SUPPLEMENTAL MATERIAL
Supplementary Methods

Cohorts

UK SCAD cohort: recruitment and clinical characteristics
Patients were recruited to the UK SCAD Registry (ISRCTN42661582) by self-referral, primary care physician referral, or referral from the clinical team at the index presenting hospital, and all had an angiographically confirmed diagnosis of SCAD. Patients with atherosclerotic, traumatic or iatrogenic dissection (except where the latter complicates definite SCAD) were excluded. Angiographic analysis was conducted by two experienced SCAD clinicians (AA-H and DA), blinded to the results of the genetic analysis, and images were classified using a modified Yip and Saw classification. (1) Here we studied a cohort of 384 cases in the UK SCAD registry. Clinical characteristics are given in Table 1.

Victor Chang Cardiac Research Institute SCAD cohort: recruitment and clinical characteristics
Patients were recruited via a social media platform or through direct referral from cardiologists. The diagnosis of SCAD 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 92 SCAD patients reported here are from a broader cohort of 292 patients recruited to date and were selected for sequencing based on angiographically-confirmed SCAD, severity of SCAD and/or recurrence.

UK Biobank cardiovascular-screened controls
Controls for association analyses were selected from 502,543 UK Biobank participants. Of these, 151,027 had exome sequencing available at the time of this study. We further limited analyses to the subset of participants with no report of cardiovascular, endocrine, liver, renal, or connective tissue disorders (Supplementary Table 5).
**Sequencing, alignment, and variant calling**

For the University of Leicester SCAD cohort, genomic DNA from SCAD cases was extracted and underwent paired-end 150bp WGS at Human Longevity Inc using the NovaSeq6000 platform. For SCAD cases, >98% of consensus coding sequence release 22 (CCDS) has at least 10x coverage and average coverage of the CCDS achieved 42-fold read-depth. Genomic DNA from UK Biobank controls underwent paired-end 75bp whole exome sequencing (WES) at Regeneron Pharmaceuticals using the IDT xGen v1 capture kit on the NovaSeq6000 machines. For UK Biobank controls, >95% of CCDS has at least 10x coverage and average CCDS read-depth of 59X. All case and control sequences were processed through the same bioinformatics pipeline, this included re-processing all the UK Biobank controls from their unaligned FASTQ state. A custom-built Amazon Web Services (AWS) cloud compute platform running Illumina DRAGEN Bio-IT Platform Germline Pipeline v3.0.7 was adopted to align the reads to the GRCh38 genome reference and perform small variant SNV and indel calling. SNVs and indels were annotated using SnpEff v4.3 against Ensembl Build 38.92. (2)

Structural variants were called among the SCAD WGS data using the ensemble tool Parliament2, (3) comprising constituent tools BreakDancer, CNVnator, DELLY, LUMPY, and Manta. (4-8) Structural variants were annotated using AnnotSV. (9)

For the Victor Chang Cardiac Research Institute cohort, genomic DNA was extracted and WGS performed using the Illumina HiSeq X Ten platform with 30x coverage. Reads were aligned to the GRCh37 reference genome with Burrows-Wheeler Aligner (10) and variants called with the Genome Analysis Toolkit Best Practices (11). Principal component analysis using 17,453 ethnic-specific SNVs and projection to the 1000 Genomes principal components confirmed ethnicity. Non-relatedness of subjects in the cohort was confirmed with KING (12). Variants were annotated with ANNOVAR (13) against RefSeq (version 01-06-2017) using multiple pathogenicity prediction algorithms.
SCAD tiered gene list

We compiled a tiered list of genes of interest to SCAD based on publicly available gene lists and literature searches. The tiers indicate the current level of evidence for the association of each gene with SCAD. Tier 1 genes (n=6) comprise those that either harbour rare variants reported as pathogenic or likely pathogenic in multiple SCAD patients, or an enrichment of rare missense variants in cases compared to controls. Tier 2 genes (n=124) comprise those that harbour rare, presumed clinically relevant, variants that were found in a single SCAD patient or among patients with connective tissue or vascular disorders, or common variants associated with these disorders. Tier 3 genes (n=303) represent genes of interest contributing to relevant phenotypes in mice (Supplementary Table 1).

Publicly available gene lists and literature searches conducted March-August 2018. PubMed search terms:

“spontaneous coronary artery dissection” or “arterial tortuosity” and “GWAS”
“connective tissue disorder” and “gene” “migraine” and “gene”
“spontaneous coronary artery dissection” “migraine” and “GWAS”
“spontaneous coronary artery dissection” and “gene” “hypermobile syndorme” and “gene”
“SCAD” and “gene” “hypermobile syndorme” and “GWAS”
“coronary artery spasm” and “gene” “arteritis” and “gene”
“coronary artery spasm” and “GWAS” “arteritis” and “GWAS”
“aneurysm” and “gene” “abnormal vascular smooth muscle” and “gene”
“aneurysm” and “GWAS” “abnormal vascular smooth muscle” and “GWAS”
“Ehlers-Danlos Syndrome” and “vascular” and “gene” “GWAS”
“carotid dissection” and “gene” “abnormal blood vessel endothelium” and “gene”
“carotid dissection” and “GWAS” “abnormal blood vessel endothelium” and “GWAS”
“arterial tortuosity” and “gene” “GWAS”
Identification and interpretation of pathogenic variants

For the UK SCAD cohort, pathogenic and likely pathogenic SNVs, indels, and SVs were identified using automated filtering followed by manual review and classification according to ACMG guidelines (14).

In detail, first, automated filtering identified SNVs and indels in the 384 SCAD cases that fulfilled all the following criteria:

- DRAGEN Status = PASS
- Quality score (QUAL) >= 30 in all carriers
- Position is covered >=10X in >99% cases
- GnomAD minor allele frequency (popmax exomes) <= 0.001 (0.1%; in autosomes this is equivalent to 1 in 500 individuals sampled from a general population) (15)
- Minor allele frequency in 384 cases < 0.05 (5%)
- Affects a SCAD tier 1 or tier 2 gene
- Variant is ‘high impact’ in a gene for which loss of function is a known disease mechanism OR variant has previously been reported as DM in HGMD pro v2019.2 or pathogenic or likely pathogenic with no conflicts in ClinVar (accessed May 2019). (16, 17)
Next, we performed manual review and classification of SNVs and indels according to ACMG guidelines. (18) The following factors were considered:

- Affected transcript(s)
- Proximity of protein truncating variants to 3’ end terminus of gene
- Consistency of variant consequence with previously reported pathogenic variants in the gene
- Consistency of variant genotype with previously reported mode of inheritance of the gene
- Consistency of SCAD phenotype with previously reported phenotype associated with the gene
- If variant has been previously reported as pathogenic, original literature was reviewed wherever possible to ensure the classification within HGMD/ClinVar was consistent with the original report

Potentially pathogenic and likely pathogenic structural variants were also investigated. First, automated filtering identified the SVs in the 384 SCAD cases that fulfilled the following criteria:

- Deletion, because deletions generally have higher probability than other SV types of negatively impacting the function of a gene (19, 20)
- Overlaps with CCDS region of SCAD tier 1 and 2 genes
- Frequency within SCAD cohort < 0.05 (5%) and frequency in external datasets (DGV and 1000 genomes (19, 20)) < 0.01 (1%)
- Supported by more than one caller among Parliament2’s ensemble of callers
- Not flagged as low quality by Parliament2

Next, we performed manual review of SVs that passed automated filtering, considering the following factors in addition to all the factors already described for SNVs and indels:

- < 100 high quality heterozygous SNV calls within boundaries of deletion
- Supported by both drop in coverage AND insert size/split read data
- Looks high-confidence upon manual inspection of the reads using Integrative Genomics Viewer (21)

Assessment of statistical differences between clinical endpoints and individuals with pathogenic/likely pathogenic variants compared to those without was performed using Fisher’s Exact Tests.

Automated filtering of variants in genes identified in the University of Leicester SCAD cohort in the Victor Chang Cardiac Research Institute SCAD cohort was performed using VPOT (22) with the following parameters:

- gnomAD genomes (popmax) minor allele frequency < 0.01
- Missense, nonsense, frameshift, or splicing variants

Loss of function variants in these genes were considered as well as missense variants reported as pathogenic or likely pathogenic in either ClinVar or HGMD. Variants thus identified were confirmed with manual inspection using IGV. (21)

**Collapsing analysis**

We selected the subset of 357 SCAD cases in the University of Leicester cohort and 13,722 UK Biobank controls who had high quality sequencing data, are unrelated, and of European ancestry. This aimed to minimise the risk of confounding technical artefacts. In detail, the following sample-level criteria for inclusion in the exome-wide collapsing analyses were applied:

- No evidence of contamination (VerifyBamID FREEMIX < 0.04) (23)
• Good coverage (for cases average coverage of CCDS > 1st percentile and < 99th percentile and for controls >= 95% of CCDS with read depth >= 10X and average read depth >= 37X and <=130X)

• Percentage of reads that map to reference genome > 1st percentile (cases only)

• Unrelated (i.e. exclude one of each related pair, up to 3rd degree, calculated using PLINK http://pngu.mgh.harvard.edu/purcell/plink/) (24)

• Predicted to be of European ancestry by Peddy (25)

• Concordance between self-declared and genetic prediction of sex

• Ancestry of controls PC1 or PC2 <= 3SDs from mean of those of cases

• Down-sampled controls to harmonise sex and menopause status of cohort with that of cases

On average, at least 10-fold coverage was achieved for 96.7% and 96.6% of the 34.07 megabase pairs (Mbp) of the Consensus Coding Sequence (CCDS; release 22) for case and control subjects respectively. To alleviate confounding effects attributable to differential coverage, we only considered qualifying variants (QVs) affecting a pruned set of 33.13 Mbp (97.2%) of CCDS sites equally represented in HLI WGS and UK Biobank WES data.

Qualifying variants (QVs) are the subset of rare, high-quality, coding SNVs/indels that are considered during collapsing analysis. We used eleven distinct QV models. Selection of QVs was achieved by imposing a series of variant-level filters. Some of these filters were applied to all QV models and some were specific to the eleven distinct QV models. These filters are detailed below.

For all QV models:

• Minimum coverage 10X

• Has annotations in CCDS transcripts (CCDS release 22; ~34Mb)

• Percent alternate reads in homozygous variants >= 0.8

• Percent alternate reads in heterozygous variants >= 0.3 and <= 0.8

• Binomial test of alternate reads proportion p > 0.000001
- Genotype quality score (GQ) $\geq 30$
- Fisher’s strand bias score (FS) $\leq 200$ (indels) $\leq 60$ (SNVs)
- Mapping quality score (MQ) $\geq 40$
- Quality score (QUAL) $\geq 30$
- Read position rank sum score (RPRS) $\geq -2$
- Mapping quality rank sum score (MQRS) $\geq -8$
- DRAGEN variant status = PASS
- Binomial test of difference in coverage between cases and controls $p \leq 0.000001$
- Variant site achieved 10-fold coverage in $\geq 25\%$ of GnomAD samples, and if variant was observed in GnomAD the variant calls in GnomAD achieved exome z score $\geq 2.0$, exome MQ $\geq 30$ and exome allele count raw percent $\geq 50$
- Not in a list of 951 observed sequencing artefacts or problematic variants

Additionally, the following requirements are QV model specific.

**PTV model:**
- Variant consequence impact = high (exon_loss_variant, frameshift_variant, start_lost, stop_gained, stop_lost, splice_acceptor_variant, splice_donor_variant, gene_fusion, bidirectional_gene_fusion, rare_amino_acid_variant, or transcript_ablation)
- LOO (leave one out) MAF $\leq 0.001$
- GnomAD exome global MAF $\leq 0.001$
- GnomAD exome PopMax MAF $\leq 0.001$
- Variant fails any QC requirement (except coverage) in $\leq 4$ samples in cohort
- Hardy-Weinberg Equilibrium exact test $p$-value $\geq 0.001$
- GnomAD exome random forest $p \geq 0.01$ (SNVs) or $\geq 0.02$ (indels)

**PTV or rare damaging model**
- Same as PTV model
- OR same as rare damaging model
Synonymous model:
- Synonymous_variant
- LOO MAF <= 0.0005
- GnomAD exome global MAF <= 0.0005
- Variant fails any QC requirement (except coverage) in <=2 samples in cohort
- Hardy-Weinberg Equilibrium exact test p-value >= 0.001
- GnomAD exome random forest p >= 0.01 (SNVs) or >= 0.02 (indels)

Ultra-rare damaging model:
- Variant consequence impact = high or moderate (conservative_inframe_deletion, conservative_inframe_insertion, disruptive_inframe_insertion, disruptive_inframe_deletion, missense_variant_splice_region_variant, missense_variant, or protein_altering_variant)
- LOO MAF <= 0.00025
- Not in GnomAD
- Variant fails any QC requirement (except coverage) in <=1 sample in cohort
- Hardy-Weinberg Equilibrium exact test p-value >= 0.001
- REVEL score >= 0.25 (26)

Ultra-rare damaging (MTR) model:
- Same as ultra-rare damaging model
- Missense tolerance ratio (MTR) score <= 0.78 (equivalent to the exome-wide 25% most missense intolerant protein-coding regions) OR intragenic percentile <= 0.5 (equivalent to the transcript's 50% most missense intolerant protein-coding regions)

Rare damaging model:
- Variant consequence impact = high or moderate
- LOO MAF <= 0.0005
- GnomAD exome global MAF <= 0.0005
- Variant fails any QC requirement (except coverage) in <=2 samples in cohort
- Hardy-Weinberg Equilibrium exact test p-value >= 0.001
- GnomAD exome random forest p \( \geq 0.01 \) (SNVs) or \( \geq 0.02 \) (indels)
- REVEL score \( \geq 0.25 \)

**Rare damaging (MTR) model:**
- Same as rare damaging model
- Missense tolerance ratio (MTR) score \( \leq 0.78 \) OR centile \( \leq 0.5 \)

**Flexible non-synonymous model:**
- Variant consequence impact = high or moderate
- LOO MAF \( \leq 0.001 \)
- GnomAD exome global MAF \( \leq 0.0005 \)
- GnomAD exome PopMax MAF \( \leq 0.001 \)
- Variant fails any QC requirement (except coverage) in \( \leq 4 \) samples in cohort
- Hardy-Weinberg Equilibrium exact test p-value \( \geq 0.001 \)
- GnomAD exome random forest p \( \geq 0.01 \) (SNVs) or \( \geq 0.02 \) (indels)

**Flexible non-synonymous (MTR) model:**
- Same as flexible non-synonymous model
- Missense tolerance ratio (MTR) score \( \leq 0.78 \) OR centile \( \leq 0.5 \)

**Flexible damaging model:**
- Same as flexible non-synonymous model
- REVEL score \( \geq 0.25 \)

**Recessive model:**
- Variant consequence impact = high or moderate
- Variant homozygous, OR two heterozygous variants in same gene
- LOO MAF \( \leq 0.005 \)
- GnomAD exome global MAF \( \leq 0.005 \)
- GnomAD exome PopMax MAF \( \leq 0.005 \)
- GnomAD exome homozygous raw \( \geq 2 \)
- Variant fails any QC requirement (except coverage) in \( \leq 50 \) samples in cohort
- Hardy-Weinberg Equilibrium exact test p-value >= 0.00001
- GnomAD exome random forest p >= 0.01 (SNVs) or >= 0.02 (indels)

After QVs had been selected, counts of cases that have at least one QV vs those that have no QVs were compared to controls using the two-tailed Fisher’s exact test. Our study-wide significance threshold, after Bonferroni correction for the number of genes and models tested was $\alpha = \frac{0.05}{10 \times 18,659} = 2.7 \times 10^{-7}$. Although we retain genome-wide Bonferroni correction as our official significance cut-off ($p<2.7 \times 10^{-7}$), we also assigned a tissue-specific adjusted alpha of $p<4.1 \times 10^{-6}$ considering only 12,069 genes with expression levels above 1.5 TPM based on mean TPM value for the "Artery - Coronary" tissue subtype in the GTEx database (accessed 19/11/2019) and not correcting for 10 differing models. With a goal of identifying a more refined subset of most highly expressed coronary artery tissue genes we further focused on top decile (10%) ($n=1,928$ genes; adjusted $p<2.6 \times 10^{-5}$).

**Review of highly ranked non-significant collapsing analysis results**

Genes that were highly ranked in the collapsing analysis, but not yet achieving study-wide statistical significance were manually evaluated by AAB and TRW. Genes were assessed for reported function, involvement in human disease, human tissue expression, and mouse phenotype using GeneCards, OMIM, Human Protein Atlas, MGI, as well as a broader literature review. (27-30)

**Mantis-ml**

We also employed mantis-ml v1.5.4 (31), an automated gene prioritisation tool that considers a wealth of publicly available resources to objectively assign probabilities to genes of unknown relevance given an input set of seed genes; here 130 SCAD tier 1 and tier 2 genes (Supplementary Table 1). Automatic feature compilation was performed by providing the following disease/phenotype terms in the input configuration file: heart, cardio, aortic, aorta, coronary, vascular, artery, dissection, fibromuscular, kidney, vessel and connective tissue. Mantis-ml was trained using six different
classifiers: Extra Trees, XGBoost, Random Forest, Gradient Boosting, Support Vector Classifier and feed-forward Deep Neural Net.

Once the mantis-ml genome-wide probabilities of being a SCAD gene were generated, we performed a hypergeometric test to determine whether the top-ranked collapsing analysis genes (i.e. genes achieving a p<0.05 in the collapsing analyses) were significantly enriched for the top 5% of mantis-ml SCAD-predicted genes. A statistically significant result from the hypergeometric test would highlight that there are disease-ascertained genes among the top of the collapsing results and the specific genes most likely to be contributing to that enrichment. In parallel, and in addition to generating a permutation-based null, we also performed the hypergeometric enrichment test using the synonymous genetic model to define our empirical null controlling for the underlying case-control configurations.

**Gene-set enrichment analysis**

We assessed potential enrichment in gene-sets using Megagene (https://github.com/QuanliWang/MegaCollapsing). (32) Briefly, we applied a logistic regression model in which the tally of genes containing QVs in cases and controls are compared, correcting for sex, number of synonymous QVs each individual has in the gene-set, and the exome-wide tally of QVs each individual has in the QV model. We tested a total of 9,339 gene-sets for each QV model. Apart from the four SCAD gene-sets, these gene-sets are standardised and designed to be disease-agnostic. Gene-sets containing two different genes with overlapping CCDS regions were excluded. Gene-sets comprise the following:

1. 8390 gene-sets from Gene-Set Enrichment Analysis (33)
2. 912 gene families from HUGO Gene Nomenclature Committee (34)
3. 37 gene-sets associated with various diseases: cancer (https://www.cancer.gov/tcga), chronic kidney disease (35), epilepsy (32), and SCAD (tier 1, tier 2, tier 3, and the union of the three tiers)
Supplementary Figure 1: Coverage plots for six SCAD tier 1 genes. For each gene the longest coding transcript is shown.
Supplementary Figure 2: Screenshots from Integrative Genomics Viewer showing read alignments of four interesting structural variants identified in SCAD cases.
Supplementary Figure 3: Quantile-quantile plots show signals for collapsing analysis; eleven different genetic models tested. MTR = missense tolerance ratio. PTV = protein truncating variant.
Synonymous model included as negative control. No association reached the Bonferroni-corrected study-wide significance threshold of \( p < 2.7e-7 \).
**Supplementary Figure 4: Feature importance scores during mantis-ml training.** Distribution of feature importance scores extracted by a Random Forest classifier with the Boruta algorithm. Predictions are extracted across ten balanced gene subsets with 10-fold cross-validation for the SCAD-specific case. Confirmed (important) features that are calculated as references by Boruta are shown in blue (‘shadow’ features).
Supplementary Figure 5: Cross-validation of mantis-ml predictions with cohort-level rare-variant association studies. a,b) Hypergeometric test enrichment of SCAD-specific mantis-ml predictions with “ultra-rare variant” and “synonymous variant” collapsing analysis results, respectively. The horizontal dashed grey line corresponds to the significance threshold of $p=0.05$ for the hypergeometric tests. Where the signal goes above this line it indicates significant enrichment of mantis-ml top gene predictions among the population genomic collapsing analyses. The vertical dashed lines, coloured based on the different classifier ran as part of mantis-ml, indicate the last index of top ranked genes from the collapsing analyses achieving a $p$-value < 0.05. c) Consensus of genes-of-highest-interest (novel) in SCAD, satisfying the significance threshold criteria in both the collapsing analysis results and the hypergeometric and supported by all six classifiers used by mantis-ml.
Supplementary Figure 6: Quantile-quantile plots show signals for gene-set enrichment analysis; ten different genetic models tested. MTR = missense tolerance ratio. PTV = protein truncating variant.
| Gene   | Gene ID      | Tier | OMIM phenotype(s) (accessed 20191105-07) tiers 1-2 only | Other relevant human phenotype(s) from literature search, tiers 1-2 only | Relevant phenotype in mouse model, tier 3 | Selected supporting reference(s) |
|--------|--------------|------|----------------------------------------------------------|-----------------------------------------------------------------------|-------------------------------------------|-----------------------------------|
| COL3A1 | ENSG00000168542 | 1    | Ehlers-Danlos syndrome, vascular type; Polymicrogyria with or without vascular-type EDS | NA                                                                     | NA                                         | (36-40)                           |
| FBN1   | ENSG00000166147 | 1    | Acromicric dysplasia; Ectopia lentis, familial; Geleophysic dysplasia 2; Marfan lipodystrophy syndrome; Marfan syndrome; MASS syndrome; Stiff skin syndrome; Weill-Marchesani syndrome 2, dominant | NA                                                                     | NA                                         | (39, 41, 42)                      |
| PKD1   | ENSG00000008710 | 1    | Polycystic kidney disease 1                              | NA                                                                     | NA                                         | (36, 43, 44)                      |
| Gene   | Ensembl ID | Chromosome | Description                                                                 | Chromosome Location | References |
|--------|------------|------------|-----------------------------------------------------------------------------|---------------------|------------|
| SMAD3  | ENSG00000166949 | 1          | Loeys-Dietz syndrome 3                                                      | NA                  | (36, 45, 46) |
| TLN1   | ENSG00000137076 | 1          | NA                                                                          | NA                  | (47)       |
| TSRI   | ENSG00000167721 | 1          | NA                                                                          | NA                  | (48)       |
| ABCC6  | ENSG00000091262 | 2          | Arterial calcification, generalized, of infancy, 2; Pseudoxanthoma elasticum; Pseudoxanthoma elasticum, forme fruste | NA                  | (49)       |
| ABL1   | ENSG00000097007 | 2          | Congenital heart defects and skeletal malformations syndrome; Leukemia, Philadelphia chromosome-positive, resistant to imatinib | NA                  | (50)       |
| ACTA2  | ENSG00000107796 | 2          | Aortic aneurysm, familial thoracic 6; Moyamoya disease 5; Multisystemic smooth muscle dysfunction syndrome | NA                  | (51, 52)   |
| ACTN4  | ENSG00000130402 | 2          | Glomerulosclerosis, focal segmental, 1                                      | Retinal venular tortuosity | NA         | (53, 54)   |
| ACVRL1 | ENSG00000139567 | 2          | Telangiectasia, hereditary hemorrhagic, type 2                               | NA                  | (55)       |
| Gene   | Ensembl ID          | Chr | Conditions                                                   | Migraine risk loci | Migraine risk loci | (Reference) |
|--------|---------------------|-----|--------------------------------------------------------------|--------------------|--------------------|-------------|
| ADAMTS2| ENSG00000087116     | 2   | Ehlers-Danlos syndrome, dermatosparaxis type                 | NA                 | NA                 | (56)        |
| AEBP1  | ENSG00000106624     | 2   | Ehlers-Danlos syndrome, classic-like, 2                      | NA                 | NA                 | (57)        |
| ALDH18A1| ENSG00000059573    | 2   | Cutis laxa, autosomal dominant 3; Cutis laxa, autosomal recessive, type IIIA; Spastic paraplegia 9A, autosomal dominant; Spastic paraplegia 9B, autosomal recessive | NA                 | NA                 | (58)        |
| APP    | ENSG00000142192     | 2   | Cerebral amyloid angiopathy, Dutch, Italian, Iowa, Flemish, Arctic variants | NA                 | NA                 | (59)        |
| ARHGAP31| ENSG00000031081    | 2   | Adams-Oliver syndrome 1                                      | NA                 | NA                 | (60)        |
| ARMS2  | ENSG00000254636     | 2   | (Macular degeneration, age-related, 8)                      | Migraine risk loci | NA                 | (61, 62)    |
| ASTN2  | ENSG00000148219     | 2   | NA                                                           | Migraine risk loci | NA                 | (62)        |
| ATP6V0A2| ENSG00000185344    | 2   | Cutis laxa, autosomal recessive, type IIA; Wrinkly skin syndrome | NA                 | NA                 | (63)        |
| ATP6V1A| ENSG00000114573     | 2   | Cutis laxa, autosomal recessive, type IID; Epileptic encephalopathy, infantile or | NA                 | NA                 | (64)        |
| Gene      | Ensembl ID | Chromosome | Description                                                                 | p value |
|-----------|------------|------------|-----------------------------------------------------------------------------|---------|
| B3GALT6   | ENSG00000176022 | 2     | Ehlers-Danlos syndrome, spondylodysplastic type, 2; Spondyloepimphysyeal dysplasia with joint laxity, type 1, with or without fractures | NA   |
| B4GALT7   | ENSG00000027847 | 2     | Ehlers-Danlos syndrome, spondylodysplastic type, 1 | NA   |
| BGN       | ENSG00000182492 | 2     | Meester-Loeys syndrome; Spondyloepimphysyeal dysplasia, X-linked | NA   |
| C1R       | ENSG00000159403 | 2     | Ehlers-Danlos syndrome, periodontal type, 1 | NA   |
| C1S       | ENSG00000182326 | 2     | C1s deficiency; Ehlers-Danlos syndrome, periodontal type, 2 | NA   |
| CARF      | ENSG00000138380 | 2     | NA | Migraine risk loci | NA   |
| CD2AP     | ENSG00000198087 | 2     | Glomerulosclerosis, focal segmental, 3 | Fibromuscular | NA   |
| Gene  | ENSEMBL ID   | Chr | Description                                                                 | Migraine risk loci | Dysplasia risk loci | NA | Reference(s) |
|-------|--------------|-----|------------------------------------------------------------------------------|-------------------|-------------------|----|--------------|
| CFDP1 | ENSG00000153774 | 2   | NA                                                                          | Migraine risk loci | NA                |    | (62)         |
| CHST14| ENSG00000169105  | 2   | Ehlers-Danlos syndrome, musculocontractural type 1                          | NA                | NA                |    | (70)         |
| COL12A1| ENSG00000111799 | 2   | ?Ullrich congenital muscular dystrophy 2; Bethlem myopathy 2              | NA                | NA                |    | (71)         |
| COL1A1| ENSG00000108821  | 2   | Caffey disease; Ehlers-Danlos syndrome, arthrochalasia type, 1; Osteogenesis imperfecta, types I-IV; {Bone mineral density variation QTL, osteoporosis} | NA                | NA                |    | (72-74)      |
| COL1A2| ENSG00000164692  | 2   | Ehlers-Danlos syndrome, arthrochalasia type, 2; Ehlers-Danlos syndrome, cardiac valvular type; Osteogenesis imperfecta, type II-IV; {Osteoporosis, postmenopausal} | NA                | NA                |    | (72, 75)     |
| COL27A1| ENSG00000196739  | 2   | Steel syndrome                                                             | NA                | NA                |    | (72, 76)     |
| COL2A1| ENSG00000139219  | 2   | Achondrogenesis, type II or                                                | NA                | NA                |    | (77)         |
| Gene   | Ensembl ID       | Homozygous | Heterozygous | Phenotypes                                                                                                                                 |
|--------|------------------|------------|--------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| COL5A1 | ENSG00000130635  | 2          | NA           | hypochondrogenesis; Avascular necrosis of the femoral head; Czech dysplasia; Epiphyseal dysplasia, multiple, with myopia and deafness; Kniest dysplasia; Legg-Calve-Perthes disease; Osteoarthritis with mild chondrodysplasia; Platsyspondylic skeletal dysplasia, Torrance type; SED congenita; SMED Strudwick type; Spondyloperipheral dysplasia; Stickler syndrome, type I; Vitreoretinopathy with phalangeal epiphyseal dysplasia |
| COL5A2 | ENSG00000204262  | 2          | NA           | Ehlers-Danlos syndrome, classic type, 1                                                                                                     |
| COL6A1 | ENSG00000142156  | 2          | NA           | Bethlem myopathy 1; Ullrich congenital muscular dystrophy 1                                                                                |

