SUPPLEMENTAL MATERIAL

Supplemental Methods

Cohort recruitment

SCAD cases were recruited via a social media platform or through direct referral from cardiologists. Informed, written consent was obtained prior to enrolment into the study. The study was approved by the St. Vincent's Hospital Human Research Ethics Committee (HREC/16/SVH/338, protocol number SVH 16/245) and conducted in accordance with the Australian National Health and Medical Research Council's National Statement on Ethical Conduct in Human Research and the CPMP/ICH Note for Guidance on Good Clinical Practice. SCAD diagnosis was confirmed by review of coronary angiogram images by an expert interventional cardiologist (DM) blinded to the results of the genetic analysis. Patient information was obtained by phone interviews, review of specialist letters and hospital records. The cohort of 91 cases had no known family history of SCAD. A subset of the Medical Genome Reference Bank (MGRB)[41] with European ancestry, consisting of 1127 Australians over 70 years of age, free from cardiovascular disease, degenerative neurological disorders, and a history of cancer, was used as a control cohort for whole genome sequencing (WGS) data. A cohort of 76 dilated cardiomyopathy probands was used as a separate control dataset for polygenic risk score analysis.[42] An independent SCAD cohort of 384 cases recruited at the University of Leicester, used for validation of selected analyses, has been described previously.[43]

Clinical cohort characteristics assessment

The cohort was examined for stressors at the time of SCAD. Chronic emotional stress included prolonged work-related bullying, caregiving for a seriously ill or disabled family member, financial distress, and intimate relationship breakdowns that occurred in the period directly preceding the subject's SCAD event. Pregnancy-related SCAD was defined as gestation until five months post-partum, as defined in other cardiovascular diseases.[44]

DNA extraction, sequencing, and processing

Genomic DNA was extracted (PureLink GenomicDNA Mini Kit; Invitrogen) from buccal cells collected using a cheek swab. WGS was performed using paired end KAPA PCR-Free v2.1 libraries on the Illumina HiSeq X Ten platform with 30x coverage (Kinghorn Centre for Clinical Genomics, Sydney). Bioinformatic processing was based on that used for the MGRB cohort.[41] Reads were aligned to the GRCh37 reference genome with Burrows-Wheeler Aligner[45] and SNVs and INDELs were called with the Genome Analysis Toolkit Best Practices pipeline.[46] All variants were annotated with Annovar[47] against RefSeq (version 01-06-2017). Principal component analysis using 17,453 SNVs and projection to the 1000 Genomes principal components were used to confirm ethnicity (akt v0.3.2).[48] Non-relatedness of subjects in the cohort was confirmed with KING.[49]

Tier 1 and Tier 2 gene screen

Our two-tiered list of 90 genes was based on eight diagnostic gene panels for CTDs, vasculopathies, and previous publications that identified gene mutations in CTD genes in SCAD patients (accessed December 2019, Supplementary Table 1). Tier 1 consisted of 75 genes confidently featured on one or more of eight CTD or vasculopathy gene panels (Supplementary Table 2) and are thus considered clinically actionable. Tier 2 contained 15 lower confidence genes from the eight panels or genes that were previously included in reports[50, 51] or identified as candidates.[52-54] SCAD cases carrying clinically actionable variants in any of these genes were contacted for follow-up relevant to the indicated disorder (Supplementary Table 3).

ACMG rare variant analysis

Variant prioritization was performed using the Variant Prioritisation Ordering Tool (VPOT).[55] Variant classification was applied to all variants annotated to any gene in either tier of the gene list that had a gnomAD (v.2.1.1 used throughout) genomes pop-max minor allele frequency (MAF) ≤ 1% and that caused either frameshift, missense or nonsense changes, or were in a canonical splice site. Variant interpretation was based on American College of Medical Genetics (ACMG) guidelines[56] as determined by VarSome.[57] As such, the criteria relating to cohort frequencies or carrier or pedigree characteristics (PS4, PS2, PM3, PM6, PP1, PP4, BS4, BP2, BP5) were not considered. All variants classified as of uncertain significance (VUS), likely pathogenic (LP) or pathogenic (P) were visually verified with the Integrative Genomics Viewer (IGV).[58] ACMG rare variant analysis for the University of Leicester cohort was performed as previously described.[43]

Splice variant analysis

Spliceogen[59] and SpliceAI[60] were used to identify potential splicing candidates within the list of rare (MAF ≤ 1% in any gnomAD genomes population) variants in Tier 1 genes. Candidate variants with a SpliceAI score ≥ 0.4 for any type of splicing alteration were visually verified and following manual review, only variants where a transcriptional consequence could be predicted were retained. Whole blood gene expression from GTEx[61] and nonsense mediated decay predictions (using NMD predictor [62] for such variants predicted to cause a frameshift or premature termination codon, otherwise manually) were used to determine the potential for detecting mis-spliced transcripts in patient whole blood.

Structural variant analysis

Structural variants (SV) were called using GRIDSS v2.8.3,[63] Manta v1.6.0,[64] and CNVnator v0.4.1.[65] Very large SVs (>1 million nucleotides) were also called using ConanVarVar.[66] Deletions, indels, insertions, and duplications were identified from the GRIDSS-called BND records in a joint-call manner, using the jointsv software (https://github.com/VCCRI/jointsv). Only variants identified by at least two methods were considered, with a call by ConanVarVar required

for large SVs. Variants present in < 2.5% of the SCAD cohort and falling within our CTD and vasculopathy genes were assessed visually and for deleteriousness.

Clinical comparisons between rare gene list variant carriers and non-carriers

The clinical characteristics of SCAD cases identified to carry a rare, potentially deleterious variant in any Tier 1 or 2 gene and those of the remaining cases, were compared. All continuous variables were compared with t-tests, while binary variables were compared only where the presence of the characteristic was observed in at least 10 cases across the whole cohort, using Fisher's exact test.

Rare variant collapsing analysis

We assessed whether our entire gene list, tiers therein, or all genes throughout the genome, showed an enrichment of carriers of rare, predicted deleterious variants in cases compared to controls. To avoid confounding results due to ethnic differences, the rare variant collapsing analysis was confined to 88 SCAD samples clustering with the 1000 Genomes European superpopulation. We used the Medical Genome Reference Bank as controls; 1127 samples that were ethnically matched to cases were selected. This bank contains WGS data of Australians predominantly of European ancestry over 70 years of age, free from cardiovascular disease, degenerative neurological disorders and cancer. Variant filtering was performed using the variant selection criteria described in previous burden analyses.[67] Variants were considered to be rare if the gnomAD genome and exome non-Finnish European MAFs were $\leq$ 1%; and were included for analysis if the consequence was a frameshift or nonsense alteration, an alteration of a canonical splice site, or a missense mutation with phred-scaled CADD > 12 and PolyPhen HDIV "P" or "D". Multiallelic variants in this cohort were excluded from the analysis, as were any variants with gnomAD exome or genome median coverage $\leq$10 for the given position. Genotypes were included only if genotype quality (GQ) $\geq$ 30; coverage was between 12 and 150 (exclusive); and, where heterozygous, the percentage of reads supporting the alternate allele exceeded 25%. Variants implicated in significant results were visually confirmed with IGV. Carriers of qualifying variants were determined per unit of analysis (individual gene or set of genes). For units with a minimum of two variant carriers, the proportion of cases and controls carrying at least one qualifying variant was compared with a one-sided

Fisher's exact test. Genome-wide results were corrected for multiple testing using the Benjamini and Hochberg's false discovery rate method, applied across all genes enriched in cases. Gene ontology enrichment analysis[68] was used for subsequent investigation of possible mechanisms.

Using the effect sizes observed in recent SCAD gene associations, we investigated our power to detect rare variant associations. For example, *TSR1* was initially identified by a rare variant enrichment analysis across 85 Han Chinese SCAD patients and 295 controls (Sun et al. 2019[52]). With 88 sporadic cases (using the European samples only) and 1127 controls, our power to detect an association of the same effect size was 95% at a significance level of < 8.94e-06 (using Bonferroni correction- as we are testing 5,591 genes that had variants in our cases).

Novel loss-of-function (LoF) variants

LoF variants across the whole genome that were absent from all gnomAD populations were identified with LOFTEE v1.0.3.[69] Variant reporting was limited to only those that were: determined by LOFTEE to be high confidence LoF variants with no flags; annotated to a gene considered to be intolerant to loss of function (LOEUF ≤ 0.35);[69] present in fewer than 10 cases; present with an allelic balance ≥ 0.15; having a read depth ≥ 8; and passing visual inspection using IGV.

Validation of genes containing novel loss-of-function variants

Genes containing LoF variants absent from gnomAD but present in any of our 91 samples were assessed in our independent University of Leicester SCAD cohort. Variants were reported if they were classified "high impact" in SnpEff; had a DRAGEN variant QC "PASS" status; were absent from gnomAD; designated a high confidence LoF variant with LOFTEE; were annotated to a transcript with a CCDS; had an intracohort heterozygous carrier frequency < 5%; present with allelic balance $\geq 30\%$ and had coverage ≥ 10; and passed visual inspection using IGV.

Pathway analysis of LoF intolerant genes with novel LoF variants

Pathway analysis was applied to genes identified as harboring novel LoF variants in at least one case. Overrepresentation analysis using Wikipathways 2019 (human) via Enrichr[70] was used to identify common pathways.

Genes containing multiple rare structural variants

To identify genes possibly related to SCAD outside of our CTD and vasculopathy list, LoF intolerant genes with any potentially damaging SVs were investigated. SVs present in a maximum of one sporadic sample, absent from SV databases, and affecting at least one exon of any gene intolerant to LoF (LOEUF $\leq$ 0.35)[69]), were identified. All resulting variants were visually confirmed.

