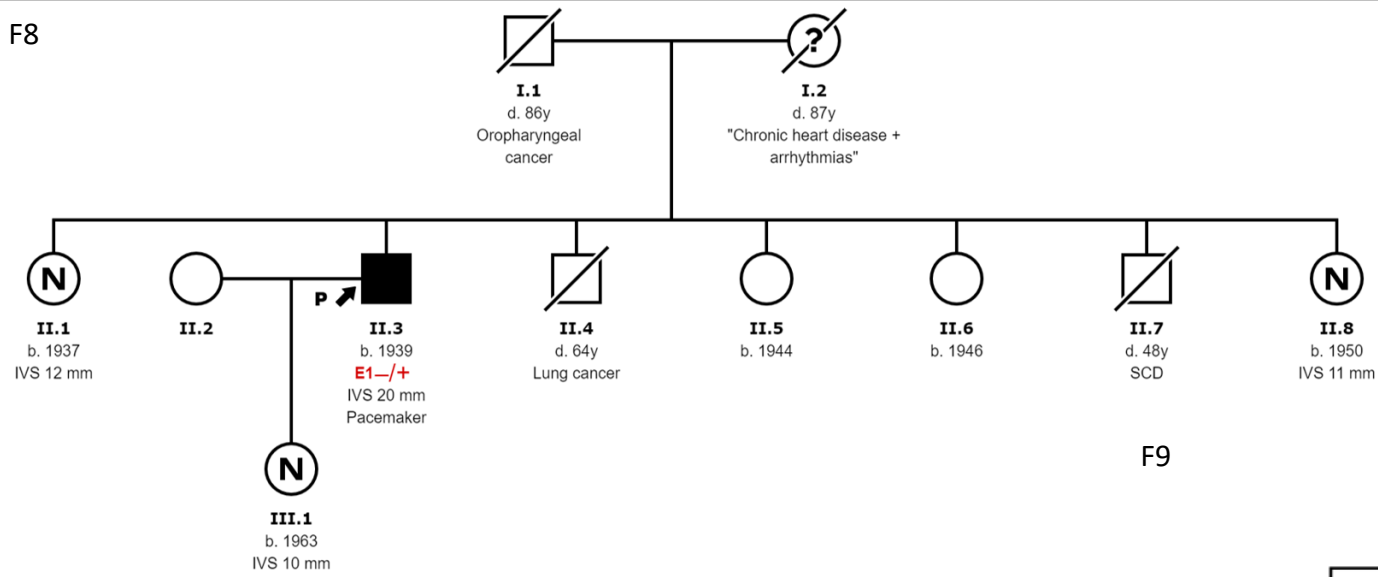
F6



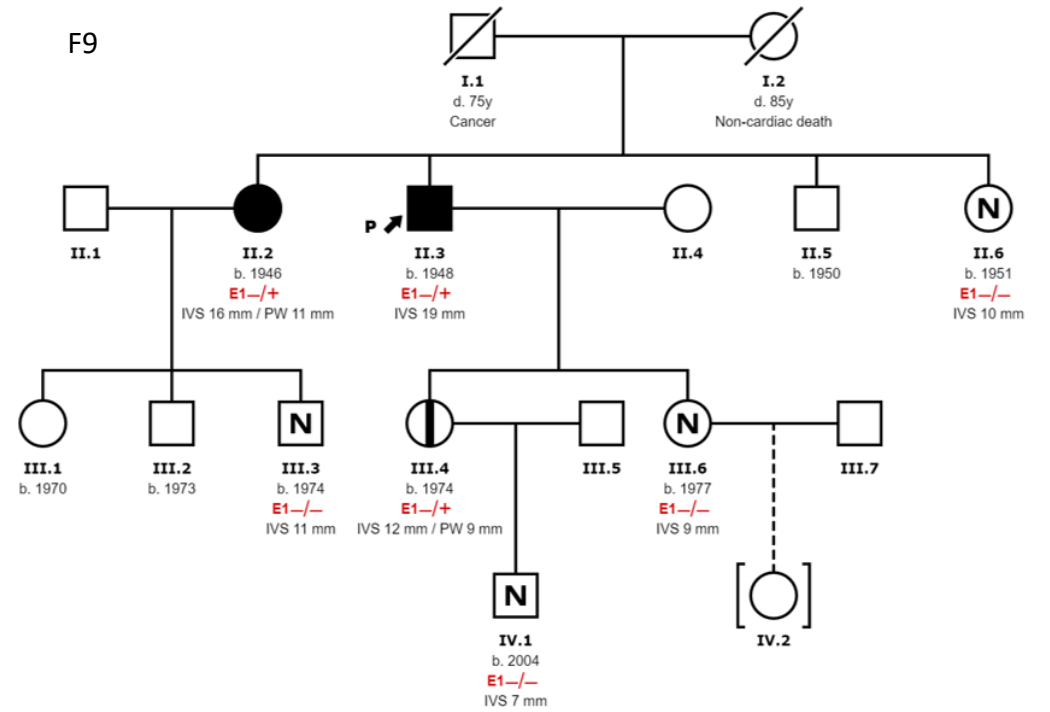
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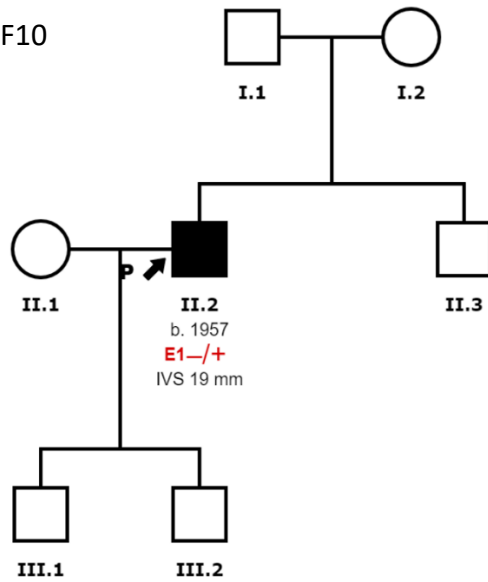
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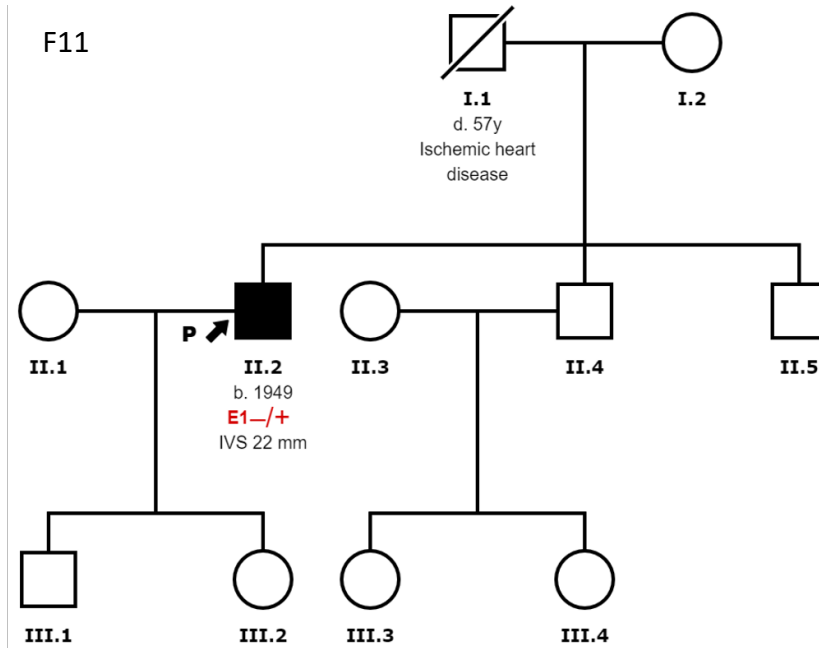
F9










F10



F11



-  Female
-  Male
-  Clinically affected (HCM)
-  Asymptomatic / could later manifest the disease
-  Not affected
-  Deceased female
-  Deceased male

**E1** CSRP3 (g.19206558C>T, c.449G>A, p.Cys150Tyr)  
 +/- = homozygous, -/+ = heterozygous, -/- = not found