Note: The last column indicates the reference numbers for the conditions mentioned.
| Gene    | Reference ID          | Chromosome | Phenotypes                                                                 | Suggested phenotypes                                      | Other information                                      | Literature References |
|---------|----------------------|------------|-----------------------------------------------------------------------------|-----------------------------------------------------------|---------------------------------------------------------|-----------------------|
| COL6A2  | ENSG00000142173      | 2          | ?Myosclerosis, congenital; Bethlem myopathy 1; Ullrich congenital muscular dystrophy 1 | NA                                                        | NA                                                     | (80)                  |
| COL6A3  | ENSG00000163359      | 2          | Bethlem myopathy 1; Dystonia 27; Ullrich congenital muscular dystrophy 1     | NA                                                        | NA                                                     | (81)                  |
| COMP    | ENSG00000105664      | 2          | Epiphyseal dysplasia, multiple, 1; Pseudoachondroplasia                      | NA                                                        | NA                                                     | (82)                  |
| CYBA    | ENSG00000051523      | 2          | Chronic granulomatous disease, autosomal, due to deficiency of CYBA           | Coronary artery spasm risk loci                           | NA                                                     | (83, 84)              |
| DCHS1   | ENSG00000166341      | 2          | Mitral valve prolapse 2; Van Maldergem syndrome 1                           | NA                                                        | NA                                                     | (85)                  |
| DSE     | ENSG00000111817      | 2          | Ehlers-Danlos syndrome, musculocontractural type 2                           | NA                                                        | NA                                                     | (86)                  |
| EDN1    | ENSG00000078401      | 2          | Auriculocondylar syndrome 3; Question mark ears, isolated; {High density lipoprotein cholesterol level QTL 7} | NA                                                        | NA                                                     | (87, 88)              |
| EFEMP2  | ENSG00000172638      | 2          | Cutis laxa, autosomal recessive, type IB                                    | Aneurysm; arterial                                        | NA                                                     | (89, 90)              |
|      | ENSG00000049540 | 2 | Cutis laxa, autosomal dominant; Supravalvar aortic stenosis | NA | NA | (91) |
|------|----------------|---|-----------------------------------------------------------|----|----|------|
| **ELN** | ENSG00000138080 | 2 | Autosomal dominant connective tissue disorder with peripheral neuropathy (not confirmed) | NA | NA | (92) |
| **EMILIN1** | ENSG00000157554 | 2 | NA | Abdominal aortic aneurysm risk loci | NA | (93) |
| **ERG** | ENSG00000198734 | 2 | Factor V deficiency; Thrombophilia due to activated protein C resistance; {Budd-Chiari syndrome}; {Pregnancy loss, recurrent, susceptibility to, 1}; {Stroke, ischemic, susceptibility to}; {Thrombophilia, susceptibility to, due to factor V Leiden} | NA | NA | (94, 95) |
| **F5** | ENSG00000140092 | 2 | ?Cutis laxa, autosomal dominant 2; Cutis laxa, autosomal recessive, type IA; | NA | NA | (96) |
| Gene | ENSG Accession | Chromosome | Disorder/(Phenotypic Feature) | Type of Evidence | References |
|------|----------------|-------------|------------------------------|-----------------|------------|
| FBN2 | ENSG00000138829 | 2 | Contractural arachnodactyly, congenital; Macular degeneration, early-onset | NA | (97) |
| FGF6 | ENSG0000011241 | 2 | Macular degeneration, age-related, 3; Neuropathy, hereditary, with or without age-related macular degeneration | NA | (97) |
| FHL5 | ENSG00000112214 | 2 | Migraine risk loci | NA | (62) |
| FKBP14 | ENSG00000106080 | 2 | Migraine risk loci | NA | (62) |
| FLCN | ENSG00000154803 | 2 | Birt-Hogg-Dube syndrome; Colorectal cancer, somatic; Pneumothorax, primary spontaneous; Renal carcinoma, chromophobe, somatic | NA | (99) |
| FLNA | ENSG00000196924 | 2 | ?FG syndrome 2; Cardiac valvular dysplasia, X-linked; Congenital short bowel syndrome; Frontometaphyseal dysplasia 1; Heterotopia, periventricular, | NA | (100) |
| Gene  | GeneID          | Chromosome | Description                                                                 |
|-------|----------------|------------|-----------------------------------------------------------------------------|
| FLNB  | ENSG00000136068| 2          | Atelosteogenesis, types I & III; Boomerang dysplasia; Larsen syndrome;      |
|       |                |            | Spondylocarpotarsal synostosis syndrome                                        |
| FOXE3 | ENSG00000186790| 2          | Anterior segment dysgenesis 2, multiple subtypes; Cataract 34, multiple types; |
|       |                |            | {Aortic aneurysm, familial thoracic 11, susceptibility to}                   |
| GJA1  | ENSG00000152661| 2          | Atrioventricular septal defect 3; Craniometaphyseal dysplasia, autosomal    |
|       |                |            | recessive; Erythrodermatodermia variabilis et progressiva 3; Hypoplastic    |
|       |                |            | left heart syndrome 1; Oculodentodigital dysplasia;                          |
|       |                |            | Palmoplantar keratoderma with congenital                                      |
|       |                |            | Coronary artery aneurysm (mice); migraine risk loci                          |

1; Intestinal pseudoobstruction, neuronal; Melnick-Needles syndrome; Otopalatodigital syndrome, type I-II; Terminal osseous dysplasia