Short Tandem Repeats (STRs) analysis

We called STRs for multiple known pathogenic loci including the *FMR1* gene region using the intersect of three tools designed to detect STRs in WGS: TREDPARSE,[71] ExpansionHunter v3.2.2,[72] and exSTRa v1.1.0.[73]

SCAD Polygenic Risk Scores (PRS)

To investigate a polygenic contribution of common SNPs to SCAD, we calculated a PRS per sample for all cases and controls, which consisted of the sum of the risk alleles weighted by their effect sizes for the five significant SNPs identified from the first SCAD GWAS,[74] or the recent SCAD PRS[75] consisting of seven SNPs (supplementary table 14). Scores were compared between cohorts using the Kruskal Wallis rank sum test.

Statistical Analysis

All statistical tests were carried out in R (v 3.6).

Supplemental Tables

Supplementary Table I*. Gene list sources.*

Source	Panel	N genes	N genes unique to this source
AmbryGenetics	TAADNext panel	35	0
CTGT	Connective tissue disorder panel	47	5
GeneDx	Heritable disorders of connective tissue panel	57	5
Invitae	Aortopathy comprehensive panel	27	1
PanelApp	Thoracic aortic aneurysm or dissection panel	63	10
PreventionGenetics	Marfan syndrome and related aortopathies panel	30	1
SonicGenetics	Aortopathy panel; vasculopathy panel	32	5
VCGS	Aortopathy panel	17	0
Henkin et al. 2016[50]	na	27	1
Kaadan et al. 2018[51]	na	35	2
Fahey et al. 2018[54]	na	1	1
Turley et al. 2019[53]	na	1	1
Sun et al. 2019[52]	na	1	1

***Supplementary Table II**. Gene list.*

Gene	Tier	Ambry Genetics	CTGT	GeneDx	Invitae	Invitae details	PanelApp	PanelAp confidence rating	Prevention Genetics	Sonic Genetics	VCGS	Henkin et al. 2016[50]	Kaadan et al. 2018[11]	Fahey et al. 2018[54]	Turley et al. 2019[53]	Sun et al. 2019[52]
ABL1	1						y	green								
ACTA2	1	y	y	y	y		y	green	y	y	y	y	y			
ACVRL1	1									y			y			
ADAMTS10	1									y						
ADAMTS2	1		y	y			y	red								
ADAMTSL4	1						y	green								
AEBP1	1		y													
ALDH18A1	1			y			y	red								
ATP6V0A2	1			y			y	red								
ATP6V1E1	1			y												
ATP7A	1		y	y			y	red								
B3GALT6	1		y	y												
B3GAT3	1			y												
B4GALT7	1		y	y			y	red								
BGN	1	y	y	y			y	green								
C1R	1		y													
C1S	1		y													
CBS	1	y	y	y	y		y	amber	y	y	y	y	y			
CHST14	1	y	y	y			y	red								
COL11A1	1			y			y	red								
COL11A2	1			y			y	red								
COL12A1	1		y	y												
COL1A1	1	y	y	y			y	green		y	y					
COL1A2	1	y	y	y			y	green		y						
COL2A1	1			y			y	red								
COL3A1	1	y	y	y	y		y	green	y	y	y	y	y			
COL4A1	1						y	red		y						

COL5A1	1	y	y	y	y		y	green	y	y	y	y	y			
COL5A2	1	y	y	y	y		y	green	y	y		y	y			
COL9A1	1			y			y	red								
COL9A2	1			y			y	red								
COL9A3	1			y			y	red								
DCHS1	1		y													
DSE	1		y	y												
EFEMP2	1	y		y	y		y	green	y	y			y			
ELN	1			y			y	green	y	y						
ENG	1									y			y			
FBLN5	1			y			y	red	y							
FBN1	1	y	y	y	y		y	green	y	y	y	y	y			
FBN2	1	y	y	y	y		y	green	y	y	y	y	y			
FKBP14	1	y	y	y			y	red								
FLCN	1		y				y	green								
FLNA	1	y	y	y	y		y	green	y	y	y	y	y			
FLNB	1									y						
FOXE3	1	y	y		y		y	red	y							
GDF2	1									y						
LOX	1	y	y	y			y	green	y							
LTBP3	1		y													
LTBP4	1			y												
MAT2A	1	y	y	y	y	preliminary evidence	y	red	y							
MED12	1	y	y	y	y		y	green	y		y	y	y			
MFAP5	1	y	y	y			y	red	y	y						
MYH11	1	y	y	y	y		y	green	y	y	y	y	y			
MYLK	1	y	y	y	y		y	green	y	y	y	y	y			
NOTCH1	1	y	y	y	y		y	green	y	y		y	y			
PKD1	1						y	amber		y			y			
PKD2	1						y	amber					y			

PLOD1	1	y	y	y	y		y	green	y	y			y				
PRDM5	1	y	y	y													
PRKG1	1	y	y	y	y		y	green	y	y		y	y				
PYCR1	1			y													
RIN2	1			y													
SKI	1	y	y	y	y		y	green	y	y	y	y	y				
SLC2A10	1	y	y	y	y		y	green	y	y	y	y	y				
SLC39A13	1		y	y			y	red									
SMAD2	1		y	y			y	green									
SMAD3	1	y	y	y	y		y	green	y	y	y	y	y				
SMAD4	1	y	y	y	y		y	green	y	y		y	y				
SMS	1								y								
TGFB2	1	y	y	y	y		y	green	y	y	y	y	y				
TGFB3	1	y	y	y	y		y	green	y				y				
TGFBR1	1	y	y	y	y		y	green	y	y	y	y	y				
TGFBR2	1	y	y	y	y		y	green	y	y	y	y	y				
TNXB	1	y		y			y	red									
ZNF469	1	y	y	y			y	red									
ABCC6	2						y	red				y					
ACVR1	2						y	red									
EMILIN1	2						y	red									
F11R	2													y			
HCN4	2				y	preliminary evidence											
HNRNPK	2						y	red									
KCNN1	2						y	red									
LMX1B	2												y				
LTBP2	2						y	red									
MTHFR	2											y					
MYLK2	2						y	red									
RASA1	2												y				

SMAD6	2				y	preliminary evidence	y	red								
TLN1	2														y	
TSR1	2															y

Supplementary Table III. *Phenotypic features sought for connective tissue disorders.*

Disorder	Features
Marfan's syndrome Congenital contractural arachnodactyly	Height (taller than predicted, thin build, long fingers) Heart (murmur) or blood vessel problems Visual problems (extreme near sightedness, dislocated lens) Curved spine Collapsed lung Crowded teeth Chest bone (collapsed or protruding) Stretch marks not related to rapid weight gain or loss Flat feet
Ehlers Danlos syndrome	Hypermobility of joints/joint dislocations/joint pain Hyper-extensibility of skin/scarring/bruising Scoliosis Reduced muscle tone Contractures Heart valve problems - (mitral valve prolapse) Gum disease Blood vessel and bleeding problems
Brain small vessel disease 1	Vascular defects Cerebral hemorrhage/bleeding disorders Brain cysts Seizures Development/learning disorders Vision problems
Congenital heart defects and skeletal malformations syndrome	Skeletal abnormalities Congenital Heart disease Unusual facial features Contractures Joint problems
Cutis laxa	Sagging (not stretchy) skin Cardiovascular abnormalities

	Inguinal or umbilical hernia Emphysema Seizures Blood vessel problems (narrowing, bulging, tearing of arteries) Loose joints Coarse hair Calcium deposits at base of skull (occipital horn syndrome)
Arterial tortuosity syndrome	Tortuosity of major arteries including the aorta Hyper-extensible skin Hypermobility of joints Arachnodactyly Diaphragmatic hernia Keratoconus Aortic regurgitation Mental dysfunction Blepharophimosis
Pseudoxanthoma elasticum	Premature atherosclerosis Skin (yellowish papular lesions) Skin laxity (neck axillae, groin) Visual distortion (angioid streaks/mineralisation of Bruch's membrane) Gastro-intestinal bleeding Coronary artery disease Intracranial aneurysm/subarachnoid hemorrhage
Familial aneurysms	Visual problems (retinal tortuosity, cataracts) Kidney problems (hematuria, impaired renal function) Muscle cramps Aneurysms (intracranial) Strokes Blood vessel problems Anemia - (hemolytic) Heart rhythm problems Migraine with aura Seizures

Fibrodysplasia ossificans progressiva	Joint and muscle problems Toe malformation
Weil-Marchesani syndrome	Short stature Broad head (brachycephaly) Joint stiffness Visual problems (round lenses/*ectopia lentis*/myopia/glaucoma) Heart/vessel defects (patent ductus/pulmonary stenosis/thoracic aneurysm/cervical artery dissection)

Supplementary Table IV. *Variants identified by ACMG (Tier 1 and 2) and splice variant (Tier 1 only) analysis in genes typically causing autosomal recessive disease where cases were heterozygous.*

Identified by ACMG								
Case	Gene	Tier	Nucleotide variant	Amino acid variant	gnomAD MAF^	Varsome ACMG criteria*		
095	*AEBP1*	1	NM_001129.5:c.1630+1G>A	NA	0.00003610	PVS1, PM2, PP3, PP5		
099	*SLC2A10*	1	NM_030777.4:c.1334delG	p.Gly445GlufsTer40	0.00008484	PVS1, PM2, PP3, PP5		
105	*ABCC6*	2	NM_001171.6:c.2787+1G>T	NA	0.0001169	PVS1, PP3, PP5		
109								
Identified by splice variant analysis								
Case	Gene	Tier	Nucleotide variant	Predicted effect	gnomAD MAF^	SpliceAI score	GTEx whole blood median TPM	Predicted to undergo NMD
095	*AEBP1*	1	NM_001129.5:c.1630+1G>A	Donor loss	0.0000361	0.99	2.092	Y
060	*SLC39A13*	1	NM_001128225.3:c.735+362G>A	Acceptor gain	0.0022	0.89	9.01	Y
074	*LTBP4*	1	ENST00000308370.7:c.476A>G	Acceptor gain	0.00001784	0.88	6.774	Y
020	*ADAMTS2*	1	NM_014244.5:c.2457+822A>G	Acceptor gain	-	0.81	2.838	Y
007	*ADAMTS10*	1	NM_030957.4:c.1337+47G>A	Donor gain	0.00331	0.67	3.093	Y

ACMG, American College of Medical Genetics; MAF, minor allele frequency; TPM, transcripts per million; NMD, nonsense-mediated decay

*ACMG classifications are automatically derived from Varsome and manually evaluated; ^gnomAD MAF refers to all populations.