(101)
| Gene   | Entrez Gene ID | Chromosome | Disease/Condition                                                                 |
|--------|----------------|------------|-----------------------------------------------------------------------------------|
| GORAB  | ENSG00000120370| 2          | alopecia; Syndactyly, type III                                                    |
|        |                |            | Geroderma osteodysplasticum                                                       |
|        |                |            | NA                                                                                |
|        |                |            | NA                                                                                |
|        |                |            | (105)                                                                             |
| GPR149 | ENSG00000174948| 2          | NA                                                                                |
|        |                |            | Migraine risk loci                                                                |
|        |                |            | NA                                                                                |
|        |                |            | (62)                                                                              |
| GRIN2A | ENSG00000183454| 2          | Epilepsy, focal, with speech disorder and with or without mental retardation     |
|        |                |            | Arteritis                                                                        |
|        |                |            | NA                                                                                |
|        |                |            | (106, 107)                                                                        |
| HEY2   | ENSG00000135547| 2          | NA                                                                                |
|        |                |            | Migraine risk loci                                                                |
|        |                |            | NA                                                                                |
|        |                |            | (62)                                                                              |
| HJURP  | ENSG00000123485| 2          | NA                                                                                |
|        |                |            | Migraine risk loci                                                                |
|        |                |            | NA                                                                                |
|        |                |            | (62)                                                                              |
| HPSE2  | ENSG00000172987| 2          | Urofacial syndrome 1                                                              |
|        |                |            | Migraine risk loci                                                                |
|        |                |            | NA                                                                                |
|        |                |            | (62, 108)                                                                         |
| ICAM1  | ENSG00000090339| 2          | (Malaria, cerebral, susceptibility to)                                            |
|        |                |            | Carotid dissection (unconfirmed)                                                  |
|        |                |            | NA                                                                                |
|        |                |            | (109)                                                                             |
| IGSF9B | ENSG00000080854| 2          | NA                                                                                |
|        |                |            | Migraine risk loci                                                                |
|        |                |            | NA                                                                                |
|        |                |            | (62)                                                                              |
| IL12B  | ENSG00000113302| 2          | Immunodeficiency 29, mycobacteriosis                                             |
|        |                |            | Arteritis                                                                        |
|        |                |            | NA                                                                                |
|        |                |            | (107, 110)                                                                        |
| IL6    | ENSG00000136244| 2          | {Crohn disease-associated growth failure}; {Diabetes, susceptibility to};         |
|        |                |            | {Intracranial hemorrhage in brain cerebrovascular malformations, susceptibility to}; {Kaposi sarcoma, susceptibility to}; {Rheumatoid |
|        |                |            | Arteritis, coronary artery spasm                                                  |
|        |                |            | NA                                                                                |
|        |                |            | (84, 111, 112)                                                                    |
| Gene | Ensembl ID | Chromosome | Description | Disease Associations |
|------|------------|-------------|-------------|----------------------|
| ITPK1 | ENSG00000100605 | 2 | NA | Migraine risk loci |
| JAG1 | ENSG00000101384 | 2 | ?Deafness, congenital heart defects, and posterior embryotoxon; Alagille syndrome 1; Tetralogy of Fallot | Migraine risk loci |
| KCNJ2 | ENSG00000123700 | 2 | Andersen syndrome; Atrial fibrillation, familial, 9; Short QT syndrome 3 | NA |
| KCNK5 | ENSG00000164626 | 2 | NA | Migraine risk loci |
| LILRB3 | ENSG00000204577 | 2 | NA | Arteritis |
| LMX1B | ENSG00000136944 | 2 | Nail-patella syndrome | NA |
| LOX | ENSG00000113083 | 2 | Aortic aneurysm, familial thoracic 10 | NA |
| LTBP3 | ENSG00000168056 | 2 | Dental anomalies and short stature; Geleophysic dysplasia 3 | NA |
| LTBP4 | ENSG00000090006 | 2 | Cutis laxa, autosomal recessive, type IC | NA |
| MAT2A | ENSG00000168906 | 2 | Thoracic aortic aneurysm (unconfirmed) | NA |
| MED12 | ENSG00000184634 | 2 | Lujan–Fryns syndrome; Ohdo syndrome, X-linked; Opitz–Kaveggia syndrome | NA |
| Gene    | Ensembl ID       | Chromosome | Condition                                                                 | Database References |
|---------|------------------|------------|---------------------------------------------------------------------------|---------------------|
| MEF2D   | ENSG00000116604  | 2          | Migraine risk loci                                                         | NA                  |
| MFAP5   | ENSG00000197614  | 2          | Aortic aneurysm, familial thoracic 9                                      | NA                  |
| MMP3    | ENSG00000149968  | 2          | (Coronary heart disease, susceptibility to, 6)                            | NA                  |
| MPPED2  | ENSG00000066382  | 2          | Migraine risk loci                                                         | NA                  |
| MRVII   | ENSG00000072952  | 2          | Migraine risk loci                                                         | NA                  |
| MTHFR   | ENSG00000177000  | 2          | Homocystinuria due to MTHFR deficiency; {Neural tube defects, susceptibility to}; {Schizophrenia, susceptibility to}; {Thromboembolism, susceptibility to}; {Vascular disease, susceptibility to} | NA                  |
| MYH11   | ENSG00000133392  | 2          | Aortic aneurysm, familial thoracic 4                                      | NA                  |
| MYLK    | ENSG00000065534  | 2          | Aortic aneurysm, familial thoracic 7                                      | NA                  |
| NCOA7   | ENSG00000111912  | 2          | Migraine risk loci                                                         | NA                  |
| NOS3    | ENSG00000164867  | 2          | {Alzheimer disease, late-onset, susceptibility to}; {Coronary artery spasm} | NA                  |
| Gene   | ENSG | Chromosome | Description                                                                 | Aortic valve disease | SCAD risk loci; Migraine risk loci | Reference |
|--------|------|------------|-----------------------------------------------------------------------------|----------------------|-----------------------------------|-----------|
| NOTCH1 | ENSG00000148400 | 2 | Adams-Oliver syndrome 5; Aortic valve disease 1 | NA                   | Migraine risk loci                | (127)     |
| NOTCH4 | ENSG00000204301 | 2 | NA                                                                          | NA                   | Migraine risk loci                | (62)      |
| NRP1   | ENSG00000099250 | 2 | NA                                                                          | Migraine risk loci   | NA                                | (62)      |
| P4HA2  | ENSG00000072682 | 2 | Myopia 25, autosomal dominant                                               | Arteritis            | NA                                | (128)     |
| PDIA2  | ENSG00000185615 | 2 | NA                                                                          | aortic valve disease | NA                                | (129)     |
| PHACTR1| ENSG00000112137 | 2 | Epileptic encephalopathy, early infantile, 70                             | SCAD risk loci; Migraine risk loci | NA                                | (62, 87) |
| PLCE1  | ENSG00000138193 | 2 | Nephrotic syndrome, type 3                                                  | Migraine risk loci   | NA                                | (62, 130) |
| PLG    | ENSG00000122194 | 2 | Dysplasminogenemia; Plasminogen deficiency, type I                         | Arteritis            | NA                                | (128, 131) |
| PLOD1  | ENSG00000083444 | 2 | Ehlers-Danlos syndrome, kyphoscoliotic type, 1                             | NA                   | NA                                | (132)     |
| Gene    | Entrez ID   | Chromosome | Condition                                                                 | Migraine risk loci | Expression | Annotation                  |
|---------|-------------|------------|----------------------------------------------------------------------------|--------------------|------------|-----------------------------|
| PRDM16  | ENSG00000142611 | 2          | Cardiomyopathy, dilated, 1LL; Left ventricular noncompaction 8             | Migraine risk loci | NA         | (62, 133)                   |
| PRDM5   | ENSG00000138738 | 2          | Brittle cornea syndrome 2                                                  | NA                 | NA         | (134)                       |
| PRKG1   | ENSG00000185532 | 2          | Aortic aneurysm, familial thoracic 8                                       | NA                 | NA         | (135)                       |
| PTGIR   | ENSG00000160013 | 2          | NA                                                                         | Fibromuscular dysplasia | NA         | (136)                       |
| PRKG1   | ENSG00000186201 | 2          | Cutis laxa, autosomal recessive, types IIB & IIB                           | NA                 | NA         | (137, 138)                  |
| RIN2    | ENSG00000132669 | 2          | Macrocephaly, alopecia, cutis laxa, and scoliosis                          | NA                 | NA         | (139)                       |
| ROBO3   | ENSG00000154134 | 2          | Gaze palsy, familial horizontal, with progressive scoliosis, 1             | NA                 | NA         | (140)                       |
| ROBO4   | ENSG00000154133 | 2          | Aortic valve disease 8                                                    | NA                 | NA         | (141)                       |
| RPS9    | ENSG00000170889 | 2          | NA                                                                         | Arteritis          | NA         | (111)                       |
| SDR9C7  | ENSG00000170426 | 2          | Ichthyosis, congenital, autosomal recessive 13                             | Migraine risk loci | NA         | (62, 142)                   |
| SDR9C7  | ENSG00000170426 | 2          | Ichthyosis, congenital, autosomal recessive 13                             | Migraine risk loci | NA         | (62, 142)                   |
| SDR9C7  | ENSG00000170426 | 2          | Ichthyosis, congenital, autosomal recessive 13                             | Migraine risk loci | NA         | (62, 142)                   |
| SDR9C7  | ENSG00000170426 | 2          | Ichthyosis, congenital, autosomal recessive 13                             | Migraine risk loci | NA         | (62, 142)                   |
| Gene   | ENSG Identifier     | Chromosome Location | Condition                                                                 | Malignancy | Malignancy Associated | (Reference) |
|--------|---------------------|---------------------|---------------------------------------------------------------------------|------------|-----------------------|-------------|
| SLC24A3 | ENSG00000185052     | 2                   | NA                                                                         | Migraine   | NA                    | (62)        |
| SLC2A10 | ENSG00000197496     | 2                   | Arterial tortuosity syndrome                                               | NA         | NA                    | (144)       |
| SLC39A13 | ENSG00000165915     | 2                   | Ehlers-Danlos syndrome, spondylodysplastic type, 3                        | NA         | NA                    | (145)       |
| SMAD4  | ENSG00000141646     | 2                   | Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome; Myhre syndrome; Pancreatic cancer, somatic; Polyposis, juvenile intestinal | NA         | NA                    | (146)       |
| SMAD6  | ENSG00000137834     | 2                   | Aortic valve disease 2; [Craniosynostosis 7, susceptibility to)            | NA         | NA                    | (147)       |
| SMYD2  | ENSG00000143499     | 2                   | NA                                                                         | Aneurysm   | NA                    | (93)        |
| STAT6  | ENSG00000166888     | 2                   | NA                                                                         | Migraine   | NA                    | (62)        |
| SUGCT  | ENSG00000175600     | 2                   | Glutaric aciduria III                                                     | Migraine   | NA                    | (62, 148)   |
| TBX20  | ENSG00000164532     | 2                   | Atrial septal defect 4                                                    | Aortic valve disease, aneurysm | NA | (149) |
| TGFB2  | ENSG000000092969     | 2                   | Loeys-Dietz syndrome 4                                                    | NA         | NA                    | (150)       |
| TGFB3  | ENSG00000119699     | 2                   | Arrhythmogenic right ventricular                                          | NA         | NA                    | (151)       |
| Gene     | Ensemble ID       | Chromosome | Description                                                                                      | OMIM   | Reference |
|----------|-------------------|------------|-------------------------------------------------------------------------------------------------|--------|-----------|
| TGFBR1   | ENSG00000106799   | 2          | dysplasia 1; Loeys-Dietz syndrome 5                                                             | NA     | (39, 152) |
| TGFBR2   | ENSG00000163513   | 2          | Loeys-Dietz syndrome 1; [Multiple self-healing squamous epithelioma, susceptibility to]            | TGFBR2 | NA        |
| TNXB     | ENSG00000168477   | 2          | Colorectal cancer, hereditary nonpolyposis, type 6; Esophageal cancer, somatic; Loeys-Dietz syndrome 2 SCAD | NA     | (153, 154) |
| TRPM8    | ENSG00000144481   | 2          | Ehlers-Danlos syndrome, classic-like, 1; Vesicoureteral reflux 8                                 | NA     | Migraine risk loci |
| UFL1     | ENSG00000014123   | 2          | NA                                                                                              | Migraine risk loci |
| YAP1     | ENSG00000137693   | 2          | Coloboma, ocular, with or without hearing impairment, cleft lip/palate, and/or mental retardation | Migraine risk loci |
| YY1AP1   | ENSG00000163374   | 2          | Grange syndrome                                                                                  | NA     | (157)     |
| ZCCHC14  | ENSG00000140948   | 2          | NA                                                                                              | Migraine risk loci |
| ZNF469   | ENSG00000225614   | 2          | Brittle cornea syndrome 1                                                                       | NA     | (158)     |
| Gene   | ENSG Accession | Expression | N/A | Description          | Value |
|--------|----------------|------------|-----|----------------------|-------|
| ADA    | ENSG00000196839 | 3          | NA  | Abnormal blood vessel morphology | (30)  |
| ADAM19 | ENSG00000135074 | 3          | NA  | Aneurysm             | (30)  |
| ADM    | ENSG00000148926 | 3          | NA  | Abnormal blood vessel morphology | (30)  |
| ADORA2A| ENSG00000128271 | 3          | NA  | Abnormal blood vessel morphology | (30)  |
| AGT    | ENSG00000135744 | 3          | NA  | Abnormal blood vessel morphology | (30)  |
| AGTR2  | ENSG00000180772 | 3          | NA  | Aneurysm             | (30)  |
| AHR    | ENSG00000106546 | 3          | NA  | Abnormal blood vessel morphology | (30)  |
| AMACR  | ENSG00000242110 | 3          | NA  | Migraine             | (30)  |
| AMOTL2 | ENSG00000114019 | 3          | NA  | Abnormal blood vessel morphology | (30)  |
| ANGPT1 | ENSG00000154188 | 3          | NA  | Abnormal blood vessel morphology | (30)  |
| Gene   | Ensembl ID          | LOC | Status | Diagnosis                              |
|--------|---------------------|-----|--------|----------------------------------------|
| ANKRD17| ENSG00000132466     | 3   | NA     | Abnormal blood vessel morphology       |
| ANO1   | ENSG00000131620     | 3   | NA     | Abnormal blood vessel morphology       |
| APELA  | ENSG00000248329     | 3   | NA     | Abnormal blood vessel morphology       |
| APOB   | ENSG00000084674     | 3   | NA     | Arteritis                              |
| APOE   | ENSG00000130203     | 3   | NA     | Aneurysm                               |
| ARHGDIA| ENSG00000141522     | 3   | NA     | Abnormal blood vessel morphology       |
| ARHGEF26| ENSG00000277101    | 3   | NA     | Abnormal blood vessel morphology       |
| ARID2  | ENSG00000189079     | 3   | NA     | Abnormal blood vessel morphology       |
| ARNTL  | ENSG00000133794     | 3   | NA     | Abnormal blood vessel morphology       |
| ATP1A2 | ENSG00000018625     | 3   | NA     | Migraine                               |
| Gene   | Gene ID          | Rank | Mutations | Normality | Condition                          | Severity |
|--------|-----------------|------|-----------|-----------|------------------------------------|----------|
| ATP7A  | ENSG00000165240 | 3    | NA        | NA        | Aneurysm                           | (30)     |
| BACH1  | ENSG00000156273 | 3    | NA        | NA        | Abnormal blood vessel morphology   | (30)     |
| BCAS3  | ENSG00000141376 | 3    | NA        | NA        | Abnormal blood vessel morphology   | (30)     |
| BCL2   | ENSG00000171791 | 3    | NA        | NA        | Abnormal blood vessel morphology   | (30)     |
| BMP4   | ENSG00000125378 | 3    | NA        | NA        | Abnormal blood vessel morphology   | (30)     |
| BMPRIA | ENSG00000107779 | 3    | NA        | NA        | Abnormal blood vessel morphology   | (30)     |
| BRAF   | ENSG00000157764 | 3    | NA        | NA        | Abnormal blood vessel morphology   | (30)     |
| C1GALT1| ENSG00000106392 | 3    | NA        | NA        | Abnormal blood vessel morphology   | (30)     |
| CACNA1A| ENSG00000141837 | 3    | NA        | NA        | Migraine                           | (30)     |
| CACNB3 | ENSG00000167535 | 3    | NA        | NA        | Abnormal blood vessel morphology   | (30)     |
| Gene   | Gene ID          | Exon | Protein | Stage | Condition                  |
|--------|------------------|------|---------|-------|-----------------------------|
| CALCRL | ENSG00000064989  | 3    | NA      | NA    | Abnormal blood vessel morphology (30) |
| CAV1   | ENSG00000105974  | 3    | NA      | NA    | Abnormal blood vessel morphology (30) |
| CAVIN1 | ENSG00000177469  | 3    | NA      | NA    | Abnormal blood vessel morphology (30) |
| CAVIN2 | ENSG00000168497  | 3    | NA      | NA    | Abnormal blood vessel morphology (30) |
| CAVIN3 | ENSG00000170955  | 3    | NA      | NA    | Abnormal blood vessel morphology (30) |
| CBS    | ENSG00000160200  | 3    | NA      | NA    | Aneurysm (30)               |
| CCM2   | ENSG00000136280  | 3    | NA      | NA    | Abnormal blood vessel morphology (30) |
| CCR5   | ENSG00000160791  | 3    | NA      | NA    | Abnormal blood vessel morphology (30) |
| CD151  | ENSG00000177697  | 3    | NA      | NA    | Abnormal blood (30)         |
| Gene    | ENSG Identifier          | Score | Expression | Class                          | Phenotype                                      |
|---------|--------------------------|-------|------------|--------------------------------|-----------------------------------------------|
| CD19    | ENSG00000177455          | 3     | NA         | NA                            | Arteritis (30)                                |
| CD40LG  | ENSG00000102245          | 3     | NA         | NA                            | Abnormal blood vessel morphology (30)         |
| CD44    | ENSG00000026508          | 3     | NA         | NA                            | Abnormal blood vessel morphology (30)         |
| CD59    | ENSG000000085063         | 3     | NA         | NA                            | Abnormal blood vessel morphology (30)         |
| CDH5    | ENSG00000179776          | 3     | NA         | NA                            | Abnormal blood vessel morphology (30)         |
| CDKN1A  | ENSG00000124762          | 3     | NA         | NA                            | Abnormal blood vessel morphology (30)         |
| CHD2    | ENSG00000173575          | 3     | NA         | NA                            | Arteritis (30)                                |
| CLIC4   | ENSG00000169504          | 3     | NA         | NA                            | Abnormal blood vessel morphology (30)         |
| CLIC5   | ENSG00000112782          | 3     | NA         | NA                            | Abnormal blood vessel morphology (30)         |
| Gene   | ENSG ID    | Gene ID | Chromosome | Expression | Phenotype                  | Score |
|--------|------------|---------|------------|------------|----------------------------|-------|
| COL15A1| ENSG00000204291 | 3      | NA         | NA         | Abnormal blood vessel morphology | (30)   |
| COL4A1 | ENSG00000187498 | 3      | NA         | NA         | Migraine                   | (30)   |
| CREBBP | ENSG0000005339   | 3      | NA         | NA         | Abnormal blood vessel morphology | (30)   |
| CRIM1  | ENSG00000150938  | 3      | NA         | NA         | Abnormal blood vessel morphology | (30)   |
| CRK    | ENSG00000167193  | 3      | NA         | NA         | Abnormal blood vessel morphology | (30)   |
| CST3   | ENSG00000101439  | 3      | NA         | NA         | Abnormal blood vessel morphology | (30)   |
| CTNNB1 | ENSG00000168036  | 3      | NA         | NA         | Abnormal blood vessel morphology | (30)   |
| CTSS   | ENSG00000163131  | 3      | NA         | NA         | Abnormal blood vessel morphology | (30)   |
| CXCL10 | ENSG00000169245  | 3      | NA         | NA         | Aneurysm                   | (30)   |
| CXCL12 | ENSG00000107562  | 3      | NA         | NA         | Abnormal blood              | (30)   |
| Gene   | EntrezGene ID | Rank | Expression | Condition                      | Disease       | Score |
|--------|---------------|------|------------|-------------------------------|---------------|-------|
| CXCRI4 | ENSG00000121966 | 3    | NA         | NA                            | Abnormal blood vessel morphology | (30)   |
| DES    | ENSG00000175084 | 3    | NA         | NA                            | Abnormal blood vessel morphology | (30)   |
| DLL4   | ENSG00000128917 | 3    | NA         | NA                            | Abnormal blood vessel morphology | (30)   |
| DNAAF4 | ENSG00000256061 | 3    | NA         | NA                            | Abnormal blood vessel morphology | (30)   |
| DYNC2H1| ENSG00000187240 | 3    | NA         | NA                            | Abnormal blood vessel morphology | (30)   |
| EDNRA  | ENSG00000151617 | 3    | NA         | NA                            | Migraine      | (30)   |
| EHD3   | ENSG00000013016 | 3    | NA         | NA                            | Abnormal blood vessel morphology | (30)   |
| EHD4   | ENSG000000103966 | 3    | NA         | NA                            | Abnormal blood vessel morphology | (30)   |
| ELK3   | ENSG00000111145 | 3    | NA         | NA                            | Abnormal blood | (30)   |
| Gene  | Accession         | Chromosome | Start | End | Gene Product|
|-------|------------------|------------|-------|-----|-------------|
| ENG   | ENSG00000106991   | 3          | NA    | NA  | Migraine    |
| ENPP1 | ENSG00000197594   | 3          | NA    | NA  | Abnormal blood vessel morphology |
| EP300 | ENSG00000100393   | 3          | NA    | NA  | Arteritis   |
| ESR1  | ENSG00000091831   | 3          | NA    | NA  | Migraine    |
| ESR2  | ENSG00000140009   | 3          | NA    | NA  | Abnormal blood vessel morphology |
| ETV2  | ENSG00000105672   | 3          | NA    | NA  | Abnormal blood vessel morphology |
| F11   | ENSG00000088926   | 3          | NA    | NA  | Abnormal blood vessel morphology |
| FAS   | ENSG00000026103   | 3          | NA    | NA  | Arteritis, abnormal blood vessel morphology |
| FAT1  | ENSG000000083857   | 3          | NA    | NA  | Aneurysm    |
| FBLN1 | ENSG00000077942   | 3          | NA    | NA  | Abnormal blood |
| Gene    | Ensembl ID | Value | Value | Disease                          | Frequency |
|---------|------------|-------|-------|----------------------------------|-----------|
| FCER1G  | ENSG00000158869 | 3     | NA    | NA                               | Arteritis (30) |
| FGF8    | ENSG00000107831  | 3     | NA    | NA                               | Abnormal blood vessel morphology (30) |
| FGFR3   | ENSG00000068078  | 3     | NA    | Migraine                         | (30)      |
| FLII    | ENSG00000151702  | 3     | NA    | NA                               | Aneurysm (30) |
| FLT1    | ENSG00000102755  | 3     | NA    | NA                               | Abnormal blood vessel morphology (30) |
| FNI     | ENSG00000115414  | 3     | NA    | Abnormal blood vessel morphology (30) |
| FOLH1   | ENSG00000086205  | 3     | NA    | Abnormal blood vessel morphology (30) |
| FOXC2   | ENSG00000176692  | 3     | NA    | Abnormal blood vessel morphology (30) |
| FOXF1   | ENSG00000103241  | 3     | NA    | Abnormal blood vessel morphology (30) |
| FOXM1   | ENSG00000111206  | 3     | NA    | Abnormal blood (30)              |           |
| Gene   | Entrez ID       | Chromosome | Expression | Function                  |
|--------|-----------------|------------|------------|---------------------------|
| GADD45A | ENSG00000116717 | 3          | NA         | Abnormal blood vessel morphology (30) |
| GATA2  | ENSG00000179348 | 3          | NA         | Abnormal blood vessel morphology (30) |
| GATA4  | ENSG00000136574 | 3          | NA         | Abnormal blood vessel morphology (30) |
| GATA6  | ENSG00000141448 | 3          | NA         | Abnormal blood vessel morphology (30) |
| GDF2   | ENSG00000263761 | 3          | NA         | Migraine (30)             |
| GDNF   | ENSG00000168621 | 3          | NA         | Abnormal blood vessel morphology (30) |
| GIPC1  | ENSG00000123159 | 3          | NA         | Aneurysm (159)            |
| GIT1   | ENSG00000108262 | 3          | NA         | Abnormal blood vessel morphology (30) |
| GPC3   | ENSG00000147257 | 3          | NA         | Abnormal blood vessel morphology (30) |
| Gene   | GeneID       | Expression | Status | Description                  |
|--------|--------------|------------|--------|------------------------------|
| GPR4   | ENSG00000177464 | 3          | NA     | Abnormal blood vessel morphology | (30) |
| GULOP  | ENSG00000234770 | 3          | NA     | Abnormal blood vessel morphology | (30) |
| H2AFV  | ENSG00000105968 | 3          | NA     | Abnormal blood vessel morphology | (30) |
| HDAC7  | ENSG00000061343 | 3          | NA     | Abnormal blood vessel morphology | (30) |
| HECTD1 | ENSG00000092148 | 3          | NA     | Abnormal blood vessel morphology | (30) |
| HEXIM1 | ENSG00000186834 | 3          | NA     | Abnormal blood vessel morphology | (30) |
| HHEX   | ENSG00000152804 | 3          | NA     | Abnormal blood vessel morphology | (30) |
| HIF1A  | ENSG00000100644 | 3          | NA     | Abnormal blood vessel morphology | (30) |
| HPRT1  | ENSG00000165704 | 3          | NA     | Abnormal blood vessel morphology | (30) |
| Gene   | ENSG ID               | Chr | Effect | Disease                      | Notes          |
|--------|-----------------------|-----|--------|------------------------------|----------------|
| HSPG2  | ENSG00000143498       | 3   | NA     | NA                           | Aneurysm       |
| HTR1A  | ENSG00000178394       | 3   | NA     | NA                           | Migraine       |
| HTRA1  | ENSG00000166033       | 3   | NA     | NA                           | Aneurysm       |
| IDUA   | ENSG00000134415       | 3   | NA     | NA                           | Abnormal blood vessel morphology |
| IFNG   | ENSG00000111537       | 3   | NA     | NA                           | Aneurysm       |
| IFNGR1 | ENSG00000034697       | 3   | NA     | NA                           | Arteritis      |
| IL1RN  | ENSG00000136689       | 3   | NA     | NA                           | Arteritis      |
| INS    | ENSG00000254647       | 3   | NA     | NA                           | Abnormal blood vessel morphology |
| ISL1   | ENSG0000016082        | 3   | NA     | NA                           | Abnormal blood vessel morphology |
| ITGA7  | ENSG00000135424       | 3   | NA     | NA                           | Abnormal blood vessel morphology |
| ITGB8  | ENSG00000105855       | 3   | NA     | NA                           | Abnormal blood vessel morphology |
| Gene   | Entrez Gene ID | Ratio | Ensembl ID | Freq | Condition                        | Remarks                              |
|--------|----------------|-------|------------|------|----------------------------------|--------------------------------------|
| JUP    | ENSG00000173801| 3     | NA         | NA   | Aneurysm                         | (30)                                 |
| KCNK18 | ENSG00000186795| 3     | NA         | NA   | Migraine                         | (30)                                 |
| KDR    | ENSG00000128052| 3     | NA         | NA   | Abnormal blood vessel morphology | (30)                                 |
| KIRREL1| ENSG00000183853| 3     | NA         | NA   | Abnormal blood vessel morphology | (30)                                 |
| KLF15  | ENSG00000163884| 3     | NA         | NA   | Abnormal blood vessel morphology | (30)                                 |
| KLF2   | ENSG00000134528| 3     | NA         | NA   | Aneurysm                         | (30)                                 |
| KRT14  | ENSG00000186847| 3     | NA         | NA   | Abnormal blood vessel morphology | (30)                                 |
| LAMA5  | ENSG00000130702| 3     | NA         | NA   | Abnormal blood vessel morphology | (30)                                 |
| LAMC1  | ENSG00000135862| 3     | NA         | NA   | Aneurysm                         | (30)                                 |
| LCK    | ENSG00000182866| 3     | NA         | NA   | Abnormal blood vessel morphology | (30)                                 |
| LDB1   | ENSG00000198728| 3     | NA         | NA   | Abnormal blood                  | (30)                                 |
| Gene   | ENSG  | ID    | Value | Value | Description                          | Value |
|--------|-------|-------|-------|-------|--------------------------------------|-------|
| LDLR   | ENSG00000130164 | 3     | NA    | NA    | Aneurysm                             | (30)  |
| LMNA   | ENSG00000160789 | 3     | NA    | NA    | Abnormal blood vessel morphology     | (30)  |
| LPAR4  | ENSG00000147145 | 3     | NA    | NA    | Abnormal blood vessel morphology     | (30)  |
| LRP1   | ENSG00000123384 | 3     | NA    | NA    | Aneurysm                             | (30)  |
| LTBP1  | ENSG00000049323 | 3     | NA    | NA    | Abnormal blood vessel morphology     | (30)  |
| MAGI2  | ENSG00000187391 | 3     | NA    | NA    | Abnormal blood vessel morphology     | (30)  |
| MAP3K7 | ENSG00000135341 | 3     | NA    | NA    | Abnormal blood vessel morphology     | (30)  |
| MAPK7  | ENSG00000166484 | 3     | NA    | NA    | Abnormal blood vessel morphology     | (30)  |
| MDK    | ENSG00000110492 | 3     | NA    | NA    | Abnormal blood vessel morphology     | (30)  |
| Gene  | Entrez Gene ID | Protein ID | Gene Name          | Disease Description                        |
|-------|----------------|------------|--------------------|--------------------------------------------|
| MEGF8 | ENSG00000105429 | 3          | NA                | Abnormal blood vessel morphology (30)      |
| METAP2| ENSG00000111142 | 3          | NA                | Abnormal blood vessel morphology (30)      |
| MGAT1 | ENSG00000131446 | 3          | NA                | Abnormal blood vessel morphology (30)      |
| MGP   | ENSG00000111341 | 3          | NA                | Aneurysm (30)                              |
| MICU2 | ENSG00000165487 | 3          | NA                | Aneurysm (30)                              |
| MMP2  | ENSG00000087245 | 3          | NA                | Arteritis (30)                             |
| MMP9  | ENSG00000100985 | 3          | NA                | Aneurysm (30)                              |
| MRTFB | ENSG00000186260 | 3          | NA                | Aneurysm (30)                              |
| MSX1  | ENSG00000163132 | 3          | NA                | Abnormal blood vessel morphology (30)      |
| MSX2  | ENSG00000120149 | 3          | NA                | Aneurysm (30)                              |
| MTAP  | ENSG00000099810 | 3          | NA                | Arteritis (30)                             |
| MT-ATP6| ENSG00000198899 | 3          | NA                | Arterial tortuosity (30)                   |
| MT-CO1| ENSG00000198804 | 3          | NA                | Migraine (30)                               |
| Gene Symbol | Ensembl ID              | Exon | NCBI GI | GO Term                          | Description               |
|-------------|-------------------------|------|---------|----------------------------------|---------------------------|
| MT-CO2      | ENSG00000198712         | 3    | NA      | NA                               | Migraine (30)             |
| MT-CO3      | ENSG00000198938         | 3    | NA      | NA                               | Arterial tortuosity (30)  |
| MT-CYB      | ENSG00000198727         | 3    | NA      | NA                               | Arterial tortuosity (30)  |
| MT-ND1      | ENSG00000198888         | 3    | NA      | NA                               | Arterial tortuosity (30)  |
| MT-ND2      | ENSG00000198763         | 3    | NA      | NA                               | Arterial tortuosity (30)  |
| MT-ND4      | ENSG00000198866         | 3    | NA      | NA                               | Arterial tortuosity (30)  |
| MT-ND4L     | ENSG00000212907         | 3    | NA      | NA                               | Arterial tortuosity (30)  |
| MT-ND5      | ENSG00000198786         | 3    | NA      | NA                               | Arterial tortuosity (30)  |
| MT-ND6      | ENSG00000198695         | 3    | NA      | NA                               | Arterial tortuosity (30)  |
| MT-TC       | ENSG00000210140         | 3    | NA      | NA                               | Migraine (30)             |
| MT-TF       | ENSG00000210049         | 3    | NA      | NA                               | Migraine (30)             |
| MT-TK       | ENSG00000210156         | 3    | NA      | NA                               | Migraine (30)             |
| MT-TL1      | ENSG00000209082         | 3    | NA      | NA                               | Migraine (30)             |
| MT-TQ       | ENSG00000210107         | 3    | NA      | NA                               | Migraine (30)             |
| MT-TS1      | ENSG00000210151         | 3    | NA      | NA                               | Migraine (30)             |
| MT-TS2      | ENSG00000210184         | 3    | NA      | NA                               | Migraine (30)             |
| MT-TV       | ENSG00000210077         | 3    | NA      | NA                               | Migraine (30)             |
| Gene   | Accession     | Ensembl ID | Stage | Expression | Phenotype                          | Value |
|--------|---------------|------------|-------|------------|------------------------------------|-------|
| MT-TW  | ENSG00000210117 | 3          | NA    | NA         | Migraine                           | (30)  |
| MUS81  | ENSG00000172732 | 3          | NA    | NA         | Aneurysm                           | (30)  |
| MYH6   | ENSG00000197616 | 3          | NA    | NA         | Abnormal blood vessel morphology   | (30)  |
| MYOCD  | ENSG00000141052 | 3          | NA    | NA         | Abnormal blood vessel morphology   | (30)  |
| NCF1   | ENSG00000158517 | 3          | NA    | NA         | Aneurysm                           | (30)  |
| NDP    | ENSG00000124479 | 3          | NA    | NA         | Migraine                           | (30)  |
| NES    | ENSG00000132688 | 3          | NA    | NA         | Abnormal blood vessel morphology   | (30)  |
| NF1    | ENSG00000196712 | 3          | NA    | NA         | Migraine                           | (30)  |
| NF2    | ENSG00000186575 | 3          | NA    | NA         | Migraine                           | (30)  |
| NFATC1 | ENSG00000131196 | 3          | NA    | NA         | Abnormal blood vessel morphology   | (30)  |
| NGF    | ENSG00000134259 | 3          | NA    | NA         | Abnormal blood vessel morphology   | (30)  |
| NKX2.5 | ENSG00000183072 | 3          | NA    | NA         | Aneurysm                           | (30)  |
| Gene   | Entrez ID       | Chromosome | Expression | Disease                      | Reference |
|--------|----------------|------------|------------|------------------------------|-----------|
| NLRP3  | ENSG0000162711 | 3          | NA         | NA                          | Migraine  |
| NOS1   | ENSG0000089250 | 3          | NA         | Abnormal blood vessel morphology | (30)     |
| NOS2   | ENSG0000007171 | 3          | NA         | Abnormal blood vessel morphology | (30)     |
| NOTCH2 | ENSG0000134250 | 3          | NA         | Aneurysm                     | (30)     |
| NOTCH3 | ENSG0000074181 | 3          | NA         | Migraine                     | (30)     |
| NPHP3  | ENSG000013971  | 3          | NA         | Aneurysm                     | (30)     |
| NPHS1  | ENSG0000161270 | 3          | NA         | Abnormal blood vessel morphology | (30)     |
| NPHS2  | ENSG000016218  | 3          | NA         | Abnormal blood vessel morphology | (30)     |
| NPPA   | ENSG0000175206 | 3          | NA         | Abnormal blood vessel morphology | (30)     |
| NTF3   | ENSG0000185652 | 3          | NA         | Aneurysm                     | (30)     |
| PARVA  | ENSG0000197702 | 3          | NA         | Aneurysm                     | (30)     |
| PAX3   | ENSG0000135903 | 3          | NA         | Abnormal blood morphol | (30)     |
| Protein | Gene ID | Exon | ENSG | Description |
|---------|---------|------|------|-------------|
| PDC     | ENSG00000116703 | 3 | NA | Abnormal blood vessel morphology (30) |
| PDGFB   | ENSG00000100311 | 3 | NA | Migraine (30) |
| PDGFRα  | ENSG00000134853 | 3 | NA | Abnormal blood vessel morphology (30) |
| PDGFRβ  | ENSG00000113721 | 3 | NA | Aneurysm (30) |
| PDPN    | ENSG00000162493 | 3 | NA | Abnormal blood vessel morphology (30) |
| PECAM1  | ENSG00000261371 | 3 | NA | Abnormal blood vessel morphology (30) |
| PGK1    | ENSG00000102144 | 3 | NA | Abnormal blood vessel morphology (30) |
| PGR     | ENSG00000082175 | 3 | NA | Abnormal blood vessel morphology (30) |
| PIEZO1  | ENSG00000103335 | 3 | NA | Abnormal blood vessel morphology (30) |
| Gene  | ENSG ID       | Gene ID     | Gene ID Length | Description                  |
|-------|---------------|-------------|----------------|-------------------------------|
| PIP   | ENSG00000159763 | 3           | NA            | Arteritis                |
| PLEKHA1 | ENSG0000107679 | 3           | NA            | Abnormal blood vessel morphology |
| PLEKHG5 | ENSG0000171680 | 3           | NA            | Abnormal blood vessel morphology |
| PLOD3 | ENSG0000106397 | 3           | NA            | Abnormal blood vessel morphology |
| PLVAP | ENSG0000130300 | 3           | NA            | Abnormal blood vessel morphology |
| PLXND1 | ENSG0000004399 | 3           | NA            | Abnormal blood vessel morphology |
| POMGNT1 | ENSG0000085998 | 3           | NA            | Aneurysm                  |
| PPARA | ENSG0000186951 | 3           | NA            | Abnormal blood vessel morphology |
| PRKCD | ENSG0000163932 | 3           | NA            | Abnormal blood vessel morphology |
| PROC  | ENSG0000115718 | 3           | NA            | Abnormal blood              |
| Gene   | Ensembl ID           | Gene ID | Type          | Condition                        |
|--------|----------------------|---------|---------------|----------------------------------|
| PROS1  | ENSG00000184500      | 3       | NA            | Abnormal blood vessel morphology (30) |
| PROXI  | ENSG00000117707      | 3       | NA            | Aneurysm (30)                    |
| PRRT2  | ENSG00000167371      | 3       | NA            | Migraine (30)                    |
| PSAP   | ENSG00000197746      | 3       | NA            | Abnormal blood vessel morphology (30) |
| PSEN1  | ENSG00000080815      | 3       | NA            | Arteritis (30)                   |
| PSEN2  | ENSG00000143801      | 3       | NA            | Arteritis (30)                   |
| PTK2   | ENSG00000169398      | 3       | NA            | Abnormal blood vessel morphology (30) |
| PTPN12 | ENSG00000127947      | 3       | NA            | Abnormal blood vessel morphology (30) |
| PTPRJ  | ENSG00000149177      | 3       | NA            | Abnormal blood vessel morphology (30) |
| RAMP2  | ENSG00000131477      | 3       | NA            | Abnormal blood vessel morphology (30) |
| Gene   | Ensembl ID     | Count | Status | Annotation                                      |
|-------|----------------|-------|--------|------------------------------------------------|
| RAPGEF1 | ENSG00000107263 | 3     | NA     | Abnormal blood vessel morphology (30)           |
| RARB  | ENSG00000077092 | 3     | NA     | Abnormal blood vessel morphology (30)           |
| RASIP1 | ENSG00000105538 | 3     | NA     | Abnormal blood vessel morphology (30)           |
| RECK  | ENSG00000122707 | 3     | NA     | Abnormal blood vessel morphology (30)           |
| REN   | ENSG00000143839 | 3     | NA     | Abnormal blood vessel morphology (30)           |
| ROBO2 | ENSG00000185008 | 3     | NA     | Migraine (30)                                  |
| ROCK1 | ENSG00000067900 | 3     | NA     | Abnormal blood vessel morphology (30)           |
| RPL11 | ENSG00000142676 | 3     | NA     | Migraine (30)                                  |
| RPL15 | ENSG00000174748 | 3     | NA     | Migraine (30)                                  |
| RPL26 | ENSG00000161970 | 3     | NA     | Migraine (30)                                  |
| RPL35A| ENSG00000182899 | 3     | NA     | Migraine (30)                                  |
| Gene   | Entrez ID     | Beta Coefficient | Log2 Fold Change | Disease                        | P-value |
|--------|---------------|------------------|------------------|-------------------------------|---------|
| RPL5   | ENSG00000122406 | 3                | NA               | NA                            | Migraine | (30)    |
| RPS10  | ENSG00000124614 | 3                | NA               | NA                            | Migraine | (30)    |
| RPS17  | ENSG00000182774 | 3                | NA               | NA                            | Migraine | (30)    |
| RPS19  | ENSG00000105372 | 3                | NA               | NA                            | Migraine | (30)    |
| RPS24  | ENSG00000138326 | 3                | NA               | NA                            | Migraine | (30)    |
| RPS26  | ENSG00000197728 | 3                | NA               | NA                            | Migraine | (30)    |
| RPS29  | ENSG00000213741 | 3                | NA               | NA                            | Migraine | (30)    |
| RPS7   | ENSG00000171863 | 3                | NA               | NA                            | Migraine | (30)    |
| RRM2B  | ENSG00000048392 | 3                | NA               | Abnormal blood vessel morphology | (30)    |
| RUNX1  | ENSG00000159216 | 3                | NA               | Aneurysm                      | (30)    |
| RYR1   | ENSG00000196218 | 3                | NA               | Abnormal blood vessel morphology | (30)    |
| S1PR1  | ENSG00000170989 | 3                | NA               | Abnormal blood vessel morphology | (30)    |
| S1PR2  | ENSG00000267534 | 3                | NA               | Abnormal blood vessel morphology | (30)    |
| Gene   | Ensembl ID          | Expression | Neuron | Disorder                                      | Score |
|--------|---------------------|------------|--------|-----------------------------------------------|-------|
| S1PR3  | ENSG00000213694     | 3          | NA     | Abnormal blood vessel morphology              | (30)  |
| SCARB1 | ENSG00000073060     | 3          | NA     | Abnormal blood vessel morphology              | (30)  |
| SCHIP1 | ENSG00000151967     | 3          | NA     | Abnormal blood vessel morphology              | (30)  |
| SCN1A  | ENSG00000144285     | 3          | NA     | Migraine                                      | (30)  |
| SCN2A  | ENSG00000136531     | 3          | NA     | Migraine                                      | (30)  |
| SELP   | ENSG00000174175     | 3          | NA     | Abnormal blood vessel morphology              | (30)  |
| SERPIND1 | ENSG00000099937   | 3          | NA     | Abnormal blood vessel morphology              | (30)  |
| SFTPC  | ENSG00000168484     | 3          | NA     | Abnormal blood vessel morphology              | (30)  |
| SGCB   | ENSG00000163069     | 3          | NA     | Aneurysm                                      | (30)  |
| SGCD   | ENSG00000170624     | 3          | NA     | Abnormal blood vessel morphology              | (30)  |
| Gene   | Entrez ID       | Gene ID       | Chromosome | Abnormal Phenotype                                      |
|--------|-----------------|---------------|------------|--------------------------------------------------------|
| SGPL1  | ENSG00000166224 | 3             | NA         | Abnormal blood vessel morphology (30)                 |
| SHC1   | ENSG00000160691 | 3             | NA         | Abnormal blood vessel morphology (30)                 |
| SHH    | ENSG00000164690 | 3             | NA         | Abnormal blood vessel morphology (30)                 |
| SLC1A3 | ENSG00000079215 | 3             | NA         | Migraine (30)                                          |
| SLC20A2| ENSG00000168575 | 3             | NA         | Migraine (30)                                          |
| SLC2A1 | ENSG00000117394 | 3             | NA         | Migraine (30)                                          |
| SMAD2  | ENSG00000175387 | 3             | NA         | Abnormal blood vessel morphology (30)                 |
| SMAD5  | ENSG00000113658 | 3             | NA         | Abnormal blood vessel morphology (30)                 |
| SMAD7  | ENSG00000101665 | 3             | NA         | Abnormal blood vessel morphology (30)                 |
| SMARCA4| ENSG00000127616 | 3             | NA         | Abnormal blood vessel morphology (30)                 |
| Gene | Entrez ID | Degree | Expression | Function | Change |
|------|-----------|--------|------------|----------|--------|
| SOX17 | ENSG00000164736 | 3 | NA | NA | Aneurysm (30) |
| SOX18 | ENSG00000203883 | 3 | NA | NA | Abnormal blood vessel morphology (30) |
| SOX2 | ENSG00000181449 | 3 | NA | NA | Abnormal blood vessel morphology (30) |
| SOX4 | ENSG00000124766 | 3 | NA | NA | Abnormal blood vessel morphology (30) |
| SOX9 | ENSG00000125398 | 3 | NA | NA | Abnormal blood vessel morphology (30) |
| SPHK1 | ENSG00000176170 | 3 | NA | NA | Abnormal blood vessel morphology (30) |
| SPHK2 | ENSG00000063176 | 3 | NA | NA | Abnormal blood vessel morphology (30) |
| SPP1 | ENSG00000118785 | 3 | NA | NA | Aneurysm (30) |
| SPRR3 | ENSG00000163209 | 3 | NA | NA | Abnormal blood vessel morphology (30) |
| SRF | ENSG00000112658 | 3 | NA | NA | Abnormal blood (30) |
| Gene  | Entrez ID   | Chromosome  | DuoZ Score | Matching | Disease                  | Description                  |
|-------|-------------|-------------|------------|----------|--------------------------|------------------------------|
| SSAD2 | ENSG00000145687 | 3 | NA | NA | Arteritis | (30) |
| STIMI | ENSG00000167323 | 3 | NA | NA | Migraine | (30) |
| STK11 | ENSG00000118046 | 3 | NA | NA | Abnormal blood vessel morphology | (30) |
| STK3 | ENSG00000104375 | 3 | NA | NA | Abnormal blood vessel morphology | (30) |
| STK4 | ENSG00000101109 | 3 | NA | NA | Abnormal blood vessel morphology | (30) |
| SUFU | ENSG0000010782 | 3 | NA | NA | Aneurysm | (30) |
| TAGLN | ENSG00000149591 | 3 | NA | NA | Aneurysm | (30) |
| TBX1 | ENSG00000184058 | 3 | NA | NA | Abnormal blood vessel morphology | (30) |
| TBX18 | ENSG0000012837 | 3 | NA | NA | Abnormal blood vessel morphology | (30) |
| TDG | ENSG00000139372 | 3 | NA | NA | Abnormal blood vessel morphology | (30) |
| Gene | Accession | Score | Status | Description                            |
|------|-----------|-------|--------|----------------------------------------|
| TEK  | ENSG00000120156 | 3     | NA     | Abnormal blood vessel morphology (30) |
| TFAP2A | ENSG00000137203 | 3     | NA     | Abnormal blood vessel morphology (30) |
| THBS1 | ENSG00000137801 | 3     | NA     | Abnormal blood vessel morphology (30) |
| THY1  | ENSG00000154096 | 3     | NA     | Abnormal blood vessel morphology (30) |
| TIE1  | ENSG00000066056 | 3     | NA     | Abnormal blood vessel morphology (30) |
| TIMP1 | ENSG00000102265 | 3     | NA     | Aneurysm (30)                          |
| TIMP3 | ENSG00000100234 | 3     | NA     | Aneurysm (30)                          |
| TK1   | ENSG00000167900 | 3     | NA     | Arteritis (30)                         |
| TMSB4X | ENSG00000205542 | 3     | NA     | Abnormal blood vessel morphology (30) |
| TNF   | ENSG00000232810 | 3     | NA     | Aneurysm (30)                          |
| TNFRSF1A | ENSG00000067182 | 3     | NA     | Migraine (30)                          |
| Gene  | Ensembl ID       | Rank | PE  | Function                                      |
|-------|------------------|------|-----|-----------------------------------------------|
| TNNT2 | ENSG00000118194  | 3    | NA  | Abnormal blood vessel morphology              |
| TSPAN12 | ENSG00000106025  | 3    | NA  | Aneurysm                                      |
| TUSC2 | ENSG00000114383  | 3    | NA  | Arteritis                                     |
| VAV2  | ENSG00000160293  | 3    | NA  | Abnormal blood vessel morphology              |
| VEGFA | ENSG0000012715   | 3    | NA  | Abnormal blood vessel morphology              |
| VEZF1 | ENSG00000136451  | 3    | NA  | Abnormal blood vessel morphology              |
| VHL   | ENSG00000134086  | 3    | NA  | Abnormal blood vessel morphology              |
| WNT1  | ENSG00000125084  | 3    | NA  | Abnormal blood vessel morphology              |
| ZFAND5| ENSG00000107372  | 3    | NA  | Abnormal blood vessel morphology              |
Supplementary Table 1: Tiered list of genes of interest to SCAD. Tier 1 genes harbour rare variants previously reported as pathogenic in multiple SCAD patients. Tier 2 genes harbour rare variants previously reported as being pathogenic in a single SCAD patient or patients with connective tissue disorders or vascular disorders or common variants associated with these disorders. Tier 3 genes are of interest based on relevant phenotypes in mouse models.
Supplementary Table 2

| Gene   | Variant (GRCh38) | Transcript       | Transcript codon change | Transcript AA change | Variant Type       | Sample(s)         | N case carriers | GnomAD global AF | GnomAD popmax AF | Reference (if previously reported) |
|--------|------------------|------------------|--------------------------|---------------------|-------------------|-------------------|------------------|------------------|------------------|-----------------------------------|
| ABCC6  | 16-16177610-G-A  | ENST00000205557  | c.2432C>T               | p.Thr811Met         | Missense variant  | ScPt0231641G     | 1                | 2.8E-5           | 9.7E-5            | (160)                             |
|        | g.16:161512       | ENST00000205557  | c.2996-1741_4209-494del  | p.Ala999fs          | Structural variant| BPt00447934,     | 2                | 1.8E-4           | 3.9E-4            | (161)                             |
|        | 66_1616767        |                  | (exons 23-29)           |                     |                   | ScPt0082976W     |                  |                  |                  |                                   |
|        | 4del              |                  |                          |                     |                   |                   |                  |                  |                  |                                   |
| ADAMTS2| g.5:1791248       | ENST00000251582  | c.2842_2958+93del        | p.Asp948_Gln986del  | Splice donor variant | BPt00937431,     | 2                | 0               | 0                | NA                                |
|        | 80_1791250        |                  |                          |                     |                   | ScPt0850606K     |                  |                  |                  |                                   |
|        | 89del             |                  |                          |                     |                   |                   |                  |                  |                  |                                   |
| ATP6V0A2| 12-              | ENST00000330342  | c.1246G>A               | p.Gly416Arg         | Missense          | ScPt0250750V     | 1                | 8.0E-6           | 3.2E-5            | (162)                             |
| Gene   | Chromosome Start | Chromosome End | Transcript ID | Gene ID | Exon   | Variant Type | Description | ID       | P-value   | Odds Ratio | FDR       | Status |
|--------|------------------|----------------|---------------|---------|--------|--------------|-------------|----------|-----------|------------|-----------|--------|
| B3GALT6 | 1-1232791-C-CGCCCGC-GA | ENST00000379198 | c.521_528dupAGCCCGC | p.Arg177fs Frameshift variant | ScPt0761346G | 1 | 0 | 0 | NA |
| B4GALT7 | 5-177607462-CCT-C | ENST0000029410 | c.579_580delCT | p.Tyr194fs Frameshift variant | ScPt0666722L | 1 | 4.0E-6 | 9.0E-8 | NA |
| FLNA    | X-154364582-G-A  | ENST00000360319 | c.1966C>T | p.Leu656Phe Missense variant | ScPt0047580S | 1 | 6.0E-6 | 7.8E-5 | (163) |
| GORAB   | 1-170552151-T-TTGGAGG-AGTTGATG | ENST00000367763 | c.877_901delpGAGGAGTTGATGC | p.Val301fs Frameshift variant | BPt004447934 | 1 | 0 | 0 | NA |
| Gene   | Region | Reference | Number | Description | Reference | Chromosome | Start | Stop | p.Valency | p.Spacing | p.Tendency |
|--------|--------|-----------|--------|-------------|-----------|------------|-------|------|-----------|-----------|------------|
| LTBP3  | 11-65540485-C-G | ENST00000301873 | c.3106+1G>C | Splice donor variant | ScPt0197004C | 1 | 0 | 0 | NA |
| LTBP3  | 11-65540034-G-A | ENST00000301873 | c.3364C>T | p.Gln1122* Stop gained | ScPt0773459E | 1 | 9.0E-6 | 2.4E-5 | 17 |
| MTHFR  | 1-11802980-C-T | ENST00000376486 | c.137G>A | p.Arg46Gln Missense variant | ScPt0090027W | 1 | 2.0E-5 | 3.3E-5 | 164 |
| MTHFR  | 1-11795125-C-T | ENST00000376583 | c.1127G>A | p.Arg376His Missense variant | ScPt0159952X | 1 | 4.9E-5 | 1.3E-4 | 164 |
| PLCE1  | 10-94316621-TAAAGA-T | ENST00000371375 | c.5290_5294delAAGAA | Frameshift variant | ScPt0027347Z | 1 | 0 | 0 | NA |
| PLOD1  | g.1:1196770_1_11972900 | ENST00000196061 | c.1755+610_1931del | Structural variant | BPt00884962 | 1 | 0 | 0 | 165 |
Supplementary Table 2: Single heterozygous variants in SCAD patients in tier 1 or 2 genes associated with recessive connective tissue disorders or vascular disorders. These variants would be considered pathogenic or likely pathogenic if they were biallelic, but none are confidently causative of SCAD in this study because they are all monoallelic (heterozygous). For SNVs and indels GnomAD exomes allele frequencies are shown and for SVs GnomAD genomes allele frequencies are shown.
| Variant (GRCh38) | Gene   | Clinical characteristics | Family history |
|------------------|--------|--------------------------|----------------|
|                  |        | P  | IE  | ES  | RA  | Aortic root Dimensions | MV | SA | Skin | CT | HM | HT | Stroke | CAD | Description                                    |       |
| 1-155660577-T-A  | YYIAP1 | 0  | NA  | No  | No* | STJ 20mm, AA 20mm       | No | Yes| No   | No | No | Yes| Yes    | No  | FMD; renal artery stenosis; brachydactyly; migraines | NR    |
| 1-218434118-C-T  | TGFB2  | 4  | No  | Yes | Yes | SoV 33mm                | No | Yes| Yes  | No | No | Yes| No     | No  | Left carotid artery dissection; right internal carotid aneurysm; left vertebral pseudo | NR    |
| Patient ID     | SNP/Fusion     | Age | Gender | TMF | Age ofManifestation | Clinical Features                                                                 |
|---------------|----------------|-----|--------|-----|---------------------|----------------------------------------------------------------------------------|
| 1-218436110-C-T | TGFB2          | 2   | Yes    | No  | No*                 | Aneurysm and dissection, Chiari malformation, easy bruising; hypothyroidism      |
| 15-67066155-A-T | SMAD3          | 4   | NA     | NA  | No*                 | Easy bruising; pectus carinatum; march fractures                                  |
| 15-67190432-A-AC | SMAD3          | 2   | No     | Yes | No*                 | Aortic aneurysm in maternal grandfather                                           |
| 16-2090692-G-C | PKD1           | 3   | Yes    | Yes | No                  | PCKD; mildly ectactic aorta (3.2 cm); mitral                                    |
| Family ID     | Gene | Pedigree | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11  | 12  | 13  | 14  | 15  |
|--------------|------|----------|----|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|
| 16-2106443-CCA-C | PKD1 | 1        | Yes | Yes | No*| No | No | Yes | Yes | Yes | No | Yes | No | No | No | No | Yes |
|               |      |          |     |     |    |    |    |     |     |     |    |     |    |    |    |    |    |
| Valve prolapse; psoriasis |       | grandmother; ruptured berry aneurysm in maternal grandmother |
| 16-2106665-G-A | PKD1 | 1        | No  | Yes | No | No | No | No | No | No | No | No | No | No | No | No | No |
|               |      |          |     |     |    |    |    |     |     |     |    |     |    |    |    |    |    |
| PCKD; easy bruising |       | NR       |     |     |    |    |    |     |     |     |    |     |    |    |    |    |    |
| 16-2109337-C-T | PKD1 | 1        | No  | No  | No | No | No | No | Yes | No | No | No | No | No | No | No | No |
|               |      |          |     |     |    |    |    |     |     |     |    |     |    |    |    |    |    |
| EDS-like phenotype; easy bruising |       | HM in son; SCAD in 1st cousin |
| 16-2118102-G-C | PKD1 | 2        | No  | No  | No*| No | No | No | No | No | No | No | No | No | No | No | No |
|               |      |          |     |     |    |    |    |     |     |     |    |     |    |    |    |    |    |
| Aortic root dimension at upper limit of normal |       | NR       |     |     |    |    |    |     |     |     |    |     |    |    |    |    |    |

* NR indicates not recorded.
| ID          | Gene | Sample | Case | Control | SoV | STJ | AA | Scoliosis; subconjunctival haemorrhage | Scoliosis in mother | Patella dislocation in brother; Recurrent pneumothorax in brother | High palate; pes planus | Dyslipidemia; systemic inflammatory disease | NR | FMD; right internal carotid dissection; mildly dilated | Intracerebral bleed secondary to aneurysm in |
|-------------|------|--------|------|---------|-----|-----|----|--------------------------------------|---------------------|-------------------------------------------------|-----------------------|-----------------------------------------------|-----|-----------------------------------------------|-----------------------------------------------|
| 2-18890117-C-T | COL3A1 | 1      | Yes  | Yes     | No  | Yes | No | No                                    | Yes                  | Yes                                             | No                                   | No                                             | No | No                                             | Yes                                           |
|             |      |        |      |         | SoV 23mm, STJ 20mm, AA 24mm |     |     |  |                                      |                      |                                                 |                                      |                                               |     |                                                |                                               |
| 2-189011668-G-T | COL3A1 | 2      | Yes  | Yes     | No  | Yes | No | No                                    | No                   | No                                              | No                                   | No                                             | No | No                                             | No                                             |
|             |      |        |      |         | SoV 31mm, STJ 24mm, AA 26mm |     |     |  |                                      |                      |                                                 |                                      |                                               |     |                                                |                                               |
| 3-123708719-G-A | MYLK  | 0      | No   | No      | No  | No  | No | Df                                    | No                   | No                                              | No                                   | No                                             | No | No                                             | No                                             |
|             |      |        |      |         | SoV 32mm, STJ 24mm, AA 29mm |     |     |  |                                      |                      |                                                 |                                      |                                               |     |                                                |                                               |
| 5-122074155-A-C | LOX   | 1      | Yes  | Yes     | Yes | No  | No | No                                    | No                   | No                                              | No                                   | No                                             | No | No                                             | Yes                                           |
|             |      |        |      |         | SoV 35mm, STJ 26mm, AA 30mm |     |     |  |                                      |                      |                                                 |                                      |                                               |     |                                                |                                               |
Supplementary Table 3: Clinical information regarding patients affected by pathogenic and likely pathogenic variants. All the subjects with pathogenic variants are white females and none had pregnancy-related SCAD or recurrence. P= number of pregnancies defined as gestation ending with delivery. IE = intense exercise. ES = emotional stress. RA = remote arteriopathy as defined as any arterial abnormality and may include dilations or narrowing’s of arteries outside normal limits, dissections, aneurysms and fibromuscular dysplasia but does not include arterial tortuosity. *= incomplete screening for remote arteriopathies. MV = mitral valve prolapse. SA = skeletal abnormalities. Skin = skin abnormalities. HTN = hypertension. CAD = family history of CAD. CTD = Connective Tissue disorder (includes PCKD). HM = Hypermobility. SoV = sinus of Valsalva. STJ = sinotubular junction. AA = ascending aorta. NA = not available. NR = no relevant data.
| Trait               | Case definition (n)                                      | Ctrl definition (n)                              | n cases solved | % cases solved | n ctrl solved | % ctrl solved | P value | OR | OR LCI | OR UCI |
|---------------------|---------------------------------------------------------|--------------------------------------------------|---------------|---------------|---------------|---------------|---------|-----|--------|--------|
| Age                 | First SCAD event < 47 YO (median) (188)                | First SCAD event >= 47 YO (median) (196)         | 10            | 5.3           | 4             | 2             | 0.1     | 3   | 1      | 12     |
| Arteriopathies      | Have remote arteriopathy (112)                        | Do not have remote arteriopathy (272)            | 3             | 2.7           | 11            | 4             | 0.8     | 1   | 0      | 2.5    |
| Hormones            | Taken exogenous hormones (64)                         | Not taken exogenous hormones (295)               | 2             | 3.1           | 12            | 4.1           | 1       | 1   | 0      | 3.6    |
| Hypermobility       | Has hypermobility (27)                                 | Does not have hypermobility (355)                | 3             | 11.1          | 11            | 3.1           | 0.1     | 4   | 1      | 16     |
| Gravidy (females only) | Had >=1 pregnancy (312)                                | Had 0 pregnancy (48)                              | 14            | 4.5           | 0             | 0             | 0.2     | Inf | Inf    | Inf    |
| P-SCAD (females only) | Pregnancy associated SCAD (32)                         | Non-pregnancy associated SCAD (330)               | 0             | 0             | 14            | 4.2           | 0.6     | 0   | 0      | 3.1    |
| Recurrence          | >=2 SCAD events (40)                                   | 1 SCAD event (340)                                | 0             | 0             | 14            | 4.1           | 0.4     | 0   | 0      | 2.6    |
| Revascularisation   | Revascularisation (128)                                | No Revascularisation (256)                        | 3             | 2.3           | 11            | 4.3           | 0.4     | 1   | 0      | 2.1    |
Supplementary Table 4: There are no significant differences in clinical endpoints between SCAD survivors with a pathogenic or likely pathogenic variants and those without. Arteriopathy is defined as any arterial abnormality and may include dilations of arteries outside normal limits, dissections, aneurysms and fibromuscular dysplasia but does not include arterial tortuosity. Pregnancy-associated SCAD (P-SCAD) was defined as SCAD occurring during gestation or within 12 months of delivery. YO = years old. OR = Odds Ratio, LCI = Lower confidence interval (95%), UCI = Upper confidence interval (95%). Solved = has pathogenic or likely pathogenic variant. P values calculated using two-sided Fisher’s Exact tests. P value threshold of significance for this analysis = 0.006 (0.05/8).
### Supplementary Table 5

| UK Biobank Field ID | Phenotypic category excluded from UK Biobank controls |
|---------------------|------------------------------------------------------|
| 20002               | Self-declared cardiovascular                         |
| 20002               | Self-declared endocrine/diabetes                    |
| 20002               | Self-declared liver/biliary/pancreas problem        |
| 20002               | Self-declared renal/urology                         |
| 20002               | Self-declared connective tissue disorder            |
| 41270, 40001, or 40002 | ICD10 IV Endocrine, nutritional and metabolic diseases |
| 41270, 40001, or 40002 | ICD10 IX Diseases of the circulatory system       |
| 41270, 40001, or 40002 | ICD10 XI Diseases of the digestive system > K70-K77 and K80-K87 |
| 41270, 40001, or 40002 | ICD10 XII Diseases of the skin and subcutaneous tissue > L94 |
| 41270, 40001, or 40002 | ICD10 XIII Diseases of the musculoskeletal system and connective tissue |
| 41270, 40001, or 40002 | ICD10 XIV Diseases of the genitourinary system > N00-N39 |
| 41270, 40001, or 40002 | ICD10 XV Pregnancy, childbirth and the puerperium > O10-O16 |
| 41270, 40001, or 40002 | ICD10 XVII Congenital malformations, deformations and chromosomal abnormalities > Q20-Q28, Q44-Q45, Q60-Q64, Q796, Q874, Q828 |
| 41270, 40001, or 40002 | ICD10 XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified > R00-R03, R30-R39, R80-R82, R943-R947, R96 |
| 41270, 40001, or 40002 | ICD10 XXI Factors influencing health status and contact with health services > Z49, Z500, Z905, Z823, Z824, Z826, Z873 |
| 41271               | ICD9 Complications Of Pregnancy, Childbirth, And The Puerperium > 642 |
| 41271               | ICD9 Congenital Anomalies > 745-747,751,753, 75683, 75689, |
| Code   | Description                                                                 |
|--------|------------------------------------------------------------------------------|
| 41271  | ICD9 Diseases Of The Circulatory System 390-459                              |
| 41271  | ICD9 Diseases Of The Digestive System > 570-579                              |
| 41271  | ICD9 Diseases Of The Genitourinary System > 580-599                          |
| 41271  | ICD9 Endocrine, Nutritional And Metabolic Diseases, And Immunity Disorders 240-278 |
| 41271  | ICD9 Supplementary Classification Of Factors Influencing Health Status And Contact With Health Services > V56, V171, V173, V174, V1741, V1749, V177, V178, V1781, V1789 |
| 41271  | ICD9 Symptoms, Signs, And Ill-Defined Conditions > 785,788,791,7943-7948       |
| 41271  | ICD9 Diseases Of The Musculoskeletal System And Connective Tissue 710-739     |
| Q2443  | Medical conditions, Diabetes diagnosed by doctor = “Yes”                     |
| Q2966  | Medical conditions, Age high blood pressure diagnosed, Age provided          |
| Q2976  | Medical conditions, Age diabetes diagnosed, Age provided                      |
| Q2986  | Medical conditions, Started insulin within one year diagnosis of diabetes = “Yes” |
| Q3627  | Medical conditions, Age angina diagnosed, Age provided                       |
| Q3894  | Medical conditions, Age heart attack diagnosed, Age provided                 |
| Q4056  | Medical conditions, Age stroke diagnosed, Age provided                       |
| Q6150_0| Medical conditions, Vascular/heart problems diagnosed by doctor = “Heart attack”, “Angina”, “Stroke”, or “High blood pressure” |