Supplementary Table V. *Phenotypic data and history for cases with (likely) pathogenic or splice-altering variants in genes causative for a CTD.*

Sample	Sex	Gene	Tier	Variant type	Condition assessed	Inheritance mode for condition^	Symptoms in case	Vascular symptoms reported in family	Notable SCAD details	Age at first SCAD	Other history*
004	F	*FBN1*	1	Likely pathogenic	Marfan syndrome	AD	None			55	
007	F	*ADAMTS10*	1	Splice	Weil-Marchesani syndrome	AR	None	Aortic dissection in maternal uncle		58	Breast cancer
020	F	*ADAMTS2*	1	Splice	Ehlers-Danlos syndrome	AR	Childhood scoliosis, some hypermobility		P-SCAD	41	Carrier of X-linked myotubular myopathy
046	F	*MFAP5*	1	Splice	Familial aneurysms	AD	Carotid artery dissection		3 SCAD episodes	53	Hypertension
060	F	*SLC39A13*	1	Splice	Ehlers-Danlos syndrome	AR	None			44	Migraines; Graves' disease; Polymyalgia rheumatica in father; unknown autoimmumne disorder in mother; rheumatoid arthritis, scleroderma, lupus (type unspecified), Graves' disease, and Raynaud's disease in sister

074	F	*FBN2*	1	Splice	Congenital contractural arachnodactyly	AD	None			41	Family history of stroke and sarcoidosis
		LTBP4	1	Splice	Cutis laxa	AR	None				
090	F	*ACVR1*	2	Likely pathogenic	Fibrodysplasia ossificans progressiva	AD	None			47	Grandmother had large "stomach" aneurysm
		ALDH18A1	1	Likely pathogenic	Cutis laxa	AD	None				
091	F	*ACVR1*	2	Likely pathogenic	Fibrodysplasia ossificans progressiva	AD	None	Cerebral aneurysm in maternal grand-aunt	P-SCAD	30	Migraines; family history of SLE and antiphospholipid syndrome; cerebral aneurysm in maternal great aunt
		PRKG1	1	Splice	Familial aneurysms	AD	None				
095	F	*AEBP1*	1	Pathogenic / splice	Ehlers-Danlos syndrome	AR	None			43	FMD; migraine
099	F	*SLC2A10*	1	Pathogenic	Arterial tortuosity syndrome	AR	None			27	Sjogren syndrome in sister, female first cousin had stroke due to aneurysm at 25 years
105	F	*ABCC6*	2	Pathogenic	Pseudoxanthoma elasticum	AR	None		3 SCAD episodes	36	FMD of carotid; lupus; stroke in maternal grandmother
108	F	*ABL1*	1	Splice	Congenital heart defects and skeletal malformations syndrome	AD	None			43	Migraines; family history of stroke and kidney disease

109	F	*ABCC6*	2	Pathogenic	Pseudoxanthoma elasticum	AR	None			41	Graves' disease; father was recently diagnosed with an autoimmune disease
115	F	*FBN1*	1	Likely pathogenic	Marfan syndrome	AD	None	Maternal aunt had aneurysm in 40s		32	
146	M	*COL3A1*	1	Pathogenic	Ehlers-Danlos syndrome	AD	None	Aortic dissection in paternal grandfather		38	Migraines
170	F	*COL4A1*	1	Likely pathogenic	Brain small vessel disease 1	AD	None	"Stomach" aneurysm in maternal grandfather	2 SCAD episodes, 1 of which, pregnancy-SCAD	35	Migraines
171	F	*COL4A1*	1	Likely pathogenic	Brain small vessel disease 1	AD	Possible carotid dissection	Multiple family members with stroke; foetal intracranial haemorrhage leading to cerebral palsy and seizures in son of case	2 SCAD episodes, 1 of which, pregnancy-SCAD	30	Migraines; tall stature; high, arched palate

P-SCAD, pregnancy related SCAD.

^Inheritance mode for specific form of condition listed which is associated with given gene; *Limited to vascular, connective tissue, inflammatory, and hormonal conditions in case and family

Supplementary Table VI. *VUS only Carriers.*

Sample	Gene	Tier	Variant
007	*DCHS1*	1	*DCHS1*(NM_003737.4):c.6062G>A
011	*ADAMTSL4*	1	*ADAMTSL4*(NM_019032.5):c.1700G>A
	C1S	1	*C1S*(NM_201442.4):c.475C>A
012	*FLNB*	1	*FLNB*(NM_001164317.2):c.2104G>A
019	*EFEMP2*	1	*EFEMP2*(NM_016938.5):c.202G>C
	SKI	1	*SKI*(NM_003036.4):c.723C>G
020	*TLN1*	2	*TLN1*(NM_006289.4):c.907C>T
024	*DSE*	1	*DSE*(NM_001080976.3):c.2842T>C
	PKD1	1	*PKD1*(NM_001009944.3):c.8543T>C
034	*FLNB*	1	*FLNB*(NM_001164317.2):c.7134C>A
	PYCR1	1	*PYCR1*(NM_006907.4):c.334C>T
	RASA1	2	*RASA1*(NM_002890.3):c.3133G>T
049	*COL12A1*	1	*COL12A1*(NM_004370.6):c.1775C>T
050	*B4GATL7*	1	*B4GALT7*(NM_007255.3):c.38G>A
053	*TNXB*	1	*TNXB*(NM_019105.8):c.12350G>A
055	*TNXB*	1	*TNXB*(NM_019105.8):c.9230C>T
061	*COL9A1*	1	*COL9A1*(NM_001851.5):c.827C>T
064	*TNXB*	1	*TNXB*(NM_019105.8):c.9254T>C
065	*TNXB*	1	*TNXB*(NM_019105.8):c.12350G>A
073	*TSR1*	2	*TSR1*(NM_018128.5):c.2333C>T
074	*COL5A1*	1	*COL5A1*(NM_001278074.1):c.452A>G

	FLNA	1	*FLNA*(NM_001110556.2):c.3323G>A
	LTBP3	1	*LTBP3*(NM_001130144.2):c.1684C>G
078	*ALDH18A1*	1	*ALDH18A1*(NM_002860.4):c.71C>T
079	*COL5A1*	1	*COL5A1*(NM_001278074.1):c.4892C>T
092	*TSR1*	2	*TSR1*(NM_018128.5):c.2333C>T
093	*TNXB*	1	*TNXB*(NM_019105.8):c.12350G>A
	TNXB	1	*TNXB*(NM_019105.8):c.2018A>C
098	*ADAMTS2*	1	*ADAMTS2*(NM_014244.5):c.1903G>A
108	*COL11A1*	1	*COL11A1*(NM_001854.4):c.2921C>A
	LTBP2	2	*LTBP2*(NM_000428.3):c.221A>G
117	*FBN2*	1	*FBN2*(NM_001999.4):c.8444A>C
	FLNB	1	*FLNB*(NM_001164317.2):c.2198G>A
122	*ABL1*	1	*ABL1*(NM_007313.2):c.1604G>A
	COL9A2	1	*COL9A2*(NM_001852.4):c.1561A>G
124	*FLNB*	1	*FLNB*(NM_001164317.2):c.4507G>A
126	*COL11A1*	1	*COL11A1*(NM_001854.4):c.1408G>C
	NOTCH1	1	*NOTCH1*(NM_017617.5):c.2128G>A
127	*FLNB*	1	*FLNB*(NM_001164317.2):c.4507G>A
	ZNF469	1	*ZNF469*(NM_001367624.2):c.11425G>A
129	*EMILIN1*	2	*EMILIN1*(NM_007046.4):c.2237G>T
	TNXB	1	*TNXB*(NM_019105.8):c.12350G>A
137	*MTHFR*	2	*MTHFR*(NM_005957.5):c.673A>G
	PRKG1	1	*PRKG1*(NM_006258.4):c.1964T>C
143	*FLNB*	1	*FLNB*(NM_001164317.2):c.2453G>A
	LTBP2	2	*LTBP2*(NM_000428.3):c.3931A>C
	PRDM5	1	*PRDM5*(NM_018699.3):c.1712A>G

145	*COL12A1*	1	*COL12A1*(NM_004370.6):c.5588G>T
147	*COL11A2*	1	*COL11A2*(NM_080680.3):c.2249T>C
148	*FBN1*	1	*FBN1*(NM_000138.5):c.4612A>G
150	*COL9A1*	1	*COL9A1*(NM_001851.5):c.2527C>T
151	*ATP6V0A2*	1	*ATP6V0A2*(NM_012463.4):c.776G>A
	COL12A1	1	*COL12A1*(NM_004370.6):c.4980C>G
154	*PLOD1*	1	*PLOD1*(NM_000302.4):c.303C>T
155	*COL9A1*	1	*COL9A1*(NM_001851.5):c.2543G>A
	TSR1	2	*TSR1*(NM_018128.5):c.1A>G
156	*MTHFR*	2	*MTHFR*(NM_005957.5):c.1409A>T
164	*KCNN1*	2	*KCNN1*(NM_002248.4):c.65G>A
193	*COL11A2*	1	*COL11A2*(NM_080680.3):c.3824C>T

Supplementary Table VII. *Splice variants with lower SpliceAI scores (<0.4) but ultra rare (<0.001) in gnomAD.*

Case	Sex	Gene	Variant (hg19)	Inheritance mode for condition	Predicted effect	gnomAD MAF (all samples)	gnomAD homozygote count	SpliceAI score
137	F	*FLNB*	NM_001164317.2:c.292+33392G>A	AD	Donor gain	-	-	0.34
099	F	*ELN*	NM_000501.4:c.232+100_232+101insACTGACCTGGACTGCACTGACGGTG	AD	Acceptor gain	-	-	0.28
010	F	*COL2A1*	NM_001844.5:c.1122+346C>G	AD	Donor gain	0.0001274	0	0.23