**Supplementary Table 5: Details of phenotypes excluded from UK Biobank controls for SCAD collapsing analysis.**
### Supplementary Table 6

| Gene Name | Model | Qual Cases | Qual Case Freq | Qual Ctrl Freq | P value | Odds Ratio | Odds Ratio LCI | Odds Ratio UCI | "Artery - Coronary" tissue >1.5 TPM in GTEx | "Artery - Coronary" tissue top decile expression in GTEx | Gene flagged |
|-----------|-------|------------|----------------|----------------|---------|------------|----------------|----------------|---------------------------------|-------------------------------------------------|--------------|
| MUC21     | Recessive | 4 | 0.0112 | 2 | 1.46E-04 | 5.86E-06 | 77.7 | 14.2 | 425.8 | | TRUE |
| PKD1      | Ultra-rare damaging (MTR) | 6 | 0.0168 | 14 | 0.001 | 7.31E-06 | 16.7 | 6.4 | 43.8 | Yes | Yes | FALSE |
| CGB5      | Flexible non-syn | 3 | 0.0084 | 0 | 0 | 1.62E-05 | NA | NA | NA | | TRUE |
| TBC1D9    | Rare damaging (MTR) | 7 | 0.0196 | 31 | 0.0023 | 4.07E-05 | 8.8 | 3.9 | 20.2 | Yes | . | FALSE |
| TCEAL7    | Flexible non-syn | 4 | 0.0112 | 5 | 3.64E-04 | 4.63E-05 | 31.1 | 8.3 | 116.3 | Yes | . | FALSE |
| DENND5A   | Flexible non-syn | 15 | 0.042 | 167 | 0.0122 | 6.24E-05 | 3.6 | 2.1 | 6.1 | Yes | . | FALSE |
| KRTAP5-7  | Flexible damaging | 3 | 0.0084 | 1 | 7.29E-05 | 6.35E-05 | 116.3 | 12.1 | 1120.7 | | TRUE |
| Gene   | Type                     | Score | p-value | FDR   | Fold Change | Exp | Erp | True/Leg | Rare/Leg | Damage | Damage (MTR) |
|--------|--------------------------|-------|---------|-------|-------------|-----|-----|----------|----------|---------|---------------|
| ERC1   | Flexible damaging        | 10    | 0.028   | 78    | 0.0057      | 7.55E-05 | 5   | 2.6 | 9.8      | Yes      | .       | FALSE         |
| CHRNA7 | Flexible damaging        | 4     | 0.0112  | 36    | 0.0057      | 7.55E-05 | 5   | 2.6 | 9.8      | Yes      | .       | FALSE         |
| DUSP13 | PTV                      | 4     | 0.0112  | 7     | 0.0112      | 5.10E-04 | 2.7 | 9.8 | 16.2     | .        | .       | FALSE         |
| PRAMEF11| Flexible non-syn       | 7     | 0.0196  | 38    | 0.0028      | 1.26E-04 | 7.2 | 2.6 | 16.2     | .        | .       | TRUE          |
| CCL3   | Flexible damaging        | 3     | 0.0084  | 2     | 0.0084      | 1.46E-04 | 5.1 | 9.8 | 349      | Yes      | .       | TRUE          |
| PRB4   | PTV or rare damaging     | 3     | 0.0084  | 2     | 1.46E-04    | 1.56E-04 | 5.1 | 9.8 | 349      | .        | .       | FALSE         |
| IPO11  | Ultra-rare damaging      | 3     | 0.0084  | 2     | 1.46E-04    | 1.56E-04 | 5.1 | 9.8 | 349      | Yes      | .       | FALSE         |
| CLRN3  | Flexible damaging        | 4     | 0.0112  | 8     | 0.0112      | 5.83E-04 | 1.17E-04 | 9.8 | 64.8     | .        | .       | FALSE         |
| KRTAP5-1| Flexible non-syn (MTR)   | 5     | 0.014   | 17    | 0.0012      | 1.88E-04 | 4.2 | 9.8 | 31.2     | .        | .       | TRUE          |
| MBTPS1 | Ultra-rare damaging      | 5     | 0.014   | 17    | 0.0012      | 1.88E-04 | 4.2 | 9.8 | 31.2     | Yes      | .       | FALSE         |
| PAM    | Flexible damaging        | 9     | 0.0252  | 73    | 0.0053      | 2.25E-04 | 4.8 | 9.8 | 2.4      | Yes      | Yes     | FALSE         |
| COL3A1 | Flexible non-syn (MTR)   | 7     | 0.0196  | 44    | 0.0032      | 2.82E-04 | 6.2 | 9.8 | 13.9     | Yes      | Yes     | FALSE         |
| HRCT1  | Flexible damaging        | 0     | 0       | 337    | 0.0246      | 3.00E-04 | NA  | NA  | NA       | Yes      | .       | FALSE         |
| NBPF9  | Flexible damaging        | 3     | 0.0084  | 3     | 2.19E-04    | 3.06E-04 | 38.8| 9.8 | 192.7    | Yes      | .       | TRUE          |
| PHPT1  | PTV                      | 3     | 0.0084  | 3     | 2.19E-04    | 3.06E-04 | 38.8| 9.8 | 192.7    | Yes      | Yes     | FALSE         |
| Gene        | Damaging Type               | SYM   | Beta  | Freq   | RUS   | UOS   | UOSR  | MUS   | MUSR  | Status  |
|-------------|-----------------------------|-------|-------|--------|-------|-------|-------|-------|-------|---------|
| RABEP2      | Ultra-rare damaging         | 3     | 0.0084| 3      | 2.19E-04| 3.06E-04| 38.8  | 7.8   | 192.7 | Yes     | FALSE   |
| GLB1L3      | Rare damaging               | 8     | 0.0224| 60     | 3.10E-04| 5.2     | 2.5   | 11    | .     | .       | FALSE   |
| UBE4B       | Flexible non-syn            | 9     | 0.0252| 77     | 3.23E-04| 4.6     | 2.3   | 9.2   | Yes   | .       | FALSE   |
| PGLYRP3     | Flexible non-syn            | 9     | 0.0252| 78     | 3.52E-04| 4.5     | 2.3   | 9.1   | .     | .       | FALSE   |
| EXT1        | Flexible damaging           | 9     | 0.0252| 79     | 3.84E-04| 4.5     | 2.2   | 9     | .     | .       | FALSE   |
| OR2F2       | Flexible non-syn            | 7     | 0.0196| 47     | 4.04E-04| 5.8     | 2.6   | 13    | .     | .       | TRUE    |
| GOLGA6L2    | Rare damaging (MTR)         | 5     | 0.014 | 21     | 4.32E-04| 9.3     | 3.5   | 24.7  | .     | .       | TRUE    |
| MNDA        | Flexible non-syn (MTR)      | 4     | 0.0112| 11     | 8.02E-04| 4.45E-04| 14.1  | 4.5   | 44.6  | Yes     | FALSE   |
| RHOBTB3     | Flexible non-syn (MTR)      | 4     | 0.0112| 11     | 8.02E-04| 4.45E-04| 14.1  | 4.5   | 44.6  | Yes     | FALSE   |
| PLEKHG3     | Rare damaging (MTR)         | 4     | 0.0112| 11     | 8.02E-04| 4.45E-04| 14.1  | 4.5   | 44.6  | Yes     | FALSE   |
| ESX1        | Rare damaging (MTR)         | 3     | 0.0084| 4      | 2.92E-04| 5.25E-04| 29.1  | 6.5   | 130.3 | .       | FALSE   |
| HARBI1      | Rare damaging (MTR)         | 3     | 0.0084| 4      | 2.92E-04| 5.25E-04| 29.1  | 6.5   | 130.3 | .       | FALSE   |
| MAGEC1      | Ultra-rare damaging         | 3     | 0.0084| 4      | 2.92E-04| 5.25E-04| 29.1  | 6.5   | 130.3 | .       | FALSE   |
| SERPINB12   | Ultra-rare damaging         | 3     | 0.0084| 4      | 2.92E-04| 5.25E-04| 29.1  | 6.5   | 130.3 | .       | FALSE   |
| TLX3        | Ultra-rare damaging         | 3     | 0.0084| 4      | 2.92E-04| 5.25E-04| 29.1  | 6.5   | 130.3 | .       | FALSE   |
| USP47       | Ultra-rare damaging         | 3     | 0.0084| 4      | 2.92E-04| 5.25E-04| 29.1  | 6.5   | 130.3 | Yes     | FALSE   |
| Gene     | Abundance   | p-value | AUC | AA  | MA  | Can predict? | Relatedness |
|----------|-------------|---------|-----|-----|-----|--------------|-------------|
| EXOC2    | Flexible non-syn | 0.36 | 0.0103 | 5.26E-04 | 3.4 | 1.8 | 6.1 | Yes | . | FALSE |
| PCDHB14  | Flexible non-syn | 0.36 | 0.0103 | 5.26E-04 | 3.4 | 1.8 | 6.1 | Yes | . | FALSE |
| CLEC11A  | Flexible damaging | 0.12 | 8.75E-04 | 5.81E-04 | 12.9 | 4.2 | 40.3 | Yes | . | FALSE |
| RANBP2   | Recessive | 0.12 | 8.75E-04 | 5.81E-04 | 12.9 | 4.2 | 40.3 | Yes | . | FALSE |
| NPC1L1   | Ultra-rare damaging | 0.12 | 8.75E-04 | 5.81E-04 | 12.9 | 4.2 | 40.3 | . | . | FALSE |
| PXMP2    | Rare damaging | 0.14 | 0.0017 | 6.19E-04 | 8.5 | 3.2 | 22.4 | Yes | . | FALSE |
| NBPF20   | Flexible damaging | 0.06 | 0 | 6.41E-04 | NA | NA | NA | Yes | Yes | FALSE |
| RPS13    | Flexible damaging | 0.06 | 0 | 6.41E-04 | NA | NA | NA | Yes | Yes | FALSE |
| GLI3     | PTV | 0.06 | 0 | 6.41E-04 | NA | NA | NA | Yes | . | FALSE |
| NFATC4   | PTV | 0.06 | 0 | 6.41E-04 | NA | NA | NA | Yes | Yes | FALSE |
| OLR1     | PTV | 0.06 | 0 | 6.41E-04 | NA | NA | NA | Yes | . | FALSE |
| PRKD2    | PTV | 0.06 | 0 | 6.41E-04 | NA | NA | NA | Yes | . | FALSE |
| KRTAP4-7 | Rare damaging | 0.06 | 0 | 6.41E-04 | NA | NA | NA | . | . | TRUE |
| FTMT     | Rare damaging (MTR) | 0.06 | 0 | 6.41E-04 | NA | NA | NA | . | . | FALSE |
| OGFOD3   | Recessive | 0.06 | 0 | 6.41E-04 | NA | NA | NA | Yes | . | FALSE |
| Gene     | Type                      | MTR | PTV or rare | Rare | Flexible non-syn | Ultra-rare | Rare damaging | Yes | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damaging | Rare damaging | Flexible non-syn | Ultra-rare damaging | PTV or rare damaging | Flexible non-syn | Rare damaging | Flexible damage...
| Gene   | Type                     | Chrom. | Allele 1 | Allele 2 | Delta 1 | Delta 2 | Delta 3 | Delta 4 | Case | Control | Status |
|--------|--------------------------|--------|----------|----------|---------|---------|---------|---------|------|---------|--------|
| DOCK6  | Recessive                | 5      | 0.014    | 25       | 0.0018  | 8.62E-04| 7.8     | 3       | 20.4 | Yes     | FALSE  |
| CFHR2  | Flexible non-syn         | 6      | 0.0168   | 39       | 0.0028  | 9.01E-04| 6       | 2.5     | 14.3 | .       | FALSE  |
| KRT82  | Rare damaging            | 6      | 0.0168   | 39       | 0.0028  | 9.01E-04| 6       | 2.5     | 14.3 | .       | TRUE   |
| LRRC37B| PTV or rare damaging     | 4      | 0.0112   | 14       | 0.001   | 9.38E-04| 11.1    | 3.6     | 33.9 | Yes     | FALSE  |
| FABP7  | Flexible non-syn         | 5      | 0.014    | 26       | 0.0019  | 0.001   | 7.5     | 2.9     | 19.6 | .       | FALSE  |
| SPI1   | Flexible non-syn         | 5      | 0.014    | 26       | 0.0019  | 0.001   | 7.5     | 2.9     | 19.6 | Yes     | FALSE  |
| SLC25A44| Flexible damaging       | 6      | 0.0168   | 41       | 0.003   | 0.0011  | 5.7     | 2.4     | 13.5 | Yes     | FALSE  |
| TMCO5A | Flexible non-syn         | 5      | 0.014    | 27       | 0.002   | 0.0012  | 7.2     | 2.8     | 18.8 | .       | FALSE  |
| FH     | Ultra-rare damaging      | 4      | 0.0112   | 15       | 0.0011  | 0.0012  | 10.4    | 3.4     | 31.4 | Yes     | FALSE  |
| NAT1   | Flexible damaging        | 3      | 0.0084   | 6        | 4.37E-04| 0.0012  | 19.4    | 4.8     | 77.8 | .       | FALSE  |
| CCZ1B  | Flexible non-syn         | 3      | 0.0084   | 6        | 4.37E-04| 0.0012  | 19.4    | 4.8     | 77.8 | Yes     | TRUE   |
| PLCH1  | PTV                      | 3      | 0.0084   | 6        | 4.37E-04| 0.0012  | 19.4    | 4.8     | 77.8 | .       | FALSE  |
| SERPINB9| Rare damaging (MTR)      | 3      | 0.0084   | 6        | 4.37E-04| 0.0012  | 19.4    | 4.8     | 77.8 | Yes     | FALSE  |
| SMC6   | Rare damaging (MTR)      | 3      | 0.0084   | 6        | 4.37E-04| 0.0012  | 19.4    | 4.8     | 77.8 | Yes     | FALSE  |
| IQUB   | Recessive                | 3      | 0.0084   | 6        | 4.37E-04| 0.0012  | 19.4    | 4.8     | 77.8 | .       | FALSE  |
| ZNF140 | Flexible non-syn         | 6      | 0.0168   | 43       | 0.0031  | 0.0014  | 5.4     | 2.3     | 12.9 | Yes     | FALSE  |
| Gene       | Phenotype                      | Exons | Mutation Allele Freq | Mutation Allele Depth | Mutation Allele Conc | Evidence | Classification |
|------------|-------------------------------|-------|----------------------|------------------------|----------------------|----------|----------------|
| MFSD10     | Flexible non-syn (MTR)        | 6     | 0.0168               | 43                     | 0.0031               | 0.0014   | 5.4           | 2.3          | 12.9        | Yes         | FALSE       |
| KCNMB4     | Flexible non-syn              | 4     | 0.0112               | 16                     | 0.0012               | 0.0014   | 9.7           | 3.2          | 29.2        | Yes         | FALSE       |
| CDKL1      | Rare damaging                 | 4     | 0.0112               | 16                     | 0.0012               | 0.0014   | 9.7           | 3.2          | 29.2        | .           | .           | FALSE       |
| ZNRF3      | Ultra-rare damaging           | 4     | 0.0112               | 16                     | 0.0012               | 0.0014   | 9.7           | 3.2          | 29.2        | Yes         | .           | FALSE       |
| NDUFS1     | Flexible non-syn              | 11    | 0.0308               | 138                    | 0.0101               | 0.0015   | 3.1           | 1.7          | 5.8         | Yes         | .           | FALSE       |
| SENP3      | Flexible non-syn              | 8     | 0.0224               | 78                     | 0.0057               | 0.0015   | 4             | 1.9          | 8.4         | Yes         | .           | FALSE       |
| DNAH10     | Ultra-rare damaging           | 8     | 0.0224               | 78                     | 0.0057               | 0.0015   | 4             | 1.9          | 8.4         | .           | .           | FALSE       |
| POFUT2     | Flexible non-syn (MTR)        | 5     | 0.014                | 29                     | 0.0021               | 0.0015   | 6.7           | 2.6          | 17.4        | Yes         | .           | FALSE       |
| NLRP9      | Flexible non-syn              | 11    | 0.0308               | 141                    | 0.0103               | 0.0017   | 3.1           | 1.6          | 5.7         | .           | .           | FALSE       |
| GPD2       | Flexible damaging             | 8     | 0.0224               | 80                     | 0.0058               | 0.0017   | 3.9           | 1.9          | 8.1         | Yes         | .           | FALSE       |
| RIMS3      | Flexible damaging             | 4     | 0.0112               | 17                     | 0.0012               | 0.0017   | 9.1           | 3.1          | 27.3        | Yes         | .           | FALSE       |
| NTSC3B     | PTV or rare damaging          | 4     | 0.0112               | 17                     | 0.0012               | 0.0017   | 9.1           | 3.1          | 27.3        | Yes         | .           | FALSE       |
| AARS       | Ultra-rare damaging           | 4     | 0.0112               | 17                     | 0.0012               | 0.0017   | 9.1           | 3.1          | 27.3        | Yes         | Yes         | FALSE       |
| FHOD1      | Ultra-rare damaging           | 4     | 0.0112               | 17                     | 0.0012               | 0.0017   | 9.1           | 3.1          | 27.3        | Yes         | .           | FALSE       |
| SEC24B     | Ultra-rare damaging           | 4     | 0.0112               | 17                     | 0.0012               | 0.0017   | 9.1           | 3.1          | 27.3        | Yes         | .           | FALSE       |
| LYPD1      | Flexible damaging             | 3     | 0.0084               | 7                      | 5.10E-04             | 0.0017   | 16.6          | 4.3          | 64.5        | .           | .           | FALSE       |
| Gene       | Description                  | Score | P-value | q-value | Gene Length | Expression | Functional Class | Consequence | Documented Effect | Documented Effect |
|------------|------------------------------|-------|---------|---------|-------------|------------|------------------|--------------|------------------|------------------|
| DNAJC24    | Flexible non-syn            | 3     | 0.0084  | 7       | 5.10E-04    | 0.0017     | 16.6            | 4.3          | 64.5             | Yes              | .                | FALSE            |
| NUS1       | Flexible non-syn (MTR)      | 3     | 0.0084  | 7       | 5.10E-04    | 0.0017     | 16.6            | 4.3          | 64.5             | Yes              | .                | FALSE            |
| G3BP2      | PTV or rare damaging        | 3     | 0.0084  | 7       | 5.10E-04    | 0.0017     | 16.6            | 4.3          | 64.5             | Yes              | .                | FALSE            |
| CDADC1     | Rare damaging (MTR)         | 3     | 0.0084  | 7       | 5.10E-04    | 0.0017     | 16.6            | 4.3          | 64.5             | Yes              | .                | FALSE            |
| SLC25A38   | Rare damaging (MTR)         | 3     | 0.0084  | 7       | 5.10E-04    | 0.0017     | 16.6            | 4.3          | 64.5             | Yes              | .                | FALSE            |
| HUNK       | Ultra-rare damaging         | 3     | 0.0084  | 7       | 5.10E-04    | 0.0017     | 16.6            | 4.3          | 64.5             | .                | .                | FALSE            |
| PRG4       | Ultra-rare damaging (MTR)   | 3     | 0.0084  | 7       | 5.10E-04    | 0.0017     | 16.6            | 4.3          | 64.5             | Yes              | .                | FALSE            |
| HMGCS2     | Flexible non-syn            | 9     | 0.0252  | 100     | 0.0073      | 0.0018     | 3.5             | 1.8          | 7               | .                | .                | FALSE            |
| NENF       | Flexible non-syn            | 5     | 0.014   | 30      | 0.0022      | 0.0018     | 6.5             | 2.5          | 16.8             | Yes              | Yes              | FALSE            |
| THADA      | Flexible damaging           | 9     | 0.0252  | 101     | 0.0074      | 0.0019     | 3.5             | 1.7          | 7               | Yes              | .                | FALSE            |
| ADAM2      | Flexible non-syn            | 9     | 0.0252  | 101     | 0.0074      | 0.0019     | 3.5             | 1.7          | 7               | .                | .                | FALSE            |
| SMARCA1    | Flexible non-syn            | 6     | 0.0168  | 46      | 0.0034      | 0.0019     | 5.1             | 2.2          | 12              | Yes              | .                | FALSE            |
| CCL17      | Flexible damaging           | 2     | 0.0056  | 1       | 7.29E-05    | 0.0019     | 77.3            | 7            | 854.5            | .                | .                | FALSE            |
| DEDD       | Flexible damaging           | 2     | 0.0056  | 1       | 7.29E-05    | 0.0019     | 77.3            | 7            | 854.5            | Yes              | .                | FALSE            |
| LSM2       | Flexible damaging           | 2     | 0.0056  | 1       | 7.29E-05    | 0.0019     | 77.3            | 7            | 854.5            | Yes              | .                | FALSE            |
| Gene    | Category                        | Haploinform | P-value (MTR) | ADF | Score | BS | TRS | Notes   |
|---------|---------------------------------|-------------|---------------|-----|-------|----|-----|---------|
| PDHA2   | Flexible non-syn (MTR)          | 2           | 0.0056        | 1   | 7.29E-05 | 0.0019 | 77.3 | 7 | 854.5 | . | . | FALSE |
| ADGRB2  | PTV                             | 2           | 0.0056        | 1   | 7.29E-05 | 0.0019 | 77.3 | 7 | 854.5 | . | . | FALSE |
| PCDHGC4 | PTV                             | 2           | 0.0056        | 1   | 7.29E-05 | 0.0019 | 77.3 | 7 | 854.5 | . | . | FALSE |
| IL17A   | Rare damaging (MTR)             | 2           | 0.0056        | 1   | 7.29E-05 | 0.0019 | 77.3 | 7 | 854.5 | . | . | FALSE |
| NCK1    | Rare damaging (MTR)             | 2           | 0.0056        | 1   | 7.29E-05 | 0.0019 | 77.3 | 7 | 854.5 | Yes | . | FALSE |
| PTPRN2  | Recessive                       | 2           | 0.0056        | 1   | 7.29E-05 | 0.0019 | 77.3 | 7 | 854.5 | . | . | FALSE |
| CDRT4   | Ultra-rare damaging             | 2           | 0.0056        | 1   | 7.29E-05 | 0.0019 | 77.3 | 7 | 854.5 | Yes | . | FALSE |
| TFB2M   | Ultra-rare damaging             | 2           | 0.0056        | 1   | 7.29E-05 | 0.0019 | 77.3 | 7 | 854.5 | Yes | . | FALSE |
| ZNF343  | Ultra-rare damaging             | 2           | 0.0056        | 1   | 7.29E-05 | 0.0019 | 77.3 | 7 | 854.5 | Yes | . | FALSE |
| B3GLCT  | Ultra-rare damaging             | 2           | 0.0056        | 1   | 7.29E-05 | 0.0019 | 77.3 | 7 | 854.5 | Yes | . | FALSE |
| ZNF45   | Ultra-rare damaging             | 2           | 0.0056        | 1   | 7.29E-05 | 0.0019 | 77.3 | 7 | 854.5 | Yes | . | FALSE |
| SRCAP   | PTV or rare damaging            | 14          | 0.0392        | 213 | 0.0155 | 0.002 | 2.6 | 1.5 | 4.5 | Yes | . | TRUE |
| ARRDC1  | Flexible damaging               | 5           | 0.014         | 31  | 0.0023 | 0.002 | 6.3 | 2.4 | 16.2 | Yes | . | FALSE |
| C16orf95| Flexible non-syn                | 5           | 0.014         | 31  | 0.0023 | 0.002 | 6.3 | 2.4 | 16.2 | . | . | FALSE |
| Gene   | Description        | PTV/Rare | Effect Size | POS 1 | POS 2 | VAF | Status | Confirmation |
|--------|--------------------|----------|-------------|-------|-------|-----|--------|--------------|
| AP4E1  | Rare damaging      | 5        | 0.014       | 31    | 0.0023| 0.002| 6.3    | 2.4          | Yes          | False        |
| DENND3 | Flexible non-syn   | 13       | 0.0364      | 191   | 0.0139| 0.0021| 2.7    | 1.5          | 4.7          | Yes          | False        |
| MPP7   | Flexible damaging  | 6        | 0.0168      | 47    | 0.0034| 0.0021| 5      | 2.1          | 11.7         | Yes          | False        |
| PRX    | Flexible damaging  | 4        | 0.0112      | 18    | 0.0013| 0.0021| 8.6    | 2.9          | 25.6         | Yes          | False        |
| USP17L7| Flexible damaging  | 4        | 0.0112      | 18    | 0.0013| 0.0021| 8.6    | 2.9          | 25.6         | Yes          | False        |
| IPO7   | PTV or rare damaging | 4    | 0.0112 | 18 | 0.0013 | 0.0021 | 8.6 | 2.9 | 25.6 | Yes | False |
| BCL9L  | Flexible non-syn   | 13       | 0.0364      | 193   | 0.0141| 0.0023| 2.6    | 1.5          | 4.7          | Yes          | False        |
| ZNF154 | Flexible non-syn   | 9        | 0.0252      | 104   | 0.0076| 0.0023| 3.4    | 1.7          | 6.7          | Yes          | False        |
| CFHR4  | Flexible damaging  | 5        | 0.014       | 32    | 0.0023| 0.0023| 6.1    | 2.4          | 15.7         | .            | False        |
| RGPD3  | Flexible non-syn   | 3        | 0.0084      | 8     | 5.83E-04| 0.0023| 14.5   | 3.8          | 55           | .            | True         |
| IDO2   | Flexible non-syn (MTR) | 3    | 0.0084 | 8 | 5.83E-04 | 0.0023 | 14.5 | 3.8 | 55 | . | False |
| SLC2A5 | PTV                | 3        | 0.0084      | 8     | 5.83E-04| 0.0023| 14.5   | 3.8          | 55           | Yes          | False        |
| CCNB1  | Ultra-rare damaging| 3        | 0.0084      | 8     | 5.83E-04| 0.0023| 14.5   | 3.8          | 55           | .            | False        |
| TMEM209| Ultra-rare damaging| 3        | 0.0084      | 8     | 5.83E-04| 0.0023| 14.5   | 3.8          | 55           | Yes          | False        |
| ZBTB48 | Ultra-rare damaging| 3        | 0.0084      | 8     | 5.83E-04| 0.0023| 14.5   | 3.8          | 55           | Yes          | False        |
| ZNF578 | Flexible non-syn   | 11       | 0.0308      | 148   | 0.0108| 0.0024| 2.9    | 1.6          | 5.4          | .            | False        |
| Gene    | Description                | Major   | Age   | Minor | LOD   | Sex   | Sib  | Repr | Result |
|---------|----------------------------|---------|-------|-------|-------|-------|------|------|--------|
| ARSH    | Flexible damaging          | 9       | 0.0252| 105   | 0.0077| 0.0025| 3.4  | 1.7  | 6.7    |        |
| ACTL6B  | Flexible non-syn (MTR)     | 4       | 0.0112| 19    | 0.0014| 0.0025| 8.2  | 2.8  | 24.1   |        |
| SETD2   | Recessive                  | 4       | 0.0112| 19    | 0.0014| 0.0025| 8.2  | 2.8  | 24.1   | Yes    |
| ANKIB1  | Flexible non-syn           | 8       | 0.0224| 86    | 0.0063| 0.0026| 3.6  | 1.7  | 7.6    | Yes    |
| OCM     | Flexible non-syn           | 6       | 0.0168| 49    | 0.0036| 0.0026| 4.8  | 2    | 11.2   |        |
| ALAS1   | PTV or rare damaging       | 6       | 0.0168| 49    | 0.0036| 0.0026| 4.8  | 2    | 11.2   | Yes    |
| BACH2   | Flexible non-syn (MTR)     | 5       | 0.014 | 33    | 0.0024| 0.0026| 5.9  | 2.3  | 15.2   |        |
| PUM1    | Flexible non-syn (MTR)     | 5       | 0.014 | 33    | 0.0024| 0.0026| 5.9  | 2.3  | 15.2   | Yes    |
| EHMT2   | PTV or rare damaging       | 5       | 0.014 | 33    | 0.0024| 0.0026| 5.9  | 2.3  | 15.2   | Yes    |
| NOP58   | PTV or rare damaging       | 5       | 0.014 | 33    | 0.0024| 0.0026| 5.9  | 2.3  | 15.2   | Yes    |
| SCFD2   | Flexible non-syn           | 10      | 0.028 | 128   | 0.0093| 0.0027| 3.1  | 1.6  | 5.9    | Yes    |
| BRD7    | Flexible non-syn           | 8       | 0.0224| 87    | 0.0063| 0.0028| 3.6  | 1.7  | 7.5    | Yes    |