Supplementary Table VIII. *Samples and genes carrying qualifying variants within our CTD gene list.*

Sample	Tier 1 gene(s)	Tier 2 gene(s)	N variants
090	*ALDH18A1*		1
037	*COL11A1*		1
065	*COL11A2*		1
049	*COL12A1*		1
087	*COL12A1*		1
031	*COL5A1*		1
060	*COL5A1*		1
079	*COL5A1*		1
001	*COL5A2*		1
155	*COL9A1*		1
022	*COL9A2*		1
007	*DCHS1*		1
024	*DSE*		1
115	*FBN1*		1
010	*FBN2*		1
149	*FBN2*		1
164	*FBN2*		1
017	*FLCN*		1
054	*FLNB*		1
131	*MYH11*		1
023	*PKD1*		1
123	*PKD1*		1

130	*PLOD1*		1
154	*PLOD1*		1
162	*PLOD1*		1
111	*RIN2*		1
109	*TGFB2*		1
134	*TGFBR2*		1
028	*TNXB*		1
064	*TNXB*		1
093	*TNXB*		1
089	*ZNF469*		1
097	*ZNF469*		1
127	*ZNF469*		1
129		*EMILIN1*	1
041	*FLNA*	*TLN1*	2
040	*ADAMTS10, ELN*		2
098	*ADAMTS2, PKD1*		2
108	*COL11A1, COL5A1*		2
193	*COL11A2, COL2A1*		2
145	*COL12A1, COL4A1*		2
099	*COL12A1, SLC2A10*		2
171	*COL1A2, COL4A1*		2
052	*COL4A1, NOTCH1*		2
121	*COL4A1, TGFB2*		2
034	*COL5A2, FLNB*		2
137	*COL5A2, PRKG1*		2

105	*COL9A3, FBN2*		2
078	*COL9A3, MYH11*		2
085	*COL9A3, TNXB*		2
019	*DCHS1, EFEMP2*		2
156	*FBN2, PKD1*		2
074	*FLNA, LTBP3*		2
051	*FLNA, NOTCH1*		2
143	*FLNB, PRDM5*		2
124	*PKD1, PKD1*		2
147	*ABL1, COL11A2*	*TSR1*	3
092	*B3GALT6, PKD2*	*TSR1*	3
020	*MYH11, NOTCH1*	*TLN1*	3
122	*ABL1, AEBP1, COL9A2*		3
053	*ABL1, MYH11, TNXB*		3
061	*ACVRL1, COL9A1, TGFB2*		3
150	*ADAMTS10, COL9A1, PKD1*		3
117	*ADAMTS10, FLNB, PKD1*		3
043	*COL11A2, PKD2, TNXB*		3
086	*COL12A1, FBN2, PKD1*		3
146	*COL3A1, FLNB, ZNF469*		3
170	*COL4A1, MYH11, TNXB*		3
091	*COL11A2, COL11A2*	*TLN1, TLN1*	4
011	*ADAMTSL4, C1S, TNXB, TNXB*		4
095	*AEBP1, FBN2, FBN2, FLNB*		4

151	*ATP6V0A2, COL12A1, COL9A3, NOTCH1*		4
012	*COL11A1, COL4A1, COL5A1, FLNB*		4
055	*ABL1, COL2A1, FLNA, MED12, TNXB*		5
159	*ATP6V0A2, COL5A1, FBN2, MYH11, PKD1*		5
126	*COL11A1, COL9A3, FBLN5, NOTCH1, PKD1, PKD1*		6

Supplementary Table IX. *Nominally significant genes identified by genome-wide collapsing analysis.*

Gene	P-value	FDR adjusted p-value	N case carriers	N case non-carriers	N control carriers	N control non-carriers	Odds ratio
AFDN	0.000121881	0.432251693	4	84	1	1126	53.21015157
ACAT2	0.00034539	0.432251693	4	84	2	1125	26.58486719
KIR2DL1	0.000367997	0.432251693	3	85	0	1127	Inf
TMEM236	0.000367997	0.432251693	3	85	0	1127	Inf
PCDHA4	0.000391543	0.432251693	8	80	19	1108	5.814034541
MARF1	0.000509594	0.432251693	10	78	32	1095	4.377716008
PCNX2	0.000541184	0.432251693	6	82	10	1117	8.14228439
PCNX3	0.001110021	0.478192981	13	75	58	1069	3.190056812
DUSP15	0.001394564	0.478192981	3	85	1	1126	39.39527901
MAJIN	0.001394564	0.478192981	3	85	1	1126	39.39527901
PIGB	0.001394564	0.478192981	3	85	1	1126	39.39527901
HCRTR1	0.001438658	0.478192981	4	84	4	1123	13.29747774
RUBCNL	0.001438658	0.478192981	4	84	4	1123	13.29747774
MRPL13	0.00144135	0.478192981	5	83	8	1119	8.393617142
ZNF134	0.00144135	0.478192981	5	83	8	1119	8.393617142
PIGM	0.00211509	0.478192981	5	83	9	1118	7.456592061
TOGARAM2	0.00211509	0.478192981	5	83	9	1118	7.456592061
TCTE1	0.002446935	0.478192981	4	84	5	1122	10.63631041
ITGA2B	0.002993141	0.478192981	5	83	10	1117	6.706891842
LUC7L	0.002993141	0.478192981	5	83	10	1117	6.706891842
SYCP2	0.002993141	0.478192981	5	83	10	1117	6.706891842
KRT12	0.003096539	0.478192981	8	80	28	1099	3.91785029

CATSPERE	0.003303588	0.478192981	3	85	2	1125	19.72810852
MAEA	0.003303588	0.478192981	3	85	2	1125	19.72810852
OR2T3	0.003303588	0.478192981	3	85	2	1125	19.72810852
RAD1	0.003303588	0.478192981	3	85	2	1125	19.72810852
TTC38	0.003677168	0.478192981	9	79	36	1091	3.446866947
BPIFA2	0.003719271	0.478192981	8	80	29	1098	3.778874862
ACOT13	0.003854008	0.478192981	4	84	6	1121	8.861188073
C3orf20	0.003854008	0.478192981	4	84	6	1121	8.861188073
FBXO39	0.003854008	0.478192981	4	84	6	1121	8.861188073
GNRH1	0.003854008	0.478192981	4	84	6	1121	8.861188073
HEXB	0.003854008	0.478192981	4	84	6	1121	8.861188073
HLA-C	0.003854008	0.478192981	4	84	6	1121	8.861188073
KLHL21	0.003854008	0.478192981	4	84	6	1121	8.861188073
ITGA7	0.004503157	0.478192981	6	82	17	1110	4.766272119
SIX6	0.004503157	0.478192981	6	82	17	1110	4.766272119
AKR1C1	0.005190473	0.478192981	2	86	0	1127	Inf
BICDL1	0.005190473	0.478192981	2	86	0	1127	Inf
C12orf65	0.005190473	0.478192981	2	86	0	1127	Inf
C2CD6	0.005190473	0.478192981	2	86	0	1127	Inf
CASTOR1	0.005190473	0.478192981	2	86	0	1127	Inf
CHCHD5	0.005190473	0.478192981	2	86	0	1127	Inf
DLX6	0.005190473	0.478192981	2	86	0	1127	Inf
FEM1B	0.005190473	0.478192981	2	86	0	1127	Inf
GM2A	0.005190473	0.478192981	2	86	0	1127	Inf
GPR171	0.005190473	0.478192981	2	86	0	1127	Inf

KAT7	0.005190473	0.478192981	2	86	0	1127	Inf
KRTAP9-9	0.005190473	0.478192981	2	86	0	1127	Inf
LIN28B	0.005190473	0.478192981	2	86	0	1127	Inf
MFSD13A	0.005190473	0.478192981	2	86	0	1127	Inf
PGGHG	0.005190473	0.478192981	2	86	0	1127	Inf
SRPRA	0.005190473	0.478192981	2	86	0	1127	Inf
TMEM174	0.005190473	0.478192981	2	86	0	1127	Inf
TMEM69	0.005190473	0.478192981	2	86	0	1127	Inf
TRIM43	0.005190473	0.478192981	2	86	0	1127	Inf
ZBTB26	0.005190473	0.478192981	2	86	0	1127	Inf
WDR17	0.005406493	0.478192981	13	75	71	1056	2.575204636
C1orf100	0.005659478	0.478192981	6	82	18	1109	4.498075118
KDELC2	0.005659478	0.478192981	6	82	18	1109	4.498075118
ALB	0.005723989	0.478192981	4	84	7	1120	7.591424562
CCDC28B	0.005723989	0.478192981	4	84	7	1120	7.591424562
MFSD14B	0.005723989	0.478192981	4	84	7	1120	7.591424562
NAP1L5	0.005723989	0.478192981	4	84	7	1120	7.591424562
NHS	0.005723989	0.478192981	4	84	7	1120	7.591424562
ZNF880	0.005723989	0.478192981	4	84	7	1120	7.591424562
KANK1	0.005730447	0.478192981	12	76	63	1064	2.663561865
CHDH	0.006261786	0.493093637	3	85	3	1124	13.15319121
FAM196A	0.006261786	0.493093637	3	85	3	1124	13.15319121
MRNIP	0.006261786	0.493093637	3	85	3	1124	13.15319121
ZBTB9	0.006261786	0.493093637	3	85	3	1124	13.15319121
COL4A1	0.007019532	0.537151571	6	82	19	1108	4.258119397

MFSD2B	0.007174271	0.537151571	5	83	13	1114	5.148880243
BNC1	0.008115824	0.537151571	4	84	8	1119	6.639021612
UGT2A3	0.008115824	0.537151571	4	84	8	1119	6.639021612
CHAT	0.008602452	0.537151571	6	82	20	1107	4.042184895
TMEM139	0.008602452	0.537151571	6	82	20	1107	4.042184895
TNRC6A	0.008602452	0.537151571	6	82	20	1107	4.042184895
ADGRE1	0.009188611	0.537151571	5	83	14	1113	4.777702178
COL4A2	0.009188611	0.537151571	5	83	14	1113	4.777702178
PPIC	0.009729107	0.537151571	8	80	35	1092	3.115461716
CD37	0.010387115	0.537151571	3	85	4	1123	9.865463287
DSC2	0.010387115	0.537151571	3	85	4	1123	9.865463287
FBXL5	0.010387115	0.537151571	3	85	4	1123	9.865463287
GGCT	0.010387115	0.537151571	3	85	4	1123	9.865463287
KLHL11	0.010387115	0.537151571	3	85	4	1123	9.865463287
MBOAT2	0.010387115	0.537151571	3	85	4	1123	9.865463287
MPHOSPH10	0.010387115	0.537151571	3	85	4	1123	9.865463287
PACRG	0.010387115	0.537151571	3	85	4	1123	9.865463287
PCNX4	0.010387115	0.537151571	3	85	4	1123	9.865463287
PDHA2	0.010387115	0.537151571	3	85	4	1123	9.865463287
PPWD1	0.010387115	0.537151571	3	85	4	1123	9.865463287
SKIDA1	0.010387115	0.537151571	3	85	4	1123	9.865463287
SLC38A11	0.010387115	0.537151571	3	85	4	1123	9.865463287
TCP10	0.010387115	0.537151571	3	85	4	1123	9.865463287
TRIM54	0.010387115	0.537151571	3	85	4	1123	9.865463287
CEP112	0.010398261	0.537151571	7	81	28	1099	3.386465468

MYO9B	0.010398261	0.537151571	7	81	28	1099	3.386465468
CHIT1	0.010427099	0.537151571	6	82	21	1106	3.845933479
GP2	0.011082258	0.537151571	4	84	9	1118	5.897099279
IKZF4	0.011082258	0.537151571	4	84	9	1118	5.897099279
OGFR	0.011082258	0.537151571	4	84	9	1118	5.897099279
REC8	0.011082258	0.537151571	4	84	9	1118	5.897099279
SOGA1	0.011082258	0.537151571	4	84	9	1118	5.897099279
NUMA1	0.01119651	0.537151571	8	80	36	1091	3.026309907
CCR9	0.011563041	0.537151571	5	83	15	1112	4.455968812
OR51G2	0.011563041	0.537151571	5	83	15	1112	4.455968812
GPAT2	0.012160745	0.537151571	7	81	29	1098	3.266950239
PARM1	0.012160745	0.537151571	7	81	29	1098	3.266950239
HIP1R	0.01251187	0.537151571	6	82	22	1105	3.668429136
C17orf107	0.01432493	0.537151571	5	83	16	1111	4.174475428
CD36	0.01432493	0.537151571	5	83	16	1111	4.174475428
GDPD5	0.014669125	0.537151571	4	84	10	1117	5.305733587
MARCH9	0.014669125	0.537151571	4	84	10	1117	5.305733587
MS4A6A	0.014669125	0.537151571	4	84	10	1117	5.305733587
NCBP3	0.014669125	0.537151571	4	84	10	1117	5.305733587
SERPINA9	0.014669125	0.537151571	4	84	10	1117	5.305733587
SGK2	0.014669125	0.537151571	4	84	10	1117	5.305733587
ABHD18	0.014835425	0.537151571	2	86	1	1126	25.99047006
ACTL10	0.014835425	0.537151571	2	86	1	1126	25.99047006
ACVR1	0.014835425	0.537151571	2	86	1	1126	25.99047006
C17orf75	0.014835425	0.537151571	2	86	1	1126	25.99047006

C4BPA	0.014835425	0.537151571	2	86	1	1126	25.99047006
CACNG4	0.014835425	0.537151571	2	86	1	1126	25.99047006
CEP295NL	0.014835425	0.537151571	2	86	1	1126	25.99047006
CSN2	0.014835425	0.537151571	2	86	1	1126	25.99047006
FRG1	0.014835425	0.537151571	2	86	1	1126	25.99047006
FSD1L	0.014835425	0.537151571	2	86	1	1126	25.99047006
GALNT3	0.014835425	0.537151571	2	86	1	1126	25.99047006
HS3ST3A1	0.014835425	0.537151571	2	86	1	1126	25.99047006
KCNK18	0.014835425	0.537151571	2	86	1	1126	25.99047006
LINS1	0.014835425	0.537151571	2	86	1	1126	25.99047006
MPV17L2	0.014835425	0.537151571	2	86	1	1126	25.99047006
MRPL12	0.014835425	0.537151571	2	86	1	1126	25.99047006
MTFR1	0.014835425	0.537151571	2	86	1	1126	25.99047006
MTMR6	0.014835425	0.537151571	2	86	1	1126	25.99047006
NGB	0.014835425	0.537151571	2	86	1	1126	25.99047006
NOS1AP	0.014835425	0.537151571	2	86	1	1126	25.99047006
OR8A1	0.014835425	0.537151571	2	86	1	1126	25.99047006
PRR23A	0.014835425	0.537151571	2	86	1	1126	25.99047006
RBM45	0.014835425	0.537151571	2	86	1	1126	25.99047006
RFESD	0.014835425	0.537151571	2	86	1	1126	25.99047006
RNF167	0.014835425	0.537151571	2	86	1	1126	25.99047006
SLC2A14	0.014835425	0.537151571	2	86	1	1126	25.99047006
TAAR8	0.014835425	0.537151571	2	86	1	1126	25.99047006
TM4SF4	0.014835425	0.537151571	2	86	1	1126	25.99047006
TOGARAM1	0.014835425	0.537151571	2	86	1	1126	25.99047006

WASHC4	0.014835425	0.537151571	2	86	1	1126	25.99047006
WASHC5	0.014835425	0.537151571	2	86	1	1126	25.99047006
CFAP206	0.014874525	0.537151571	6	82	23	1104	3.506219086
CHRNE	0.014874525	0.537151571	6	82	23	1104	3.506219086
GCNT2	0.014874525	0.537151571	6	82	23	1104	3.506219086
TMEM131L	0.014874525	0.537151571	6	82	23	1104	3.506219086
CALB2	0.01575619	0.537151571	3	85	5	1122	7.890369843
CECR2	0.01575619	0.537151571	3	85	5	1122	7.890369843
CELA2A	0.01575619	0.537151571	3	85	5	1122	7.890369843
CERS4	0.01575619	0.537151571	3	85	5	1122	7.890369843
CRYGD	0.01575619	0.537151571	3	85	5	1122	7.890369843
EAF2	0.01575619	0.537151571	3	85	5	1122	7.890369843
FAM13C	0.01575619	0.537151571	3	85	5	1122	7.890369843
MED1	0.01575619	0.537151571	3	85	5	1122	7.890369843
SAFB2	0.01575619	0.537151571	3	85	5	1122	7.890369843
SATB1	0.01575619	0.537151571	3	85	5	1122	7.890369843
SGMS1	0.01575619	0.537151571	3	85	5	1122	7.890369843
ALPK3	0.016319678	0.546367192	7	81	31	1096	3.051007275
BCAR1	0.016319678	0.546367192	7	81	31	1096	3.051007275
IQCE	0.016319678	0.546367192	7	81	31	1096	3.051007275
CEP192	0.01749951	0.561045149	5	83	17	1110	3.926137623
OR8K5	0.01749951	0.561045149	5	83	17	1110	3.926137623
VPS33B	0.01749951	0.561045149	5	83	17	1110	3.926137623
POLM	0.017532014	0.561045149	6	82	24	1103	3.357376457
SEC16A	0.01874386	0.561045149	8	80	40	1087	2.714149554

HEATR4	0.018914937	0.561045149	4	84	11	1116	4.819458124
MPP5	0.018914937	0.561045149	4	84	11	1116	4.819458124
PHF8	0.018914937	0.561045149	4	84	11	1116	4.819458124
TREML1	0.018914937	0.561045149	4	84	11	1116	4.819458124
ZNF598	0.018914937	0.561045149	4	84	11	1116	4.819458124
SLC2A11	0.020500327	0.561045149	6	82	25	1102	3.220420591
ZSCAN20	0.020500327	0.561045149	6	82	25	1102	3.220420591
AMBRA1	0.021109608	0.561045149	5	83	18	1109	3.704572357
DROSHA	0.021109608	0.561045149	5	83	18	1109	3.704572357
PDZRN3	0.021109608	0.561045149	5	83	18	1109	3.704572357
PI3	0.021109608	0.561045149	5	83	18	1109	3.704572357
CFI	0.022410817	0.561045149	3	85	6	1121	6.572748347
EHD2	0.022410817	0.561045149	3	85	6	1121	6.572748347
ERC2	0.022410817	0.561045149	3	85	6	1121	6.572748347
GRM3	0.022410817	0.561045149	3	85	6	1121	6.572748347
LPXN	0.022410817	0.561045149	3	85	6	1121	6.572748347
MAPK7	0.022410817	0.561045149	3	85	6	1121	6.572748347
PDGFB	0.022410817	0.561045149	3	85	6	1121	6.572748347
RBMXL3	0.022410817	0.561045149	3	85	6	1121	6.572748347
REEP4	0.022410817	0.561045149	3	85	6	1121	6.572748347
TPSD1	0.022410817	0.561045149	3	85	6	1121	6.572748347
OR9G4	0.023794361	0.561045149	6	82	26	1101	3.093984156
ARHGAP11A	0.023850694	0.561045149	4	84	12	1115	4.414869021
DTNA	0.023850694	0.561045149	4	84	12	1115	4.414869021
EGFLAM	0.023850694	0.561045149	4	84	12	1115	4.414869021