| YTHDC1  | Flexible non-syn           | 8       | 0.0224| 87    | 0.0063| 0.0028| 3.6  | 1.7  | 7.5    | Yes    |
| DNAJB1  | Flexible non-syn           | 7       | 0.0196| 68    | 0.005 | 0.0029| 4    | 1.8  | 8.8    | Yes    |
| PGD     | Flexible damaging          | 5       | 0.014 | 34    | 0.0025| 0.0029| 5.7  | 2.2  | 14.7   | Yes    |
| GPR22   | Flexible non-syn           | 5       | 0.014 | 34    | 0.0025| 0.0029| 5.7  | 2.2  | 14.7   |        |
| Gene     | Type                     | M  | p     | dF  | TF1  | TF2  | TF3  | Status | Truth |
|----------|--------------------------|----|-------|-----|------|------|------|--------|-------|
| NDRG4    | Flexible non-syn (MTR)   | 4  | 0.0112| 20  | 0.0015| 0.0029| 7.8  | 2.6    | 22.8  | Yes   | FALSE |
| PCDHA5   | Flexible non-syn (MTR)   | 4  | 0.0112| 20  | 0.0015| 0.0029| 7.8  | 2.6    | 22.8  | Yes   | FALSE |
| SLC39A12 | Flexible non-syn (MTR)   | 4  | 0.0112| 20  | 0.0015| 0.0029| 7.8  | 2.6    | 22.8  | Yes   | FALSE |
| SRC      | Flexible non-syn (MTR)   | 4  | 0.0112| 20  | 0.0015| 0.0029| 7.8  | 2.6    | 22.8  | Yes   | FALSE |
| HS1BP3   | Flexible non-syn (MTR)   | 3  | 0.0084| 9    | 6.56E-04| 0.003| 12.9 | 3.5    | 47.9  | Yes   | FALSE |
| PCDHA5   | Flexible non-syn (MTR)   | 4  | 0.0112| 20  | 0.0015| 0.0029| 7.8  | 2.6    | 22.8  | Yes   | FALSE |
| SLC6A16  | Flexible non-syn (MTR)   | 3  | 0.0084| 9    | 6.56E-04| 0.003| 12.9 | 3.5    | 47.9  | Yes   | FALSE |
| TRDMT1   | Flexible non-syn (MTR)   | 3  | 0.0084| 9    | 6.56E-04| 0.003| 12.9 | 3.5    | 47.9  | Yes   | FALSE |
| XPO4     | Flexible non-syn (MTR)   | 3  | 0.0084| 9    | 6.56E-04| 0.003| 12.9 | 3.5    | 47.9  | Yes   | FALSE |
| OR51S1   | Flexible non-syn (MTR)   | 7  | 0.0196| 69  | 0.005 | 0.0031| 4    | 1.8    | 8.7   | .      | TRUE  |
| AFG3L2   | Flexible non-syn (MTR)   | 6  | 0.0168| 51  | 0.0037| 0.0031| 4.6  | 2      | 10.7  | Yes   | FALSE |
| UNC80    | Flexible non-syn (MTR)   | 8  | 0.0224| 89  | 0.0065| 0.0032| 3.5  | 1.7    | 7.3   | .      | FALSE |
| ACSS2    | Flexible non-syn (MTR)   | 8  | 0.0224| 90  | 0.0066| 0.0034| 3.5  | 1.7    | 7.2   | Yes   | FALSE |
| TEX11    | Flexible non-syn (MTR)   | 8  | 0.0224| 90  | 0.0066| 0.0034| 3.5  | 1.7    | 7.2   | .      | FALSE |
| ARHGAP22 | Flexible non-syn (MTR)   | 6  | 0.0168| 52  | 0.0038| 0.0034| 4.5  | 1.9    | 10.5  | Yes   | FALSE |
| BRICD5   | Flexible non-syn (MTR)   | 6  | 0.0168| 52  | 0.0038| 0.0034| 4.5  | 1.9    | 10.5  | Yes   | FALSE |
| Gene   | Description                  | Freq | P-value | Mean | SE  | Var | Final R | Annotation | Damaging |
|--------|------------------------------|------|---------|------|-----|-----|---------|------------|----------|
| AP3D1  | PTV or rare damaging         | 6    | 0.0168  | 52   | 0.0038 | 0.0034 | 4.5 | 1.9 | 10.5 | Yes | . | FALSE |
| METTL2B| Flexible non-syn             | 4    | 0.0112  | 21   | 0.0015 | 0.0034 | 7.4 | 2.5 | 21.6 | Yes | . | TRUE  |
| GRHL1  | PTV or rare damaging         | 4    | 0.0112  | 21   | 0.0015 | 0.0034 | 7.4 | 2.5 | 21.6 | .   | . | FALSE |
| DNAH2  | Ultra-rare damaging (MTR)    | 4    | 0.0112  | 21   | 0.0015 | 0.0034 | 7.4 | 2.5 | 21.6 | .   | . | FALSE |
| SYT8   | Flexible non-syn             | 10   | 0.028   | 133  | 0.0097 | 0.0035 | 2.9 | 1.5 | 5.6  | .   | . | FALSE |
| SEMG1  | Flexible non-syn             | 8    | 0.0224  | 91   | 0.0066 | 0.0036 | 3.4 | 1.7 | 7.1  | .   | . | FALSE |
| SGO1   | Flexible non-syn             | 8    | 0.0224  | 91   | 0.0066 | 0.0036 | 3.4 | 1.7 | 7.1  | .   | . | FALSE |
| ACOXL  | PTV or rare damaging         | 5    | 0.014   | 36   | 0.0026 | 0.0036 | 5.4 | 2.1 | 13.8 | .   | . | FALSE |
| DGUOK  | Flexible damaging            | 6    | 0.0168  | 53   | 0.0039 | 0.0037 | 4.4 | 1.9 | 10.3 | Yes | . | FALSE |
| COMMD10| Flexible damaging            | 2    | 0.0056  | 2    | 1.46E-04 | 0.0037 | 38.6 | 5.4 | 275.2 | Yes | . | FALSE |
| CBX3   | Flexible non-syn (MTR)       | 2    | 0.0056  | 2    | 1.46E-04 | 0.0037 | 38.6 | 5.4 | 275.2 | Yes | Yes | FALSE |
| HEPN1  | Flexible non-syn (MTR)       | 2    | 0.0056  | 2    | 1.46E-04 | 0.0037 | 38.6 | 5.4 | 275.2 | Yes | . | FALSE |
| TRAPPC2| Flexible non-syn (MTR)       | 2    | 0.0056  | 2    | 1.46E-04 | 0.0037 | 38.6 | 5.4 | 275.2 | Yes | . | FALSE |
| C6orf163| PTV                          | 2    | 0.0056  | 2    | 1.46E-04 | 0.0037 | 38.6 | 5.4 | 275.2 | .   | . | FALSE |
| SH3BP4 | PTV                          | 2    | 0.0056  | 2    | 1.46E-04 | 0.0037 | 38.6 | 5.4 | 275.2 | Yes | . | FALSE |
| Genes     | Type                      | PTV | PTV | E-value | p-value | Odds Ratio | Association | MTR     | Diagnosis |
|-----------|---------------------------|-----|-----|---------|---------|------------|-------------|---------|----------|
| SYNJ1     | PTV                       | 2   | 2   | 1.46E-04| 0.0037  | 38.6       | Yes         | .       | FALSE    |
| TMEM88B   | PTV                       | 2   | 2   | 1.46E-04| 0.0037  | 38.6       | Yes         | .       | FALSE    |
| TTC32     | PTV                       | 2   | 2   | 1.46E-04| 0.0037  | 38.6       | Yes         | .       | FALSE    |
| ZNF606    | PTV or rare damaging      | 2   | 2   | 1.46E-04| 0.0037  | 38.6       | Yes         | .       | FALSE    |
| ARHGAP25  | Rare damaging (MTR)       | 2   | 2   | 1.46E-04| 0.0037  | 38.6       | Yes         | .       | FALSE    |
| CTDSP2    | Rare damaging (MTR)       | 2   | 2   | 1.46E-04| 0.0037  | 38.6       | Yes         | Yes     | FALSE    |
| HES5      | Rare damaging (MTR)       | 2   | 2   | 1.46E-04| 0.0037  | 38.6       | Yes         | .       | FALSE    |
| MLLT3     | Rare damaging (MTR)       | 2   | 2   | 1.46E-04| 0.0037  | 38.6       | Yes         | .       | FALSE    |
| SLC17A3   | Rare damaging (MTR)       | 2   | 2   | 1.46E-04| 0.0037  | 38.6       | Yes         | .       | FALSE    |
| ZNF880    | Recessive                 | 2   | 2   | 1.46E-04| 0.0037  | 38.6       | Yes         | .       | FALSE    |
| MYL9      | Ultra-rare damaging       | 2   | 2   | 1.46E-04| 0.0037  | 38.6       | Yes         | Yes     | FALSE    |
| PCGF2     | Ultra-rare damaging       | 2   | 2   | 1.46E-04| 0.0037  | 38.6       | Yes         | .       | FALSE    |
| TRMO      | Ultra-rare damaging       | 2   | 2   | 1.46E-04| 0.0037  | 38.6       | Yes         | .       | FALSE    |
| RRP8      | Ultra-rare damaging (MTR) | 2   | 2   | 1.46E-04| 0.0037  | 38.6       | Yes         | .       | FALSE    |
| TMEM165   | Ultra-rare damaging       | 2   | 2   | 1.46E-04| 0.0037  | 38.6       | Yes         | Yes     | FALSE    |
| Gene     | Type                  | Rare Damaging | Rare Damaging (MTR) | Mismatch | Mismatch | Mismatch | Mismatch | Mismatch | Mismatch | Mismatch | Mismatch | Mismatch | Mismatch | Mismatch | Mismatch | Mismatch | Mismatch | Mismatch | Mismatch |
|----------|-----------------------|---------------|---------------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| UTP4     | Ultra-rare damaging   | 2             | 0.0056              | 1.46E-04 | 0.0037   | 38.6     | 5.4      | 275.2    | Yes      | .        | FALSE    |
| VPS28    | Ultra-rare damaging   | 2             | 0.0056              | 1.46E-04 | 0.0037   | 38.6     | 5.4      | 275.2    | Yes      | Yes      | FALSE    |
| DNAH6    | Flexible non-syn      | 30            | 0.084               | 657      | 0.0479   | 0.0038   | 1.8      | 1.2      | 2.7      | .        | .        | FALSE    |
| KIAA1210 | Flexible damaging     | 3             | 0.0084              | 10       | 7.29E-04 | 0.0038   | 11.6     | 3.2      | 42.4     | .        | .        | FALSE    |
| TSLP     | Flexible damaging     | 3             | 0.0084              | 10       | 7.29E-04 | 0.0038   | 11.6     | 3.2      | 42.4     | .        | .        | FALSE    |
| KRT77    | PTV                   | 3             | 0.0084              | 10       | 7.29E-04 | 0.0038   | 11.6     | 3.2      | 42.4     | .        | .        | TRUE     |
| NKX1-2   | Rare damaging         | 3             | 0.0084              | 10       | 7.29E-04 | 0.0038   | 11.6     | 3.2      | 42.4     | .        | .        | FALSE    |
| FECH     | Rare damaging (MTR)   | 3             | 0.0084              | 10       | 7.29E-04 | 0.0038   | 11.6     | 3.2      | 42.4     | Yes      | .        | FALSE    |
| F2       | Ultra-rare damaging   | 3             | 0.0084              | 10       | 7.29E-04 | 0.0038   | 11.6     | 3.2      | 42.4     | .        | .        | FALSE    |
| RALGAPA1 | PTV or rare damaging  | 8             | 0.0224              | 92       | 0.0067   | 0.0039   | 3.4      | 1.6      | 7        | Yes      | .        | FALSE    |
| HDAC9    | Flexible damaging     | 4             | 0.0112              | 22       | 0.0016   | 0.0039   | 7.1      | 2.4      | 20.6     | Yes      | .        | FALSE    |
| PLEKHA1  | Rare damaging         | 4             | 0.0112              | 22       | 0.0016   | 0.0039   | 7.1      | 2.4      | 20.6     | Yes      | .        | FALSE    |
| IRF3     | Rare damaging (MTR)   | 4             | 0.0112              | 22       | 0.0016   | 0.0039   | 7.1      | 2.4      | 20.6     | Yes      | .        | FALSE    |
| Gene       | Type                     | Mutations | Allele | Genotype | Minor Allele Frequency | Haplogroup | Clade   | mtDNA   | SNP      | Mitochondrial Genome | Status | Expression | Redo | Redo | Redo | MTR   |
|------------|--------------------------|-----------|--------|----------|------------------------|------------|---------|---------|----------|----------------------|--------|------------|------|------|------|-------|
| GLRB       | Flexible damaging        | 6         | 0.0168 | 54       | 0.0039                 | 0.004      | 4.3     | 1.8     | 10.1     | Yes                 | .      | .          | .    | .    | .    | FALSE |
| ZSCAN16    | Flexible non-syn         | 5         | 0.014  | 37       | 0.0027                 | 0.004      | 5.3     | 2.1     | 13.4     | Yes                 | .      | .          | .    | .    | .    | FALSE |
| AURKB      | Flexible non-syn         | 8         | 0.0224 | 93       | 0.0068                 | 0.0041     | 3.4     | 1.6     | 7        | .                   | .      | .          | .    | .    | .    | FALSE |
| SH3KBP1    | Flexible non-syn         | 7         | 0.0196 | 73       | 0.0053                 | 0.0041     | 3.7     | 1.7     | 8.2      | Yes                 | .      | .          | .    | .    | .    | FALSE |
| KRT10      | PTV or rare damaging     | 7         | 0.0196 | 73       | 0.0053                 | 0.0041     | 3.7     | 1.7     | 8.2      | Yes                 | Yes    | TRUE       | .    | .    | .    | FALSE |
| CDHR4      | Flexible non-syn         | 11        | 0.0308 | 160      | 0.0117                 | 0.0043     | 2.7     | 1.4     | 5        | .                   | .      | .          | .    | .    | .    | FALSE |
| ZNF142     | Flexible damaging        | 7         | 0.0196 | 74       | 0.0054                 | 0.0044     | 3.7     | 1.7     | 8.1      | Yes                 | .      | .          | .    | .    | .    | FALSE |
| SEC23A     | Flexible non-syn         | 7         | 0.0196 | 74       | 0.0054                 | 0.0044     | 3.7     | 1.7     | 8.1      | Yes                 | .      | .          | .    | .    | .    | FALSE |
| CLCA4      | PTV or rare damaging     | 7         | 0.0196 | 74       | 0.0054                 | 0.0044     | 3.7     | 1.7     | 8.1      | .                   | .      | .          | .    | .    | .    | FALSE |
| PLXNB1     | Flexible non-syn         | 15        | 0.042  | 253      | 0.0184                 | 0.0045     | 2.3     | 1.4     | 4        | Yes                 | Yes    | TRUE       | .    | .    | .    | FALSE |
| KRTAP21-3  | Flexible non-syn         | 4         | 0.0112 | 23       | 0.0017                 | 0.0045     | 6.7     | 2.3     | 19.6     | .                   | .      | .          | .    | .    | .    | TRUE  |
| SNN        | Flexible non-syn         | 4         | 0.0112 | 23       | 0.0017                 | 0.0045     | 6.7     | 2.3     | 19.6     | Yes                 | .      | .          | .    | .    | .    | FALSE |
| ASB16      | Flexible non-syn (MTR)   | 4         | 0.0112 | 23       | 0.0017                 | 0.0045     | 6.7     | 2.3     | 19.6     | .                   | .      | .          | .    | .    | .    | FALSE |
| ASPHD2     | Flexible non-syn (MTR)   | 4         | 0.0112 | 23       | 0.0017                 | 0.0045     | 6.7     | 2.3     | 19.6     | .                   | .      | .          | .    | .    | .    | FALSE |
| SNX3I      | Flexible non-syn (MTR)   | 4         | 0.0112 | 23       | 0.0017                 | 0.0045     | 6.7     | 2.3     | 19.6     | .                   | .      | .          | .    | .    | .    | FALSE |
| RASGRP3    | Flexible non-syn         | 8         | 0.0224 | 95       | 0.0069                 | 0.0046     | 3.3     | 1.6     | 6.8      | Yes                 | .      | .          | .    | .    | .    | FALSE |
| Gene     | Annotation               | Variant Count | Counts in HBRD | OCS | OCS2 | HBRD2 | HBRD | FTD | HBRD2 (FCD) |
|----------|--------------------------|---------------|----------------|-----|------|-------|------|-----|-------------|
| KIF21A  | PTV or rare damaging     | 8             | 0.0224         | 95  | 0.0069 | 0.0046 | 3.3  | 1.6 | 6.8         | Yes          | .             | FALSE        |
| PCNT    | Flexible non-syn         | 33            | 0.0924         | 753 | 0.0549 | 0.0047 | 1.8  | 1.2 | 2.5         | Yes          | .             | FALSE        |
| SCG3    | Flexible non-syn         | 6             | 0.0168         | 56  | 0.0041 | 0.0047 | 4.2  | 1.8 | 9.7         | .            | .             | FALSE        |
| KCNS3   | PTV or rare damaging     | 6             | 0.0168         | 56  | 0.0041 | 0.0047 | 4.2  | 1.8 | 9.7         | Yes          | .             | FALSE        |
| PIK3C2G | Rare damaging            | 6             | 0.0168         | 56  | 0.0041 | 0.0047 | 4.2  | 1.8 | 9.7         | .            | .             | FALSE        |
| COL18A1 | Ultra-rare damaging      | 6             | 0.0168         | 56  | 0.0041 | 0.0047 | 4.2  | 1.8 | 9.7         | Yes          | Yes          | FALSE        |
| TRIB3   | Flexible non-syn         | 9             | 0.0252         | 117 | 0.0085 | 0.0048 | 3    | 1.5 | 6           | Yes          | .             | TRUE         |
| GAS2L1  | Flexible damaging        | 3             | 0.0084         | 11  | 8.02E-04 | 0.0048 | 10.6 | 2.9 | 38          | Yes          | .             | FALSE        |
| LEO1    | Flexible damaging        | 3             | 0.0084         | 11  | 8.02E-04 | 0.0048 | 10.6 | 2.9 | 38          | Yes          | .             | FALSE        |
| ADSL    | Flexible non-syn (MTR)   | 3             | 0.0084         | 11  | 8.02E-04 | 0.0048 | 10.6 | 2.9 | 38          | Yes          | .             | FALSE        |
| CTSG    | Flexible non-syn (MTR)   | 3             | 0.0084         | 11  | 8.02E-04 | 0.0048 | 10.6 | 2.9 | 38          | Yes          | .             | FALSE        |
| GSG1    | Flexible non-syn (MTR)   | 3             | 0.0084         | 11  | 8.02E-04 | 0.0048 | 10.6 | 2.9 | 38          | .            | .             | FALSE        |
| MKRN1   | Flexible non-syn (MTR)   | 3             | 0.0084         | 11  | 8.02E-04 | 0.0048 | 10.6 | 2.9 | 38          | Yes          | .             | FALSE        |
| ONECUT3 | Flexible non-syn (MTR)   | 3             | 0.0084         | 11  | 8.02E-04 | 0.0048 | 10.6 | 2.9 | 38          | .            | .             | FALSE        |
| PRELID3A| Flexible non-syn (MTR)   | 3             | 0.0084         | 11  | 8.02E-04 | 0.0048 | 10.6 | 2.9 | 38          | Yes          | .             | FALSE        |
| SSMEM1  | Flexible non-syn (MTR)   | 3             | 0.0084         | 11  | 8.02E-04 | 0.0048 | 10.6 | 2.9 | 38          | .            | .             | FALSE        |
| Gene      | Synonymation Type | MTR Risk | Z-score | P-value | OR     | Reg CIS | LG | CALL | Annotation Status |
|-----------|-------------------|----------|---------|---------|--------|---------|----|------|-------------------|
| ZC3H15   | Flexible non-syn (MTR) | 3        | 0.0084  | 11      | 8.02E-04 | 0.0048  | 10.6 | 2.9  | 38 | Yes | . | FALSE |
| KARS     | Rare damaging (MTR) | 3        | 0.0084  | 11      | 8.02E-04 | 0.0048  | 10.6 | 2.9  | 38 | Yes | Yes | FALSE |
| RNF19A   | Rare damaging (MTR) | 3        | 0.0084  | 11      | 8.02E-04 | 0.0048  | 10.6 | 2.9  | 38 | Yes | . | FALSE |
| SLC1A3   | Rare damaging (MTR) | 3        | 0.0084  | 11      | 8.02E-04 | 0.0048  | 10.6 | 2.9  | 38 | Yes | . | FALSE |
| AP3M2    | Ultra-rare damaging | 3        | 0.0084  | 11      | 8.02E-04 | 0.0048  | 10.6 | 2.9  | 38 | Yes | . | FALSE |
| SLC7A6   | Ultra-rare damaging | 3        | 0.0084  | 11      | 8.02E-04 | 0.0048  | 10.6 | 2.9  | 38 | Yes | . | FALSE |
| CNKSR2   | Flexible non-syn | 5        | 0.014   | 39      | 0.0028   | 0.0049  | 5    | 2    | 12.7 | . | . | FALSE |
| ZNF224   | Flexible non-syn (MTR) | 5       | 0.014   | 39      | 0.0028   | 0.0049  | 5    | 2    | 12.7 | Yes | . | FALSE |
| GRXCR2   | Flexible non-syn | 7        | 0.0196  | 76      | 0.0055   | 0.0051  | 3.6  | 1.6  | 7.8 | . | . | FALSE |
| TMEM74   | Flexible non-syn | 6        | 0.0168  | 57      | 0.0042   | 0.0051  | 4.1  | 1.8  | 9.6 | . | . | FALSE |
| GPX2     | Flexible damaging | 4        | 0.0112  | 24      | 0.0017   | 0.0051  | 6.5  | 2.2  | 18.7 | . | . | FALSE |
| CDK5RAP3 | Flexible non-syn (MTR) | 4     | 0.0112  | 24      | 0.0017   | 0.0051  | 6.5  | 2.2  | 18.7 | Yes | Yes | FALSE |
| DCLK3    | Flexible non-syn (MTR) | 4      | 0.0112  | 24      | 0.0017   | 0.0051  | 6.5  | 2.2  | 18.7 | . | . | FALSE |
| FBOX11   | Flexible non-syn (MTR) | 4     | 0.0112  | 24      | 0.0017   | 0.0051  | 6.5  | 2.2  | 18.7 | Yes | . | FALSE |
| LITAF    | Flexible non-syn | 5        | 0.014   | 40      | 0.0029   | 0.0054  | 4.9  | 1.9  | 12.4 | Yes | Yes | FALSE |
| STPG1    | Flexible non-syn | 5        | 0.014   | 40      | 0.0029   | 0.0054  | 4.9  | 1.9  | 12.4 | Yes | . | FALSE |
| Gene       | Type               | Evidence | Frequency | Depth | Depth of Loss | p-Value | Rsq | Allele COUNT | Homozygosity | MAF | Result |  |  |
|------------|--------------------|----------|-----------|-------|---------------|---------|-----|--------------|--------------|-----|--------|  |  |
| CALHM6     | Flexible non-syn   |          | 6         | 0.0168| 58            | 0.0042  | 0.0055| 4            | 1.7          | 9.4 | Yes    |  |  |
| KIAA1217   | Flexible non-syn   |          | 18        | 0.0504| 340           | 0.0248  | 0.0056| 2.1          | 1.3          | 3.4 | Yes    |  |  |
| SIGLEC1    | Flexible damaging  |          | 10        | 0.028 | 143           | 0.0104  | 0.0056| 2.7          | 1.4          | 5.2 | Yes    |  |  |
| HIF3A      | Flexible non-syn   |          | 10        | 0.028 | 143           | 0.0104  | 0.0056| 2.7          | 1.4          | 5.2 | Yes    |  |  |
| ANKRD27    | Flexible non-syn   |          | 14        | 0.0392| 232           | 0.0169  | 0.0058| 2.4          | 1.4          | 4.1 | Yes    |  |  |
| BAIAP3     | Rare damaging      |          | 8         | 0.0224| 99            | 0.0072  | 0.0058| 3.2          | 1.5          | 6.5 |  |  |  |
| LRRC40     | Flexible non-syn   |          | 7         | 0.0196| 78            | 0.0057  | 0.0058| 3.5          | 1.6          | 7.6 | Yes    |  |  |
| FBXW10     | Flexible non-syn   |          | 4         | 0.0112| 25            | 0.0018  | 0.0058| 6.2          | 2.1          | 17.9|  |  |  |
| ANKS1B     | Flexible non-syn (MTR) |     | 4         | 0.0112| 25            | 0.0018  | 0.0058| 6.2          | 2.1          | 17.9| Yes    |  |  |
| PLEKHG2    | Flexible non-syn   |          | 17        | 0.0476| 306           | 0.0223  | 0.0059| 2.2          | 1.3          | 3.6 | Yes    |  |  |
| AKAP11     | Flexible non-syn   |          | 12        | 0.0336| 192           | 0.014   | 0.0059| 2.5          | 1.4          | 4.4 | Yes    |  |  |
| CYP1B1     | Flexible non-syn   |          | 9         | 0.0252| 121           | 0.0088  | 0.0059| 2.9          | 1.5          | 5.8 | Yes    |  |  |
| IFNE       | Flexible damaging  |          | 3         | 0.0084| 12            | 8.75E-04| 0.0059| 9.7          | 2.7          | 34.5|  |  |  |
| ZNF408     | Flexible damaging  |          | 3         | 0.0084| 12            | 8.75E-04| 0.0059| 9.7          | 2.7          | 34.5| Yes    |  |  |
| AKAP10     | Flexible non-syn (MTR) |   | 3         | 0.0084| 12            | 8.75E-04| 0.0059| 9.7          | 2.7          | 34.5| Yes    |  |  |
| NAP1L2     | Flexible non-syn (MTR) |     | 3         | 0.0084| 12            | 8.75E-04| 0.0059| 9.7          | 2.7          | 34.5| Yes    |  |  |
| Gene   | Annotation                      | Chr | Prob | nLOD | lod  | pval | TMM | TMM/NA | Yes/No | Result |
|--------|---------------------------------|-----|------|------|------|------|-----|--------|--------|--------|
| ARRDC4 | PTV or rare damaging            | 3   | 0.0084 | 12   | 8.75E-04 | 0.0059 | 2.7 | 34.5   | Yes   | FALSE  |
| NUDT22 | Rare damaging                   | 3   | 0.0084 | 12   | 8.75E-04 | 0.0059 | 2.7 | 34.5   | Yes   | FALSE  |
| ALDOA  | Ultra-rare damaging             | 3   | 0.0084 | 12   | 8.75E-04 | 0.0059 | 2.7 | 34.5   | Yes   | FALSE  |
| C8A    | Ultra-rare damaging             | 3   | 0.0084 | 12   | 8.75E-04 | 0.0059 | 2.7 | 34.5   | .      | FALSE  |
| NUDT12 | Flexible non-syn                | 6   | 0.0168 | 59   | 0.0043  | 0.006  | 4   | 1.7    | 9.2    | Yes    |
| STAC   | Flexible non-syn                | 6   | 0.0168 | 59   | 0.0043  | 0.006  | 4   | 1.7    | 9.2    | Yes    |
| RNF175 | Flexible damaging               | 5   | 0.014  | 41   | 0.003   | 0.006  | 4.7 | 1.9    | 12.1   | .      |
| ABTB1  | PTV or rare damaging            | 5   | 0.014  | 41   | 0.003   | 0.006  | 4.7 | 1.9    | 12.1   | Yes    |
| NOL3   | PTV or rare damaging            | 5   | 0.014  | 41   | 0.003   | 0.006  | 4.7 | 1.9    | 12.1   | Yes    |
| IGFN1  | Rare damaging (MTR)             | 5   | 0.014  | 41   | 0.003   | 0.006  | 4.7 | 1.9    | 12.1   | .      |
| ITPR1  | Flexible non-syn                | 12  | 0.0336 | 193  | 0.0141  | 0.0061 | 2.4 | 1.3    | 4.4    | Yes    |
| MCM7   | Flexible non-syn                | 12  | 0.0336 | 193  | 0.0141  | 0.0061 | 2.4 | 1.3    | 4.4    | Yes    |
| MTHFR  | Recessive                       | 7   | 0.0196 | 79   | 0.0058  | 0.0061 | 3.5 | 1.6    | 7.5    | Yes    |
| FAM25A | Flexible damaging               | 2   | 0.0056 | 3    | 2.19E-04 | 0.0061 | 25.8| 4.3    | 154.7  | .      |
| MUC7   | Flexible damaging               | 2   | 0.0056 | 3    | 2.19E-04 | 0.0061 | 25.8| 4.3    | 154.7  | .      |
| SMIM9  | Flexible damaging               | 2   | 0.0056 | 3    | 2.19E-04 | 0.0061 | 25.8| 4.3    | 154.7  | .      |
| Gene    | Classification                  | Chromosome | p-value | q-value | Log odds | OR      | Risk allele | Haplotype 1 | Haplotype 2 | MTR    |
|---------|----------------------------------|------------|---------|---------|----------|---------|-------------|-------------|-------------|--------|
| GTPBP10 | Flexible non-syn (MTR)           | 2          | 0.0056  | 3       | 2.19E-04 | 0.0061  | 25.8        | 4.3         | 154.7       | Yes    |
| PCDHB8  | Flexible non-syn (MTR)           | 2          | 0.0056  | 3       | 2.19E-04 | 0.0061  | 25.8        | 4.3         | 154.7       | .      |
| STYX    | Flexible non-syn (MTR)           | 2          | 0.0056  | 3       | 2.19E-04 | 0.0061  | 25.8        | 4.3         | 154.7       | Yes    |
| BTLA    | PTV                              | 2          | 0.0056  | 3       | 2.19E-04 | 0.0061  | 25.8        | 4.3         | 154.7       | .      |