SLC36A2	0.023850694	0.561045149	4	84	12	1115	4.414869021
TPRN	0.023850694	0.561045149	4	84	12	1115	4.414869021
CELSR1	0.024029871	0.561045149	12	76	78	1049	2.121628147
BHMT	0.025175432	0.561045149	5	83	19	1108	3.506989001
PCDHA7	0.025175432	0.561045149	5	83	19	1108	3.506989001
COBL	0.027427791	0.561045149	6	82	27	1100	2.976900759
CASKIN2	0.027504775	0.561045149	7	81	35	1092	2.693004438
AKIP1	0.028276287	0.561045149	2	86	2	1125	13.01225761
BCAT1	0.028276287	0.561045149	2	86	2	1125	13.01225761
C17orf49	0.028276287	0.561045149	2	86	2	1125	13.01225761
CCDC134	0.028276287	0.561045149	2	86	2	1125	13.01225761
CYTH2	0.028276287	0.561045149	2	86	2	1125	13.01225761
DNAJC30	0.028276287	0.561045149	2	86	2	1125	13.01225761
DUOXA2	0.028276287	0.561045149	2	86	2	1125	13.01225761
EBF4	0.028276287	0.561045149	2	86	2	1125	13.01225761
FRS2	0.028276287	0.561045149	2	86	2	1125	13.01225761
FZD6	0.028276287	0.561045149	2	86	2	1125	13.01225761
GNA15	0.028276287	0.561045149	2	86	2	1125	13.01225761
GRPEL2	0.028276287	0.561045149	2	86	2	1125	13.01225761
HOXC10	0.028276287	0.561045149	2	86	2	1125	13.01225761
IDI1	0.028276287	0.561045149	2	86	2	1125	13.01225761
IKZF3	0.028276287	0.561045149	2	86	2	1125	13.01225761
KIAA0895	0.028276287	0.561045149	2	86	2	1125	13.01225761
NAA40	0.028276287	0.561045149	2	86	2	1125	13.01225761
NSA2	0.028276287	0.561045149	2	86	2	1125	13.01225761

OR10Z1	0.028276287	0.561045149	2	86	2	1125	13.01225761
OR9A4	0.028276287	0.561045149	2	86	2	1125	13.01225761
PCDHGB5	0.028276287	0.561045149	2	86	2	1125	13.01225761
PENK	0.028276287	0.561045149	2	86	2	1125	13.01225761
PLCXD3	0.028276287	0.561045149	2	86	2	1125	13.01225761
POLB	0.028276287	0.561045149	2	86	2	1125	13.01225761
PPP1R3C	0.028276287	0.561045149	2	86	2	1125	13.01225761
REL	0.028276287	0.561045149	2	86	2	1125	13.01225761
SASH3	0.028276287	0.561045149	2	86	2	1125	13.01225761
SDR9C7	0.028276287	0.561045149	2	86	2	1125	13.01225761
SLAMF9	0.028276287	0.561045149	2	86	2	1125	13.01225761
SLC2A4	0.028276287	0.561045149	2	86	2	1125	13.01225761
SNX15	0.028276287	0.561045149	2	86	2	1125	13.01225761
TAB2	0.028276287	0.561045149	2	86	2	1125	13.01225761
TNPO1	0.028276287	0.561045149	2	86	2	1125	13.01225761
TTLL8	0.028276287	0.561045149	2	86	2	1125	13.01225761
KCTD19	0.029408001	0.561045149	8	80	44	1083	2.458789055
STAB2	0.029408001	0.561045149	8	80	44	1083	2.458789055
CERK	0.029499882	0.561045149	4	84	13	1114	4.072570641
EARS2	0.029499882	0.561045149	4	84	13	1114	4.072570641
HACD4	0.029499882	0.561045149	4	84	13	1114	4.072570641
PCDHA3	0.029499882	0.561045149	4	84	13	1114	4.072570641
PFKFB1	0.029499882	0.561045149	4	84	13	1114	4.072570641
EPB41L2	0.029714407	0.561045149	5	83	20	1107	3.328982604
HHLA2	0.029714407	0.561045149	5	83	20	1107	3.328982604

SGSM1	0.029714407	0.561045149	5	83	20	1107	3.328982604
SNX21	0.029714407	0.561045149	5	83	20	1107	3.328982604
TRPV4	0.029714407	0.561045149	5	83	20	1107	3.328982604
TBC1D9B	0.030085959	0.561045149	9	79	53	1074	2.306522146
ARMC3	0.030363736	0.561045149	3	85	7	1120	5.63090496
ASL	0.030363736	0.561045149	3	85	7	1120	5.63090496
CALCR	0.030363736	0.561045149	3	85	7	1120	5.63090496
FAM89A	0.030363736	0.561045149	3	85	7	1120	5.63090496
FJX1	0.030363736	0.561045149	3	85	7	1120	5.63090496
GRM2	0.030363736	0.561045149	3	85	7	1120	5.63090496
OR52D1	0.030363736	0.561045149	3	85	7	1120	5.63090496
PPP4R3B	0.030363736	0.561045149	3	85	7	1120	5.63090496
PRMT3	0.030363736	0.561045149	3	85	7	1120	5.63090496
RASA1	0.030363736	0.561045149	3	85	7	1120	5.63090496
SH3PXD2B	0.030363736	0.561045149	3	85	7	1120	5.63090496
TMTC2	0.030363736	0.561045149	3	85	7	1120	5.63090496
TRPC4AP	0.030363736	0.561045149	3	85	7	1120	5.63090496
TSTA3	0.030363736	0.561045149	3	85	7	1120	5.63090496
TXLNB	0.030363736	0.561045149	3	85	7	1120	5.63090496
PLEKHA7	0.030961154	0.561045149	7	81	36	1091	2.615960829
ANK2	0.031412972	0.561045149	6	82	28	1099	2.86832926
CAPN2	0.031412972	0.561045149	6	82	28	1099	2.86832926
TMPRSS9	0.032623149	0.561045149	8	80	45	1082	2.402016769
FAM81B	0.034741063	0.561045149	5	83	21	1106	3.167901199
REV3L	0.034741063	0.561045149	5	83	21	1106	3.167901199

SDCBP2	0.035760843	0.561045149	6	82	29	1098	2.766796582
ADAMTS6	0.035878629	0.561045149	4	84	14	1113	3.778352847
APBB2	0.035878629	0.561045149	4	84	14	1113	3.778352847
DUXA	0.035878629	0.561045149	4	84	14	1113	3.778352847
EAF1	0.035878629	0.561045149	4	84	14	1113	3.778352847
FER1L5	0.035878629	0.561045149	4	84	14	1113	3.778352847
NRBP1	0.035878629	0.561045149	4	84	14	1113	3.778352847
P2RX6	0.035878629	0.561045149	4	84	14	1113	3.778352847
PCDHAC1	0.035878629	0.561045149	4	84	14	1113	3.778352847
PLEKHH1	0.035878629	0.561045149	4	84	14	1113	3.778352847
POLK	0.035878629	0.561045149	4	84	14	1113	3.778352847
PROSER2	0.035878629	0.561045149	4	84	14	1113	3.778352847
RSPH1	0.035878629	0.561045149	4	84	14	1113	3.778352847
SPATA5L1	0.035878629	0.561045149	4	84	14	1113	3.778352847
COL24A1	0.038730587	0.561045149	7	81	38	1089	2.473821421
FBP2	0.038730587	0.561045149	7	81	38	1089	2.473821421
CCDC40	0.03956572	0.561045149	9	79	56	1071	2.176784585
ADRA1A	0.039603641	0.561045149	3	85	8	1119	4.924482542
CASQ2	0.039603641	0.561045149	3	85	8	1119	4.924482542
COX18	0.039603641	0.561045149	3	85	8	1119	4.924482542
DCDC1	0.039603641	0.561045149	3	85	8	1119	4.924482542
FLT1	0.039603641	0.561045149	3	85	8	1119	4.924482542
MDGA2	0.039603641	0.561045149	3	85	8	1119	4.924482542
MICALL1	0.039603641	0.561045149	3	85	8	1119	4.924482542
NPL	0.039603641	0.561045149	3	85	8	1119	4.924482542

PROZ	0.039603641	0.561045149	3	85	8	1119	4.924482542
SIAE	0.039603641	0.561045149	3	85	8	1119	4.924482542
SMAD9	0.039603641	0.561045149	3	85	8	1119	4.924482542
WDR64	0.039603641	0.561045149	3	85	8	1119	4.924482542
ZNF805	0.039603641	0.561045149	3	85	8	1119	4.924482542
UGT1A4	0.040266964	0.561045149	5	83	22	1105	3.021442067
AVIL	0.040480862	0.561045149	6	82	30	1097	2.672372655
COL17A1	0.040480862	0.561045149	6	82	30	1097	2.672372655
PTPN7	0.040480862	0.561045149	6	82	30	1097	2.672372655
CCDC120	0.042995966	0.561045149	4	84	15	1112	3.524053365
PCDHA11	0.042995966	0.561045149	4	84	15	1112	3.524053365
PIK3R2	0.042995966	0.561045149	4	84	15	1112	3.524053365
SGSM2	0.042995966	0.561045149	4	84	15	1112	3.524053365
SLC34A1	0.042995966	0.561045149	4	84	15	1112	3.524053365
STK3	0.042995966	0.561045149	4	84	15	1112	3.524053365
UNC13A	0.042995966	0.561045149	4	84	15	1112	3.524053365
ULK4	0.043699109	0.561045149	8	80	48	1079	2.245835805
AAGAB	0.044924752	0.561045149	2	86	3	1124	8.678378283
ABHD6	0.044924752	0.561045149	2	86	3	1124	8.678378283
ACMSD	0.044924752	0.561045149	2	86	3	1124	8.678378283
AGTRAP	0.044924752	0.561045149	2	86	3	1124	8.678378283
BICDL2	0.044924752	0.561045149	2	86	3	1124	8.678378283
C17orf74	0.044924752	0.561045149	2	86	3	1124	8.678378283
CCT3	0.044924752	0.561045149	2	86	3	1124	8.678378283
CGB2	0.044924752	0.561045149	2	86	3	1124	8.678378283

CLRN2	0.044924752	0.561045149	2	86	3	1124	8.678378283
CLUL1	0.044924752	0.561045149	2	86	3	1124	8.678378283
CXorf36	0.044924752	0.561045149	2	86	3	1124	8.678378283
CYP26B1	0.044924752	0.561045149	2	86	3	1124	8.678378283
CYP4X1	0.044924752	0.561045149	2	86	3	1124	8.678378283
DEFB119	0.044924752	0.561045149	2	86	3	1124	8.678378283
DGCR6	0.044924752	0.561045149	2	86	3	1124	8.678378283
ENDOG	0.044924752	0.561045149	2	86	3	1124	8.678378283
EREG	0.044924752	0.561045149	2	86	3	1124	8.678378283
FAM171A2	0.044924752	0.561045149	2	86	3	1124	8.678378283
FGD3	0.044924752	0.561045149	2	86	3	1124	8.678378283
GDF10	0.044924752	0.561045149	2	86	3	1124	8.678378283
GPC5	0.044924752	0.561045149	2	86	3	1124	8.678378283
GPR37	0.044924752	0.561045149	2	86	3	1124	8.678378283
GPR39	0.044924752	0.561045149	2	86	3	1124	8.678378283
HNRNPM	0.044924752	0.561045149	2	86	3	1124	8.678378283
HUS1	0.044924752	0.561045149	2	86	3	1124	8.678378283
LGMN	0.044924752	0.561045149	2	86	3	1124	8.678378283
MANSC4	0.044924752	0.561045149	2	86	3	1124	8.678378283
MBLAC2	0.044924752	0.561045149	2	86	3	1124	8.678378283
MTRF1L	0.044924752	0.561045149	2	86	3	1124	8.678378283
MUC22	0.044924752	0.561045149	2	86	3	1124	8.678378283
MYRFL	0.044924752	0.561045149	2	86	3	1124	8.678378283
NAB2	0.044924752	0.561045149	2	86	3	1124	8.678378283
NELFB	0.044924752	0.561045149	2	86	3	1124	8.678378283

NPTXR	0.044924752	0.561045149	2	86	3	1124	8.678378283
OR10AD1	0.044924752	0.561045149	2	86	3	1124	8.678378283
PABPC4	0.044924752	0.561045149	2	86	3	1124	8.678378283
PAFAH1B2	0.044924752	0.561045149	2	86	3	1124	8.678378283
PSAT1	0.044924752	0.561045149	2	86	3	1124	8.678378283
PTPRE	0.044924752	0.561045149	2	86	3	1124	8.678378283
RFC4	0.044924752	0.561045149	2	86	3	1124	8.678378283
RND1	0.044924752	0.561045149	2	86	3	1124	8.678378283
RRAGD	0.044924752	0.561045149	2	86	3	1124	8.678378283
SAV1	0.044924752	0.561045149	2	86	3	1124	8.678378283
SLC25A13	0.044924752	0.561045149	2	86	3	1124	8.678378283
SUPT20HL1	0.044924752	0.561045149	2	86	3	1124	8.678378283
SUPT7L	0.044924752	0.561045149	2	86	3	1124	8.678378283
TXLNA	0.044924752	0.561045149	2	86	3	1124	8.678378283
UHRF1BP1	0.044924752	0.561045149	2	86	3	1124	8.678378283
VPS39	0.044924752	0.561045149	2	86	3	1124	8.678378283
ZDHHC24	0.044924752	0.561045149	2	86	3	1124	8.678378283
ZNF101	0.044924752	0.561045149	2	86	3	1124	8.678378283
FAM149A	0.045580947	0.561045149	6	82	31	1096	2.583983491
CDK13	0.04630068	0.561045149	5	83	23	1104	2.887797704
MAPK12	0.04630068	0.561045149	5	83	23	1104	2.887797704
MCM5	0.04630068	0.561045149	5	83	23	1104	2.887797704
MINDY4	0.04630068	0.561045149	5	83	23	1104	2.887797704
PLEKHG3	0.04630068	0.561045149	5	83	23	1104	2.887797704
EFCAB7	0.047691468	0.561045149	7	81	40	1087	2.346159448

ATP7B	0.047887495	0.561045149	8	80	49	1078	2.198068543
MAPKBP1	0.047887495	0.561045149	8	80	49	1078	2.198068543
DNAH7	0.049426545	0.561045149	16	72	129	998	1.718295763

FDR, false discovery rate; Inf, infinity

Supplementary Table X. *Novel variants predicted to cause LoF in genes intolerant to LoF.*

Sample	Sex	Gene	Variant (hg19)	Affected transcripts and exons	Coronary artery pext
052	F	*ACACA*	chr17-35536331-C-T	ENST00000335166 exon 40/55; ENST00000353139* exon 41/56; ENST00000360679 exon 39/54; ENST00000394406 exon 41/56; ENST00000592427 exon 3/4; NM_198834.3* exon 41/56; NM_198836.2 exon 41/56; NM_198837.1 exon 39/54; NM_198838.1 exon 40/55; NM_198839.2 exon 45/60	0.188963211
BPt0061 8529 (UK)	M	*ACACA*	chr17-35482716-C-A^	ENST00000612895 exon 45/53	0.73494983
115	F	*AHR*	chr7-17379316-C-T	ENST00000242057* exon 10/11; NM_001621.5* exon 10/11	0.954151177
170	F	*CD68*	chr17-7483368-GCACT-	ENST00000250092* exon 2/6; ENST00000380498 exon 2/6; ENST00000584502 exon 2/3; NM_001040059.2 exon 2/6; NM_001251.3* exon 2/6	0.985203797
063	F	*DNAJC13*	chr3-132242434-T-	ENST00000260818* exon 51/56; NM_001329126.2 exon 52/57; NM_015268.4* exon 51/56	0.845611787
123	F	*INTS8*	chr8-95850807-T-G	ENST00000447247 exon 8/26; ENST00000520526 exon 4/22; ENST00000523731* exon 8/27; NM_017864.4* exon 8/27	0.311714429
131	M	*MEX3A*	chr1-156051687-C-A	ENST00000532414* exon 1/2; NM_001093725.2* exon ½	1
109	F	*NASP*	chr1-46080014--CT	ENST00000350030* exon 9/15; ENST00000351223 exon 8/14; ENST00000372052 exon 7/13; ENST00000402363 exon 10/16; ENST00000528238 exon 6/8; ENST00000531612 exon 3/9; ENST00000537798 exon 7/13; NM_001195193.1 exon 7/13; NM_002482.4* exon 9/15; NM_152298.4 exon 8/14	0.660536267
037	F	*NCBP3*	chr17-3716462-G-	ENST00000576523 exon 1/2	0.678737713
020	F	*NEDD4L*	chr18-55816792-G-	NM_001144968.2 exon 1/31; NM_001144969.2 exon 1/30	0.04494382
115	F	*NTNG2*	chr9-135042407-C-	ENST00000360670 exon 2/8; ENST00000372179 exon 2/6; ENST00000393228 exon 2/7; ENST00000393229* exon 2/8; NM_032536.4* exon 2/8	0.829268293
159	F	*NUP85*	chr17-73221237-C-T	ENST00000245544* exon 8/19; ENST00000447371 exon 7/17; ENST00000541827 exon 7/18; ENST00000579324 exon 7/18; ENST00000579557 exon 1/7; ENST00000583877 exon 2/5; NM_001303276.1 exon 7/18; NM_024844.5* exon 8/19	0.39498731

095	F	*OTUD4*	chr4-146071803-G-	ENST00000447906 exon 13/21; ENST00000454497* exon 13/21; ENST00000514973 exon 13/14; NM_001102653.1* exon 13/21; NM_001366057.1 exon 13/21	0.893514812
156	F	*RBM26*	chr13-79939762--C	ENST00000267229* exon 9/21; ENST00000438724 exon 9/21; ENST00000438737 exon 9/22; NM_001286631.1 exon 9/22; NM_001286632.1 exon 9/21; NM_001366735.2 exon 9/22; NM_022118.5* exon 9/21	0.538535645
010	F	*RIMS1*	chr6-72935416-C-G	NM_001350421.2 exon 2/25; NM_001350424.2 exon 2/22; NM_001350428.2 exon 2/23; NM_001350430.2 exon 2/23; NM_001350437.2 exon 2/26; NM_001350450.2 exon 2/22; NM_001350459.2 exon 2/25; NM_001350462.2 exon 2/26; NM_001350471.2 exon 2/25	not estimated for exon 2
049	F	*SAMHD1*	chr20-35579902-G-A	ENST00000262878* exon 1/16; NM_001363729.2 exon 1/15; NM_001363733.2 exon 1/16; NM_015474.3 exon 1/16	0.965120927
162	M	*SIPA1L3*	chr19-38579369--A	ENST00000222345* exon 4/22; NM_015073.3* exon 4/22	0.925581395
136	F	*SKIL*	chr3-170078966-C-T	ENST00000259119 exon 2/7; ENST00000413427 exon 1/6; ENST00000426052 exon 3/8; ENST00000458537* exon 1/6; NM_001145097.2 exon 1/6; NM_001145098.3 exon 3/8; NM_001248008.1* exon 1/6; NM_005414.5 exon 2/7	0.906399236
129	F	*SYNRG*	chr17-35944807-A-	ENST00000339208* exon 6/22; ENST00000345615 exon 6/20; ENST00000346661 exon 6/21; ENST00000394378 exon 6/22; ENST00000502449 exon 6/20; ENST00000585472 exon 6/21; ENST00000591288 exon 6/20; NM_001163544.3* exon 6/21; NM_001163545.3 exon 6/21; NM_001163546.3 exon 6/20; NM_001163547.3 exon 6/20; NM_007247.6 exon 6/22; NM_080550.5 exon 6/20; NM_198882.3 exon 6/22	0.778220452
007	F	*TAF9B*	chrX-77395065-TC-	ENST00000341864* exon 1/7; NM_015975.5* exon 1/7	0.985272459
109	F	*TERT*	chr5-1268649-C-	ENST00000310581* exon 9/16; ENST00000334602 exon 9/15; NM_001193376.2 exon 9/15; NM_198253.3* exon 9/16	NaN
014	F	*TOMM40L*	chr1-161197501-C-	ENST00000367987 exon 4/9; ENST00000367988* exon 5/10; NM_032174.6* exon 5/10	0.795
001	F	*USP25*	chr21-17163902--T	ENST00000285679* exon 5/24; ENST00000285681 exon 5/25; ENST00000351097 exon 5/11; ENST00000400183 exon 5/26; NM_001283041.2 exon 5/26; NM_001283042.3 exon 5/25; NM_013396.6* exon 5/24	0.959153902
164	F	*WWP1*	chr8-87460452--A	ENST00000265428 exon 17/23; ENST00000341922 exon 14/20; ENST00000349423 exon 12/18; ENST00000517970* exon 19/25; ENST00000520453 exon 6/7; NM_007013.4* exon 19/25	0.890309556
172	F	*ZFP69B*	chr1-40916728-G-A	NM_001369565.1 exon 2/6; NM_023070.3* exon 1/5	0.604651163

pext, proportion expression across transcripts (a measure of the proportion of the total transcriptional output from a gene that would be affected by the variant annotation in question)[76]; * indicates canonical transcript. ^ University of Leicester SCAD cohort patient, variant position is the hg19 liftover.