| LYZ     | PTV                              | 2          | 0.0056  | 3       | 2.19E-04 | 0.0061  | 25.8        | 4.3         | 154.7       | Yes    |
| MCMBP   | PTV                              | 2          | 0.0056  | 3       | 2.19E-04 | 0.0061  | 25.8        | 4.3         | 154.7       | Yes    |
| PPOX    | PTV                              | 2          | 0.0056  | 3       | 2.19E-04 | 0.0061  | 25.8        | 4.3         | 154.7       | .      |
| RCAN3   | PTV                              | 2          | 0.0056  | 3       | 2.19E-04 | 0.0061  | 25.8        | 4.3         | 154.7       | .      |
| ZBTB10  | PTV                              | 2          | 0.0056  | 3       | 2.19E-04 | 0.0061  | 25.8        | 4.3         | 154.7       | Yes    |
| ZNF789  | Rare damaging                    | 2          | 0.0056  | 3       | 2.19E-04 | 0.0061  | 25.8        | 4.3         | 154.7       | Yes    |
| ACSM2B  | Rare damaging (MTR)              | 2          | 0.0056  | 3       | 2.19E-04 | 0.0061  | 25.8        | 4.3         | 154.7       | .      |
| C3orf20 | Rare damaging (MTR)              | 2          | 0.0056  | 3       | 2.19E-04 | 0.0061  | 25.8        | 4.3         | 154.7       | .      |
| LRRC1   | Rare damaging (MTR)              | 2          | 0.0056  | 3       | 2.19E-04 | 0.0061  | 25.8        | 4.3         | 154.7       | Yes    |
| PSD3    | Rare damaging (MTR)              | 2          | 0.0056  | 3       | 2.19E-04 | 0.0061  | 25.8        | 4.3         | 154.7       | Yes    |
| PCDHA4  | Recessive                        | 2          | 0.0056  | 3       | 2.19E-04 | 0.0061  | 25.8        | 4.3         | 154.7       | .      |
| SOX30   | Recessive                        | 2          | 0.0056  | 3       | 2.19E-04 | 0.0061  | 25.8        | 4.3         | 154.7       | .      |
| Gene     | Status             | Rare |
|----------|--------------------|------|
| BUD13    | Ultra-rare damaging | 2    |
| FAF2     | Ultra-rare damaging | 3    |
| FAM83A   | Ultra-rare damaging | 2    |
| GAB2     | Ultra-rare damaging | 2    |
| RNFT1    | Ultra-rare damaging | 2    |
| SLC25A26 | Ultra-rare damaging | 2    |
| ARNTL    | Ultra-rare damaging (MTR) | 2    |
| B3GAT1   | Ultra-rare damaging (MTR) | 2    |
| CACNA2D1 | Ultra-rare damaging (MTR) | 2    |
| FCGRT    | Ultra-rare damaging (MTR) | 2    |
| ITGA5    | Ultra-rare damaging (MTR) | 2    |
| PLEKHA5  | Ultra-rare damaging | 2    |
| Gene       | Type                          | Maf  | ICD  | ACD  | Freq | BAF | p  | T | Status | PTV or Rare Damage |
|------------|-------------------------------|------|------|------|------|-----|----|---|--------|-------------------|
| **PPP3CC** | Ultra-rare damaging (MTR)     | 2    | 0.0056 | 3 | 2.19E-04 | 0.0061 | 25.8 | 4.3 | 154.7 | Yes | . | FALSE |
| **SLC39A13** | Ultra-rare damaging (MTR)     | 2    | 0.0056 | 3 | 2.19E-04 | 0.0061 | 25.8 | 4.3 | 154.7 | Yes | . | FALSE |
| **IGSF1**  | Flexible non-syn              | 11   | 0.0308 | 169 | 0.0123 | 0.0062 | 2.5 | 1.4 | 4.7 | . | . | FALSE |
| **TTI1**   | Flexible non-syn              | 10   | 0.028 | 145 | 0.0106 | 0.0062 | 2.7 | 1.4 | 5.2 | Yes | . | FALSE |
| **WDR18**  | Flexible non-syn              | 6    | 0.0168 | 60 | 0.0044 | 0.0064 | 3.9 | 1.7 | 9.1 | Yes | . | FALSE |
| **PLD2**   | PTV or rare damaging          | 6    | 0.0168 | 60 | 0.0044 | 0.0064 | 3.9 | 1.7 | 9.1 | Yes | . | FALSE |
| **GALC**   | Flexible non-syn              | 7    | 0.0196 | 80 | 0.0058 | 0.0065 | 3.4 | 1.6 | 7.4 | Yes | . | FALSE |
| **TXNRD1** | Flexible non-syn              | 7    | 0.0196 | 80 | 0.0058 | 0.0065 | 3.4 | 1.6 | 7.4 | Yes | . | FALSE |
| **TRNAU1AP** | Flexible non-syn             | 5    | 0.014 | 42 | 0.0031 | 0.0065 | 4.6 | 1.8 | 11.8 | Yes | . | FALSE |
| **VPS26A** | Flexible non-syn              | 5    | 0.014 | 42 | 0.0031 | 0.0065 | 4.6 | 1.8 | 11.8 | Yes | . | FALSE |
| **MCM10**  | Flexible damaging             | 4    | 0.0112 | 26 | 0.0019 | 0.0066 | 6 | 2.1 | 17.2 | . | . | FALSE |
| **CTSB**   | Flexible non-syn (MTR)        | 4    | 0.0112 | 26 | 0.0019 | 0.0066 | 6 | 2.1 | 17.2 | Yes | Yes | FALSE |
| **LIMK2**  | Flexible non-syn (MTR)        | 4    | 0.0112 | 26 | 0.0019 | 0.0066 | 6 | 2.1 | 17.2 | Yes | . | FALSE |
| Gene     | Description                  | Allele 1 | AA Change | Allele 2 | Copy Number | p-Value 1 | p-Value 2 | Copy Number 2 | Analysis 1 | Analysis 2 | Analysis 3 | Analysis 4 | Analysis 5 | Analysis 6 |
|----------|------------------------------|----------|-----------|----------|-------------|-----------|-----------|---------------|-------------|-------------|-------------|-------------|-------------|-------------|
| VNIR2    | PTV                          | 4        | 0.0112    | 26       | 0.0019      | 0.0066    | 6         | 2.1           | 17.2        | .           | .           | FALSE       |             |
| RUSC2    | PTV or rare damaging         | 4        | 0.0112    | 26       | 0.0019      | 0.0066    | 6         | 2.1           | 17.2        | Yes         | .           | FALSE       |             |
| PFKL     | Rare damaging (MTR)          | 4        | 0.0112    | 26       | 0.0019      | 0.0066    | 6         | 2.1           | 17.2        | Yes         | Yes         | FALSE       |             |
| WDR33    | Ultra-rare damaging          | 4        | 0.0112    | 26       | 0.0019      | 0.0066    | 6         | 2.1           | 17.2        | Yes         | .           | FALSE       |             |
| IGSF3    | Flexible non-syn             | 10       | 0.028     | 147      | 0.0107      | 0.0067    | 2.7       | 1.4           | 5.1         | .           | .           | FALSE       |             |
| FRMD8    | Flexible non-syn             | 8        | 0.0224    | 102      | 0.0074      | 0.0069    | 3.1       | 1.5           | 6.3         | Yes         | .           | FALSE       |             |
| FRY      | Flexible non-syn             | 14       | 0.0392    | 241      | 0.0176      | 0.007    | 2.3       | 1.3           | 4           | Yes         | .           | FALSE       |             |
| CFAP53   | Flexible non-syn             | 9        | 0.0252    | 125      | 0.0091      | 0.0071    | 2.8       | 1.4           | 5.6         | .           | .           | FALSE       |             |
| ATP5MF-PTCD1 | Flexible non-syn (MTR) | 5        | 0.014     | 43       | 0.0031      | 0.0071    | 4.5       | 1.8           | 11.5        | Yes         | .           | TRUE        |             |
| PTCD1    | Flexible non-syn (MTR)       | 5        | 0.014     | 43       | 0.0031      | 0.0071    | 4.5       | 1.8           | 11.5        | Yes         | .           | TRUE        |             |
| ZFAT     | Flexible non-syn (MTR)       | 5        | 0.014     | 43       | 0.0031      | 0.0071    | 4.5       | 1.8           | 11.5        | Yes         | .           | FALSE       |             |
| TBC1D1   | PTV or rare damaging         | 5        | 0.014     | 43       | 0.0031      | 0.0071    | 4.5       | 1.8           | 11.5        | Yes         | .           | FALSE       |             |
| LSM14B   | Flexible damaging            | 3        | 0.0084    | 13       | 9.47E-04    | 0.0071    | 8.9       | 2.5           | 31.5        | Yes         | .           | FALSE       |             |
| ABRAXAS1 | Flexible non-syn (MTR)       | 3        | 0.0084    | 13       | 9.47E-04    | 0.0071    | 8.9       | 2.5           | 31.5        | Yes         | .           | FALSE       |             |
| RSPH9    | Flexible non-syn (MTR)       | 3        | 0.0084    | 13       | 9.47E-04    | 0.0071    | 8.9       | 2.5           | 31.5        | .           | .           | FALSE       |             |
| Gene     | Function               | N  | P-value 1 | P-value 2 | VS   | BMI  | Status | Label     |
|----------|------------------------|----|-----------|-----------|------|------|--------|-----------|
| TGFB2    | Flexible non-syn (MTR) | 3  | 0.0084    | 13        | 9.47E-04 | 0.0071 | 8.9    | 2.5       | 31.5    | Yes | .      | FALSE    |
| CPEB4    | PTV or rare damaging   | 3  | 0.0084    | 13        | 9.47E-04 | 0.0071 | 8.9    | 2.5       | 31.5    | Yes | .      | FALSE    |
| CATSPERE | Rare damaging          | 3  | 0.0084    | 13        | 9.47E-04 | 0.0071 | 8.9    | 2.5       | 31.5    | .    | .      | FALSE    |
| CDH7     | Rare damaging (MTR)    | 3  | 0.0084    | 13        | 9.47E-04 | 0.0071 | 8.9    | 2.5       | 31.5    | .    | .      | FALSE    |
| SMAD2    | Rare damaging (MTR)    | 3  | 0.0084    | 13        | 9.47E-04 | 0.0071 | 8.9    | 2.5       | 31.5    | Yes | .      | FALSE    |
| MEP1A    | Ultra-rare damaging    | 3  | 0.0084    | 13        | 9.47E-04 | 0.0071 | 8.9    | 2.5       | 31.5    | .    | .      | FALSE    |
| TH       | Ultra-rare damaging    | 3  | 0.0084    | 13        | 9.47E-04 | 0.0071 | 8.9    | 2.5       | 31.5    | .    | .      | FALSE    |
| KIAA0556 | Flexible non-syn       | 17 | 0.0476    | 321       | 0.0234   | 0.0073 | 2.1    | 1.3       | 3.4     | Yes | .      | FALSE    |
| KCNA5    | Flexible damaging      | 8  | 0.0224    | 103       | 0.0075   | 0.0073 | 3      | 1.5       | 6.3     | Yes | Yes   | FALSE    |
| PHYKPL   | Flexible non-syn       | 8  | 0.0224    | 103       | 0.0075   | 0.0073 | 3      | 1.5       | 6.3     | Yes | .      | FALSE    |
| TBX2     | Flexible damaging      | 7  | 0.0196    | 82        | 0.006    | 0.0074 | 3.3    | 1.5       | 7.3     | Yes | Yes   | FALSE    |
| SMTNL2   | Flexible non-syn       | 7  | 0.0196    | 82        | 0.006    | 0.0074 | 3.3    | 1.5       | 7.3     | .    | .      | FALSE    |
| SLC6A8   | Flexible non-syn (MTR) | 4  | 0.0112    | 27        | 0.002    | 0.0074 | 5.7    | 2         | 16.5    | Yes | .      | TRUE     |
| FAM187B  | Flexible non-syn       | 7  | 0.0196    | 83        | 0.006    | 0.0078 | 3.3    | 1.5       | 7.2     | .    | .      | TRUE     |
| SEMA3F   | Flexible damaging      | 5  | 0.014     | 44        | 0.0032   | 0.0078 | 4.4    | 1.7       | 11.2    | Yes | .      | FALSE    |
| ZSCAN2   | Flexible non-syn (MTR) | 5  | 0.014     | 44        | 0.0032   | 0.0078 | 4.4    | 1.7       | 11.2    | .    | .      | FALSE    |
| Gene   | Type                      | Score | PPV  | P = 0.014 | p < 0.014 | p < 0.0005 | Weight | TMB | Pathogenicity | 50% Mutations | Status | Malignant                                      |
|--------|---------------------------|-------|------|-----------|-----------|------------|--------|-----|---------------|---------------|--------|-----------------------------------------------|
| IGSF10 | PTV                       | 5     | 0.014| 44        | 0.0032    | 0.0078     | 4.4    | 1.7 | Yes           | .             | .      | FALSE                                         |
| GCDH   | PTV or rare damaging      | 5     | 0.014| 44        | 0.0032    | 0.0078     | 4.4    | 1.7 | Yes           | .             | .      | FALSE                                         |
| KLKB1  | Flexible damaging         | 8     | 0.0224| 105       | 0.0077    | 0.008      | 3      | 1.4 | 6.1           | .             | .      | FALSE                                         |
| F11    | Flexible non-syn          | 8     | 0.0224| 105       | 0.0077    | 0.008      | 3      | 1.4 | 6.1           | .             | .      | FALSE                                         |
| AZGP1  | Flexible non-syn          | 6     | 0.0168| 63        | 0.0046    | 0.008      | 3.7    | 1.6 | 8.6           | Yes          | .      | FALSE                                         |
| ZNF358 | Flexible non-syn (MTR)    | 4     | 0.0112| 28        | 0.002     | 0.0083     | 5.5    | 1.9 | 15.9          | Yes           | Yes    | FALSE                                         |
| CCDC171| Rare damaging (MTR)       | 4     | 0.0112| 28        | 0.002     | 0.0083     | 5.5    | 1.9 | 15.9          | .             | .      | FALSE                                         |
| SEC31B | Rare damaging (MTR)       | 4     | 0.0112| 28        | 0.002     | 0.0083     | 5.5    | 1.9 | 15.9          | Yes           | .      | FALSE                                         |
| GCNI   | Ultra-rare damaging       | 4     | 0.0112| 28        | 0.002     | 0.0083     | 5.5    | 1.9 | 15.9          | Yes           | .      | FALSE                                         |
| REEP1  | Flexible damaging         | 3     | 0.0084| 14        | 0.001     | 0.0084     | 8.3    | 2.4 | 29            | Yes           | .      | FALSE                                         |
| DLG2   | Flexible non-syn (MTR)    | 3     | 0.0084| 14        | 0.001     | 0.0084     | 8.3    | 2.4 | 29            | .             | .      | FALSE                                         |
| MGARP  | Flexible non-syn (MTR)    | 3     | 0.0084| 14        | 0.001     | 0.0084     | 8.3    | 2.4 | 29            | Yes           | .      | FALSE                                         |
| LHPP   | PTV or rare damaging      | 3     | 0.0084| 14        | 0.001     | 0.0084     | 8.3    | 2.4 | 29            | Yes           | .      | FALSE                                         |
| NCSTN  | PTV or rare damaging      | 3     | 0.0084| 14        | 0.001     | 0.0084     | 8.3    | 2.4 | 29            | Yes           | .      | FALSE                                         |
| B4GALNT2| Rare damaging             | 3     | 0.0084| 14        | 0.001     | 0.0084     | 8.3    | 2.4 | 29            | .             | .      | FALSE                                         |
| IVNS1ABP| Ultra-rare damaging      | 3     | 0.0084| 14        | 0.001     | 0.0084     | 8.3    | 2.4 | 29            | Yes           | .      | FALSE                                         |
| Gene   | Type of Mutation | allele frequency | ratio | Freq | Freq | Freq | Yes/No | True/False |
|--------|------------------|------------------|-------|------|------|------|---------|-------------|
| SOX9   | Ultra-rare damaging | 0.0084          | 0.001 | 0.0084 | 8.3  | 2.4  | 29 | Yes .  | FALSE      |
| ABCB11 | Ultra-rare damaging | 0.0084          | 0.001 | 0.0084 | 8.3  | 2.4  | 29 | . .     | FALSE      |
| KRT86  | Flexible non-syn  | 0.0224          | 0.0077 | 0.0085 | 2.9  | 1.4  | 6.1 | Yes .   | TRUE       |
| CD70   | Flexible non-syn  | 0.014           | 0.0033 | 0.0085 | 4.3  | 1.7  | 10.9| . .     | FALSE      |
| AVIL   | Rare damaging     | 0.014           | 0.0033 | 0.0085 | 4.3  | 1.7  | 10.9| Yes .   | FALSE      |
| CFAP46 | Flexible non-syn (MTR) | 0.0308         | 0.0129 | 0.0086 | 2.4  | 1.3  | 4.5 | . .     | FALSE      |
| NASP   | Flexible non-syn  | 0.0252          | 0.0094 | 0.0086 | 2.7  | 1.4  | 5.4 | Yes .   | FALSE      |
| CAMTA1 | Flexible damaging | 0.0168          | 0.0047 | 0.0086 | 3.6  | 1.6  | 8.5 | Yes Yes | FALSE      |
| TMEM140| Flexible non-syn  | 0.0168          | 0.0047 | 0.0086 | 3.6  | 1.6  | 8.5 | Yes .   | FALSE      |
| SAP130 | Flexible non-syn  | 0.0196          | 0.0062 | 0.0088 | 3.2  | 1.5  | 7 | Yes .   | FALSE      |
| PTGES3 | Flexible damaging | 0.0056          | 2.92E-04 | 0.009 | 19.3 | 3.5  | 105.8| Yes Yes | FALSE      |
| SMLR1  | Flexible damaging | 0.0056          | 2.92E-04 | 0.009 | 19.3 | 3.5  | 105.8| . .     | FALSE      |
| C12orf60| Flexible non-syn (MTR) | 0.0056        | 2.92E-04 | 0.009 | 19.3 | 3.5  | 105.8| Yes .   | FALSE      |
| NPPA   | Flexible non-syn (MTR) | 0.0056         | 2.92E-04 | 0.009 | 19.3 | 3.5  | 105.8| Yes Yes | FALSE      |
| SIGLECL1| Flexible non-syn (MTR) | 0.0056        | 2.92E-04 | 0.009 | 19.3 | 3.5  | 105.8| . .     | FALSE      |
| Gene   | Description                  | p-value | Benjamini | FDR   | OR   | CI-Lower | CI-Upper | Score | Gene Type | Markers | VAF | Status |
|--------|------------------------------|---------|-----------|-------|------|----------|----------|-------|-----------|---------|-----|--------|
| TFEC   | Flexible non-syn (MTR)       | 2       | 0.0056    | 4     | 2.92E-04 | 0.009    | 19.3    | 3.5       | 105.8     | FALSE   |       |
| ZNF417 | Flexible non-syn (MTR)       | 2       | 0.0056    | 4     | 2.92E-04 | 0.009    | 19.3    | 3.5       | 105.8     | TRUE    | .      |
| KCNA10 | PTV                         | 2       | 0.0056    | 4     | 2.92E-04 | 0.009    | 19.3    | 3.5       | 105.8     | FALSE   | .      |
| ZNF561 | PTV                         | 2       | 0.0056    | 4     | 2.92E-04 | 0.009    | 19.3    | 3.5       | 105.8     | FALSE   | .      |
| ATP6V1D| PTV or rare damaging        | 2       | 0.0056    | 4     | 2.92E-04 | 0.009    | 19.3    | 3.5       | 105.8     | FALSE   | .      |
| CDC23  | PTV or rare damaging        | 2       | 0.0056    | 4     | 2.92E-04 | 0.009    | 19.3    | 3.5       | 105.8     | FALSE   | .      |
| RAB6A  | Rare damaging               | 2       | 0.0056    | 4     | 2.92E-04 | 0.009    | 19.3    | 3.5       | 105.8     | FALSE   | .      |
| CLTB   | Rare damaging (MTR)         | 2       | 0.0056    | 4     | 2.92E-04 | 0.009    | 19.3    | 3.5       | 105.8     | FALSE   | .      |
| MTX3   | Rare damaging (MTR)         | 2       | 0.0056    | 4     | 2.92E-04 | 0.009    | 19.3    | 3.5       | 105.8     | FALSE   | .      |
| PI4K2A | Rare damaging (MTR)         | 2       | 0.0056    | 4     | 2.92E-04 | 0.009    | 19.3    | 3.5       | 105.8     | FALSE   | .      |
| AHCYL1 | Ultra-rare damaging         | 2       | 0.0056    | 4     | 2.92E-04 | 0.009    | 19.3    | 3.5       | 105.8     | FALSE   | .      |
| CELA1  | Ultra-rare damaging         | 2       | 0.0056    | 4     | 2.92E-04 | 0.009    | 19.3    | 3.5       | 105.8     | FALSE   | .      |
| ENDO1  | Ultra-rare damaging         | 2       | 0.0056    | 4     | 2.92E-04 | 0.009    | 19.3    | 3.5       | 105.8     | TRUE    | .      |
| FAM3B  | Ultra-rare damaging         | 2       | 0.0056    | 4     | 2.92E-04 | 0.009    | 19.3    | 3.5       | 105.8     | FALSE   | .      |
| RILP   | Ultra-rare damaging         | 2       | 0.0056    | 4     | 2.92E-04 | 0.009    | 19.3    | 3.5       | 105.8     | FALSE   | .      |
| RSPH1  | Ultra-rare damaging         | 2       | 0.0056    | 4     | 2.92E-04 | 0.009    | 19.3    | 3.5       | 105.8     | FALSE   | .      |
| Gene   | Variant Type | p-Value 10^4 | p-Value 10^-4 | iHS    | MAF    | Effect Size | Frequency | p-Value |注解  |
|--------|--------------|--------------|--------------|--------|--------|-------------|-----------|---------|------|
| STK31  | Ultra-rare damaging | 2.0056       | 2.92E-04     | 0.009  | 19.3   | 3.5         | 105.8     | .       | FALSE|
| ZNF765 | Ultra-rare damaging | 2.0056       | 2.92E-04     | 0.009  | 19.3   | 3.5         | 105.8     | .       | FALSE|
| AGAP1  | Ultra-rare damaging | 2.0056       | 2.92E-04     | 0.009  | 19.3   | 3.5         | 105.8     | Yes     | FALSE|
| AHCY   | Ultra-rare damaging | 2.0056       | 2.92E-04     | 0.009  | 19.3   | 3.5         | 105.8     | Yes     | FALSE|
| ITCH   | Ultra-rare damaging | 2.0056       | 2.92E-04     | 0.009  | 19.3   | 3.5         | 105.8     | Yes     | FALSE|
| MAP3K20| Ultra-rare damaging | 2.0056       | 2.92E-04     | 0.009  | 19.3   | 3.5         | 105.8     | Yes     | FALSE|
| MDC1   | Ultra-rare damaging | 2.0056       | 2.92E-04     | 0.009  | 19.3   | 3.5         | 105.8     | Yes     | FALSE|
| PPP2R2D| Ultra-rare damaging | 2.0056       | 2.92E-04     | 0.009  | 19.3   | 3.5         | 105.8     | Yes     | FALSE|
| RGL3   | Ultra-rare damaging | 2.0056       | 2.92E-04     | 0.009  | 19.3   | 3.5         | 105.8     | Yes     | FALSE|
| RGS19  | Ultra-rare damaging | 2.0056       | 2.92E-04     | 0.009  | 19.3   | 3.5         | 105.8     | Yes     | FALSE|
| Gene       | Classification  | p-value | FDR  | Fold Change | p-value | FDR  | Class    | Novel?  | Status  |
|------------|-----------------|---------|------|-------------|---------|------|----------|---------|---------|
| RHOBTB2    | Ultra-rare damaging | 0.0056  | 4    | 2.92E-04    | 0.009   | 3.5  | Yes      | .       | FALSE   |
| CFAP73     | Flexible non-syn  | 0.0168  | 65   | 0.0047      | 0.0091  | 3.6  | 1.5      | 8.3     | .       | FALSE   |
| ERCC4      | Rare damaging    | 0.0168  | 65   | 0.0047      | 0.0091  | 3.6  | 1.5      | 8.3     | Yes     | FALSE   |
| RHNO1      | Flexible non-syn  | 0.014   | 46   | 0.0034      | 0.0092  | 4.2  | 1.7      | 10.7    | Yes     | FALSE   |
| CCDC38     | Flexible non-syn (MTR) | 0.014   | 46   | 0.0034      | 0.0092  | 4.2  | 1.7      | 10.7    | .       | FALSE   |
| TRIM71     | PTV or rare damaging | 0.014   | 46   | 0.0034      | 0.0092  | 4.2  | 1.7      | 10.7    | .       | TRUE    |
| SLC22A13   | Rare damaging    | 0.014   | 46   | 0.0034      | 0.0092  | 4.2  | 1.7      | 10.7    | .       | FALSE   |
| SOGA1      | Flexible damaging | 0.0112  | 29   | 0.0021      | 0.0093  | 5.4  | 1.9      | 15.3    | Yes     | .       | FALSE   |
| THBS1      | Flexible non-syn (MTR) | 0.0112  | 29   | 0.0021      | 0.0093  | 5.4  | 1.9      | 15.3    | Yes     | Yes     | FALSE   |
| ANKRD6     | Flexible damaging | 0.0224  | 108  | 0.0079      | 0.0094  | 2.9  | 1.4      | 6       | Yes     | .       | TRUE    |
| IL12RB2    | Flexible non-syn  | 0.0224  | 108  | 0.0079      | 0.0094  | 2.9  | 1.4      | 6       | .       | .       | FALSE   |
| SLC12A7    | Flexible non-syn (MTR) | 0.0252  | 132  | 0.0096      | 0.0098  | 2.7  | 1.3      | 5.3     | Yes     | .       | FALSE   |
| CHRNB2     | Flexible non-syn  | 0.0168  | 66   | 0.0048      | 0.0098  | 3.5  | 1.5      | 8.2     | .       | .       | FALSE   |
| HEATR5B    | Flexible damaging | 0.0196  | 87   | 0.0063      | 0.0099  | 3.1  | 1.4      | 6.8     | Yes     | .       | FALSE   |
| Gene       | Model Type       | Evidence | p Value  | 95% CI    | OR    | p Value  | 95% CI    | IsFlagged | IsFlagged | IsFlagged |
|------------|------------------|----------|----------|-----------|-------|----------|-----------|-----------|-----------|-----------|
| OR6K2      | Flexible non-syn | 7        | 0.0196   | 0.0063    | 0.0099| 3.1      | 1.4       | 6.8       | .         | .         | TRUE      |
| CORT       | Flexible non-syn | 3        | 0.0084   | 0.0011    | 0.0099| 7.7      | 2.2       | 26.9      | .         | .         | FALSE     |
| CD320      | Flexible non-syn (MTR) | 3   | 0.0084   | 0.0011    | 0.0099| 7.7      | 2.2       | 26.9      | Yes       | Yes       | FALSE     |
| CDYL2      | Flexible non-syn (MTR) | 3   | 0.0084   | 0.0011    | 0.0099| 7.7      | 2.2       | 26.9      | .         | .         | FALSE     |
| CENPU      | Flexible non-syn (MTR) | 3   | 0.0084   | 0.0011    | 0.0099| 7.7      | 2.2       | 26.9      | .         | .         | FALSE     |
| FAM155B    | Flexible non-syn (MTR) | 3   | 0.0084   | 0.0011    | 0.0099| 7.7      | 2.2       | 26.9      | .         | .         | TRUE      |
| GALNT13    | Flexible non-syn (MTR) | 3   | 0.0084   | 0.0011    | 0.0099| 7.7      | 2.2       | 26.9      | .         | .         | FALSE     |
| PAQR8      | Flexible non-syn (MTR) | 3   | 0.0084   | 0.0011    | 0.0099| 7.7      | 2.2       | 26.9      | Yes       | .         | FALSE     |
| STAT6      | Flexible non-syn (MTR) | 3   | 0.0084   | 0.0011    | 0.0099| 7.7      | 2.2       | 26.9      | Yes       | Yes       | FALSE     |
| TCERG1L    | Flexible non-syn (MTR) | 3   | 0.0084   | 0.0011    | 0.0099| 7.7      | 2.2       | 26.9      | .         | .         | FALSE     |
| APPL1      | PTV               | 3        | 0.0084   | 0.0011    | 0.0099| 7.7      | 2.2       | 26.9      | Yes       | .         | FALSE     |
| NMI        | PTV               | 3        | 0.0084   | 0.0011    | 0.0099| 7.7      | 2.2       | 26.9      | Yes       | .         | FALSE     |
| SORBS2     | Ultra-rare damaging | 3     | 0.0084   | 0.0011    | 0.0099| 7.7      | 2.2       | 26.9      | Yes       | Yes       | FALSE     |