Supplementary Table XI. *SVs in LoF-intolerant Genes*

Sample	Called by	Chr	Start	End	SV type	SV length	LoF-intolerant gene impacted	Exons and transcripts affected	GnomAD SV type (AF)	Other genes impacted
122	manta, GRIDSS	2	115464406	115464905	Del	499	*DPP10*	NM_001321810.2 exon 2; NM_001321905.2 exon 2	Similar del (1.98e-3)	-
051	manta, CNVnator	5	58706291	58737141	Del	30850	*PDE4D*	NM_001349242.1 exons 2-3	Larger del (4.6e-5)	-
108	manta, CNVnator	9	14472708	14539585	Del	66877	*NFIB*	NM_001369458.1 exon 1; NM_001369459.1 exon 1; NM_001369462.1 exon 1; NM_001369468.1 exon 1	-	-
156	manta, CNVnator	9	95474546	95605123	Del	130577	*BICD2*	All transcripts (NM_001003800.2*, ENST00000356884.6*, NM_015250.4, ENST00000375512.3) all exons	-	*LOC101929748, ANKRD19P*
130	manta, GRIDSS	10	35170017	35318413	Tand dup	148396	*CUL2*	NM_001198777.2, NM_0011987787.2, NM_001198779.1*, NM_003591.4, ENST00000537177.1*, ENST00000374749.3, ENST00000374751.3,	Two dups impacting the same (and other) exons (combined AF: 1.84e-4)	-

								ENST00000602371.1 exons 16 onwards; NM_001324375.2 exons 14 onwards; NM_001324376.2, ENST00000374748.1 exons 17 onwards; ENST00000374746.1 exons 15-19; ENST00000374742.1 exons 16 onwards		
049	manta, CNVnator	21	33105833	33530612	Tand dup	424779	*HUNK*	All transcripts (NM_014586.2*, ENST00000270112.2*, ENST00000430354.1, ENST00000465574.1, ENST00000439107.1) all exons	-	*LINC00159*
098	manta, CNVnator	X	152750583	153011928	Tand dup	261345	*HAUS7*	NM_001385483.1, ENST00000370210.1, ENST00000421080.2 exon 1	-	*BGN, CCNQ, LOC105373383, DUSP9, PNCK, BCAP31*
	manta, CNVnator	X	152750583	153011928	Tand dup	261345	*ATP2B3*	All transcripts (NM_001001344.2*, ENST00000263519.4*, NM_021949.3, ENST00000349366.2, ENST000000359149.3, ENST00000370181.2, ENST00000370186.1, ENST00000393842.1, ENST00000460549.1,	-	*BGN, CCNQ, LOC105373383, DUSP9, PNCK, BCAP31*

								ENST00000496610.1) all exons		
	manta, CNVnator	X	152750583	153011928	Tand dup	261345	*SLC6A8*	All transcripts (NM_005629.4*, ENST00000253122.5*, NM_001142805.2, NM_001142806.1, ENST00000413787.1, ENST00000429147.1, ENST00000430077.2, ENST00000442457.1, ENST00000457723.1) all exons	-	*BGN, CCNQ, LOC105373383, DUSP9, PNCK, BCAP31*
	manta, CNVnator	X	152750583	153011928	Tand dup	261345	*ABCD1*	All transcripts (NM_000033.4*, ENST00000218104.3*, ENST00000370129.4, ENST00000443684.1) all exons	dup of all of *ABCD1* (7.58e-3)	*BGN, CCNQ, LOC105373383, DUSP9, PNCK, BCAP31*

* Canonical transcript

Supplementary Table XII: *SNPs comprising SCAD PGS calculations.*

SNP	**Annotated gene(s)**	**Effect allele**	**Turley *et al* 2020 weight***	**Saw *et al* 2020 weight^**
rs4970935	*ECM1, C1orf54, ADAMTSL4, MRPS21*	C	1.77	NA
rs9349379	*PHACTR1*	A	1.71	0.4
rs11172113	*LRP1*	T	1.69	0.41
rs28451064	*LINC00310*	G	2.18	0.6

rs2015637	*FBN1*	C	1.79	NA
rs12740679	*C1orf51*	G	NA	0.59
rs78349783	*NOX3*	G	NA	0.56
rs78377252	*NBEAL1*	A	NA	1.18
rs11207415	*HSD52*	T	NA	0.38

*Reported odds ratio; ^Reported beta

Supplementary Table XIII: *COL4A4 variants identified in 91 SCAD cases.*

Sample	Sex	Nucleotide variant	Amino acid variant	Evidence	GnomAD MAF	Phenotype
126	F	NM_000092.5:c.2628_2654dupACGGCCTGGGGCACATGGTCCCCCAGG	p.Arg877_Gly885dup	LP (PM1-2, PM4, PP3)	0.000004011	Alport Syndrome and SCAD
010	F	NM_000092.5:c.443C>G	p.Pro148Arg	LP (PM1-2, PP2-3)	-	SCAD
092	F	NM_000092.5:c.1202C>T	p.Ala401Val	Donor loss SpliceAI = 0.31	0.002347	SCAD

Allele frequencies refer to all gnomAD populations, and both exome and genome data.

Supplementary Table XIV: *Collapsing analysis in cases and controls for the previously reported genes, TSR1, TLN1, and F11R.*

Gene	Case carriers % (n = 88)	Control carriers % (n = 1127)	P-value
TSR1	2.3%	3.1%	0.76
TLN1	3.4%	0.9%	0.06
F11R	0%	0.5%	1

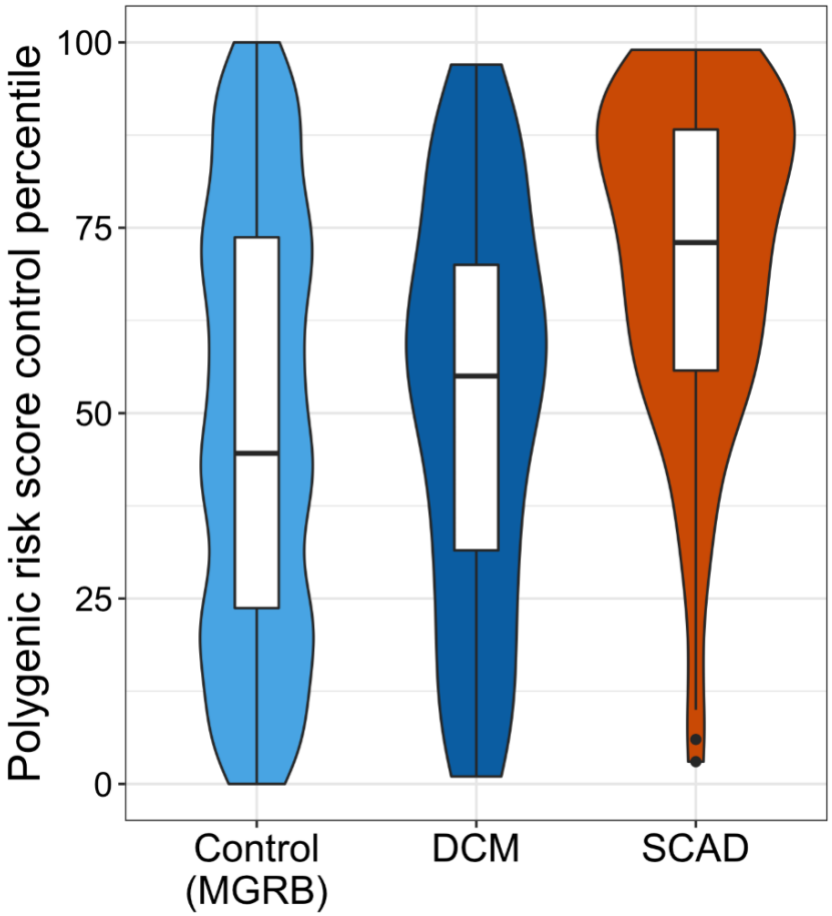
Case and control carrier proportions were assessed with a one-sided Fisher's Exact test, and p-values are uncorrected.

Supplementary Table XV: *Definitions of ACMG criteria contributing to likely pathogenic or pathogenic classification for candidate gene variants, taken from Richards et al. 2015*[16].

Criterion	Definition
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
PM1	Located in a mutational hot spot and/or critical and well-established functional domain (e.g., active site of an enzyme) without benign variation
PM2	Absent from controls (or at extremely low frequency if recessive)
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.)

Supplemental Figures and Figure Legends

Supplementary Figure I. *Polygenic risk score percentile amongst SCAD and DCM patients relative to MGRB control samples.* Control scores were used to create a reference distribution of scores, created from the 5 SNPs identified in a SCAD GWAS by Turley et al 2020.[74] Violin plots indicate the percentile score distribution relative to the control distribution, while boxplots indicate the score quartiles. The median score for the SCAD group fell into the 73rd percentile of the control population (p-value = 2.052e-10), while the DCM median score was in the 55th control percentile (p-value = 1.067e-06). No difference was found between control and DCM scores (p-value = 0.9703).


Polygenic risk score control percentile
100
75
50
25
0
Control
(MGRB)
DCM
SCAD