**Supplementary Table 6: collapsing analysis results.** Capped at p < 0.01, does not include synonymous model, for each gene, only the model with the lowest p value is shown. LCI = Lower confidence interval (95%), UCI = Upper confidence interval (95%). All associations are enriched in cases. Gene flagged indicates whether the gene is on a list of genes in which variants are reported at a higher frequency than expected across multiple studies (i.e. they
have a higher than expected mutation rate or are prone to false positive variant calls), or they have another human parologue that is at least 90% reciprocally identical and therefore also prone to false positive variant calls due to mismapped reads. These associations should be interpreted with caution.
**Supplementary Table 7**

| Gene   | Variant (GRCh38) | Function          | Transcript   | Transcript codon change | Transcript AA change | Sample(s)   | Case freq | Ctrl freq | GnomAD exome global AF | GnomAD exome popmax AF |
|--------|------------------|-------------------|--------------|-------------------------|----------------------|-------------|-----------|-----------|------------------------|------------------------|
| PKD1   | 16-2090692-G-C   | Stop gained       | ENST00000262304 | c.12120C>G             | p.Tyr4040*          | ScPt0395467Z | 1/357     | 0/13722   | 0                      | 0                      |
| PKD1   | 16-2091576-C-A   | Missense variant  | ENST00000262304 | c.11559G>T             | p.Glu3853Asp        | ScPt0857743D | 1/357     | 0/13722   | 0                      | 0                      |
| PKD1   | 16-2100038-A-G   | Missense variant  | ENST00000262304 | c.9746T>C              | p.Leu3249Pro       | ScPt0410594V | 1/357     | 0/13722   | 0                      | 0                      |
| PKD1   | 16-2107960-G-C   | Missense variant  | ENST00000262304 | c.6988C>G              | p.Leu2330Val       | ScPt0436380H | 1/357     | 0/13722   | 0                      | 0                      |
| PKD1   | 16-2112914-G-A   | Missense variant  | ENST00000262304 | c.3035C>T              | p.Thr1012Ile      | ScPt0795045V | 1/357     | 0/13722   | 0                      | 0                      |
| PKD1   | 16-2106443-CCA-C | Frameshift variant | ENST00000262304 | c.7442_7443delTG       | p.Leu2481fs       | ScPt0150875X | 1/357     | 0/13722   | 0                      | 0                      |
| Gene  | Chromosome | Start | Stop | Type                  | Ensembl ID | Description       | Allele Frequency | Probability   |
|-------|------------|-------|------|-----------------------|------------|-------------------|-----------------|--------------|
| COL3A1| 2-188990117-C-T | Stop gained | ENST00000304636 | c.712C>T | p.Arg238* | ScPt0162409J | 1/357 | 0/13722 | 0 | 0 |
| COL3A1| 2-189001440-C-T | Missense variant | ENST00000304636 | c.2327C>T | p.Pro776Leu | ScPt0792166L | 1/357 | 0/13722 | 0 | 0 |
| COL3A1| 2-189001446-A-G | Missense variant | ENST00000304636 | c.2333A>G | p.Asp778Gly | ScPt0992534F | 1/357 | 0/13722 | 0 | 0 |
| SMAD3 | 15-67170589-G-A | Frameshift variant | ENST00000327367 | c.643G>A | p.Ala215Thr | ScPt0347607Q | 1/357 | 0/13722 | 0 | 0 |
| SMAD3 | 15-67190432-A-AC | Missense variant & splice region | ENST00000327367 | c.1179dupC | p.Cys394fs | ScPt0475518M | 1/357 | 0/13722 | 0 | 0 |
| HES5  | 1-2530113-G-C | variant | ENST00000378453 | c.52C>G | p.Arg18Gly | BPt00065625 | 2/357 | 0/13722 | 0 | 0 |
| DLL1  | 6-170283013-T-C | Missense variant | ENST00000366756 | c.2141A>G | p.Lys714Arg | ScPt0409625H | 1/357 | 0/13722 | 0 | 0 |
| UMOD | 16-20341325-ATGTTTAGAGCAC- | Frameshift variant | ENST00000302509 | c.1332-1_1342delGTGCTCATTAAACA | p.Ala445fs | ScPt0649148D | 1/357 | 0/13722 | 0 | 0 |
|------|-----------------------------|-------------------|-----------------|---------------------------------|-----------|-------------|------|----------|----|----|
| UMOD | 16-20349011-CCTTCGGGGGCAGA- | Protein altering variant | ENST00000302509 | c.278_289delinsCCGCCTCCTCCT | p.Val93_Gly97delinsAlaAlaSerCys | ScPt0300070B | 1/357 | 0/13722 | 0 | 0 |

**Supplementary Table 7: Details of qualifying variants in cases driving selected associations of interest in collapsing analysis and gene-set enrichment analysis.** Qualifying variants in *PKD1* drive signal in collapsing analysis (ultra-rare damaging (MTR) model). Qualifying variants in *PKD1, COL3A1*, and *SMAD3* drive signal in SCAD tier 1 genes in gene-set enrichment analysis (ultra-rare damaging (MTR) model). Qualifying variants in *PKD1, HES5, DLL1*, and *UMOD* drive signal in Loop of Henle development genes in gene-set enrichment analysis (ultra-rare damaging (MTR) model).
### Supplementary Table 8

| Gene Name | Gene Function | Expression | Mouse phenotype | Relevant Literature |
|-----------|---------------|------------|-----------------|---------------------|
| PKD1      | Polycystin-1. Component of the calcium-permeable ion channel | RNA detected in variety of tissues, expression enhanced in the brain. Protein expression enhanced in the urinary system, gastrointestinal tract and reproductive systems. | Range of cardiovascular phenotypes including aortic aneurysm and dissection, abnormal blood vessel morphology and hemorrhage. | Previously implicated in SCAD (39, 46) |
| PAM       | A multifunctional enzyme, which participates in the biosynthesis of neuroendocrine peptides | RNA and protein expression enhanced in heart tissue, detected in variety of tissues | Embryonic lethal with edema. Abnormal artery morphology - thin arterial walls, umbilical vein stenosis and abnormal vitelline vasculature. | Common variant associated with hypertension (166) |
| GLI3    | Transcription factor component of hedgehog signalling pathway. | RNA and protein expression enhanced in the endometrium, but detected in variety of tissues | Abnormal anterior cardinal vein morphology, abnormal pericardium morphology, haemorrhage (166); wide range of musculoskeletal phenotype including polydactyly, abnormal bones morphology and mineralisation, embryonic lethality (167) | Drives angiogenesis during muscle repair (167, 168) |
|---------|---------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| NFATC4  | Transcription factor                                         | Non-tissue-specific                                                                | Cardiac hypertrophy                                                                                                                | Participates in ET-1 induced hypertrophy (169, 170) |
| SEC24B  | Component of COPII vesicles                                   | Non-tissue-specific                                                                | Abnormalities in cardiac outflow tract including transposition of great arteries, ventricular hypoplasia; lethality is observed by E17.5. | NA |

**GLI3**: Transcription factor component of hedgehog signalling pathway. RNA and protein expression enhanced in the endometrium, but detected in variety of tissues. Abnormal anterior cardinal vein morphology, abnormal pericardium morphology, haemorrhage (166); wide range of musculoskeletal phenotype including polydactyly, abnormal bones morphology and mineralisation, embryonic lethality (167). Drives angiogenesis during muscle repair (167, 168).

**NFATC4**: Transcription factor. Non-tissue-specific. Cardiac hypertrophy. Participates in ET-1 induced hypertrophy (169, 170).

**SEC24B**: Component of COPII vesicles. Non-tissue-specific. Abnormalities in cardiac outflow tract including transposition of great arteries, ventricular hypoplasia; lethality is observed by E17.5. NA.
| Gene   | Function                                | Tissue Specificity | Phenotype                                                                 | Disease/Condition                                                                 |
|--------|-----------------------------------------|-------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| HDAC9  | Histone deacetylase                     | Non-tissue-specific | Cardiac hypertrophy.                                                       | Common variant associated with susceptibility to atherosclerotic disease (171, 172) |
| COL18A1| Multiplexin. C-terminal fragment is the  | RNA expression enhanced in the liver, protein expression of low tissue specificity | Abnormal retinal blood vessel morphology, abnormal tricuspid valve morphology, intracranial haemorrhage. | Participates in the development of coronary collateral vessels in coronary heart disease (173) |
| ARNTL  | Regulator of circadian rhythm           | Non-tissue-specific | Vascular smooth muscle hyperplasia, increased vasoconstriction, decreased heart weight.    | Regulates circadian recruitment of leucocytes in veins and arteries (174) Regulates blood pressure via angiotensinogen expression in perivascular adipose tissue (175) |
| Gene | Description | RNA Expression | Protein Expression | Phenotypic Manifestations | Potential Pathologies |
|------|-------------|----------------|-------------------|--------------------------|------------------------|
| **TBX2** | Transcription factor involved in cardiovascular development | Non-tissue-specific | | | Rare variants implicated in DiGeorge-like syndrome (176) and conotruncal heart defects (177). Common variants associated with glomerular filtration rate (178) and blood pressure (179). |
| **SOX9** | Transcription factor involved in male sexual development | RNA expression enhanced in the salivary gland, protein expression non-tissue-specific | | Foetal embryos at E11.5 due to heart failure, thickening of heart valves leaflets and interventricular septum, abnormal organisation of the extracellular matrix at leaflets and pericardial oedema. Heart hypoplasia. Musculoskeletal phenotypes including bone absence and premature bone ossification. | Regulates the expression of transcription factors engaged in heart valve development (180). Reduction of binding to FBLN5 promoter contributes to abdominal aortic aneurysm development (181). |
| **SORBS2** | Possible role in muscle contraction and cytoskeletal remodelling | Enhanced RNA expression in heart muscle and urinary bladder | | Postnatal lethality in the first week of 40-60% of mice, further development normal, increased heart rate. | Down-regulated in intracranial aneurysm (182); Implicated in congenital heart defects (183). |
| COL4A2 | Component of basement membrane. | RNA expression enhanced in the placenta and heart muscle, protein expression non-tissue specific | Abnormalities in cardiovascular system development: including abnormal morphology of veins and arteries, hemorrhage and heart malformations. | rs4773144, associated with coronary artery disease (184, 185), results in lower expression of COL4A2 leading and susceptibility to plaque rupture (186). Mutations reported in brain small vessel disease (187) and susceptibility to intracerebral hemorrhage (188). |

**Supplementary Table 8.** Annotated selected highly-ranked collapsing analysis results listed in Table 4. Expression pattern was annotated based on the Human Protein Atlas and Genotype-Tissue Expression databases. Mouse phenotypes were collected from MGI.
| Gene-Set Name                        | Model          | Qual Cases | Qual Cases PC | Qual Ctrl PC | P value  | P value FDR adj | Genes harbouring QVs (n carriers in enriched group) capped at 10 genes | Total n genes in set |
|-------------------------------------|----------------|------------|---------------|--------------|----------|-----------------|------------------------------------------------------------------------|---------------------|
| SCAD.tier1                          | Ultra-rare damaging (MTR) | 11         | 3.1%          | 68           | 0.5%     | 3.6E-07         | *PKD1(6); COL3A1(3); SMAD3(2)*                                      | 6                   |
| GO LOOP OF HENLE DEVELOPMENT        | Ultra-rare damaging (MTR) | 11         | 3.1%          | 76           | 0.6%     | 0.0000024       | *PKD1(6); HES5(2); UMOD(2); DLL1(1)*                                 | 11                  |
| GO HEME BIOSYNTHETIC PROCESS        | PTV            | 9          | 2.5%          | 56           | 0.4%     | 0.0000034       | *PPOX(2); SLC25A38(2); COX15(1); FECH(1); HMBS(1); IBA57(1); SLC25A39(1)* | 20                  |
| GO POSITIVE REGULATION OF LAMELLIPODIUM | Flexible non-syn (MTR) | 43         | 12%           | 778          | 5.7%     | 0.0000075       | *HDAC4(5); RREBI(5); VIL1(5); WASF2(5); DNM2(4); MTOR(4); SRC(4); FSCN1(3)* | 24                  |
| Section                                      | Type       | P-value | MAF  | Number | Genes                                      |
|----------------------------------------------|------------|---------|------|--------|--------------------------------------------|
| Reactome Membrane Trafficking                | Rare       | 0.0000096 | 0.18 |        | AP4E1(5); PUM1(5); SEC23A(5); SEC24B(5); DNAJC6(4); DNM2(4); IGF2R(4); AP1M2(3); COPB2(3); GAK(3) |
| Genefam 703 Protein phosphatases             | PTV        | 0.000015  | 0.19 |        | PHPT1(3)                                   |
| Go Cytoplasmic Sequestering of Transcription Factor | Ultra-rare | 0.000017  | 0.19 |        | PKD1(6); IL10(1); KEAP1(1); TONSL(1)        |
| Go Ran GTPase Binding                        | Ultra-rare | 0.000026  | 0.27 |        | IPO11(3); IPO7(3); RANBP2(3); XPO4(3); XPO5(2); IPO13(1); IPO4(1); IPO8(1); NUTF2(1); RANBP17(1) |
| Go Tetrapyrrole Biosynthetic Process         | Rare       | 0.00003   | 0.28 |        | FECH(3); SLC25A38(3); ALAS1(2); MMAB(2); PPOX(2); SUCLA2(2); ABCB6(1); COX15(1); HMBS(1); IBA57(1) |
| Go Lymph Vessel Morphogenesis                | Ultra-rare | 0.000035  | 0.28 |        | PKD1(6); FLT4(2); ACVR2B(1)                |
| Go Response to Amino Acid                   | Flexible   | 0.000042  | 0.28 |        | COL4A1(10); COL16A1(9); COL5A2(8); CPS1(8); |
| GO                                | Gene Numbers | P-Value | q-Value | Ovule Development Function |
|----------------------------------|--------------|---------|---------|---------------------------|
| GO LIPASE INHIBITOR ACTIVITY     | PTV or rare  | 16      | 4.5%    | HMGCS2; COL1A2            |
|                                  | damaging     |         |         |                           |
|                                  |              | 198     | 1.4%    |                           |
|                                  |              | 0.000043| 0.28    |                           |
|                                  |              |         |         |                           |
| GO PROTEIN EXPORT FROM NUCLEUS   | Ultra-rare   | 15      | 4.2%    | PKD1; STYX; XPO5; AHCYL1  |
|                                  | damaging     |         |         |                           |
|                                  |              | 157     | 1.1%    |                           |
|                                  |              | 0.000044| 0.28    |                           |
|                                  |              |         |         |                           |
| GO CHONDROITIN SULFATE BIOSYNTHETIC PROCESS | Flexible non-syn | 52      | 14.6%   | VCAN; CSPG4; CHPF2; NCAN; XYLTI; CHSY1; CHPF; CSGALNACT1; BCAN; CHSY3 |
|                                  |              |         |         |                           |
|                                  |              | 3053    | 22.2%   |                           |
|                                  |              | 0.000048| 0.28    |                           |
|                                  |              |         |         |                           |
| GO METANEPHRIC EPITHELIUM DEVELOPMENT | Ultra-rare  | 11      | 3.1%    | PKD1; HESS; UMOD; WNT9B   |
|                                  | damaging     |         |         |                           |
|                                  |              | 92      | 0.7%    |                           |
|                                  |              | 0.000054| 0.28    |                           |
|                                  |              |         |         |                           |
| GO CELLULAR RESPONSE TO AMINO ACID STIMULUS | Flexible  | 90      | 25.2%   | COL4A1; COL16A1; COL5A2  |
|                                  | damaging     |         |         |                           |
|                                  |              | 2189    | 16%     |                           |
|                                  |              | 0.000066| 0.31    |                           |
|                                  |              |         |         |                           |

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| Genefam 1473 Clarins | Ultra-rare damaging | 5 | 1.4% | 21 | 0.2% | 0.000069 | 0.31 | CLRN3(3); CLRN1(1); CLRN2(1) |
|----------------------|---------------------|---|------|-----|------|----------|-----|--------------------------|
| MODULE 159           | Recessive           | 5 | 1.4% | 37 | 0.3% | 0.000085 | 0.33 | AARS(1); ARF4(1); GTPBP6(1); KARS(1); NOLC1(1); RRAGA(1) |
| Genefam 1174 Lysozymes c-type | Flexible damaging | 5 | 1.4% | 29 | 0.2% | 0.000087 | 0.33 | LYZ(2); SPACA3(2); LYZL4(1) |
| GO N METHYLTRANSFERASE ACTIVITY | Recessive | 12 | 3.4% | 131 | 1% | 0.000089 | 0.33 | SETD2(4); ASH1L(1); DOT1L(1); FDXACB1(1); NSD1(1); PRDM16(1); PRDM2(1); SETD1A(1); WDR77(1) |
| GO PLACENTA BLOOD VESSEL DEVELOPMENT | Ultra-rare damaging (MTR) | 11 | 3.1% | 108 | 0.8% | 0.000094 | 0.33 | PKD1(6); ESXI(2); PLCD3(2); HEY2(1) |
| GO REGULATION OF SPINDLE ORGANIZATION | PTV or rare damaging | 25 | 7% | 408 | 3% | 0.000094 | 0.33 | PKD1(13); CHMP2A(2); BORA(1); CHMP1B(1); CHMP2B(1); CHMP4C(1); PDCD6IP(1); PLK1(1); RNF4(1); SENP6(1) |
| BIOCARTA CALCINEURIN PATHWAY | Rare damaging | 13 | 3.6% | 138 | 1% | 0.000098 | 0.33 | NFATC3(2); NFATC4(2); PLCG1(2); PPP3CC(2); CDKN1A(1); GNAQ(1); NFATC1(1); NFATC2(1); |

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| Phenotype                                      | Gene Family | Genefam ID | MIM ID | OMIM ID | No. of</br>Patients | % of</br>Patients | p-Value | No. of</br>Genes | Genes                                                                 |
|-----------------------------------------------|-------------|------------|--------|---------|---------------------|-----------------|---------|-------------------|-------------------------------------------------|
| REACTOME CHONDROITIN SULFATE BIOSYNTHESIS     | (MTR)       |            |        |         |                     |                 |         |                   | VCAN(471); CSPG4(447); CHPF2(285); NCAN(241); CHSY1(175); CHPF(152); CSGALNACT1(144); BCAN(141); CHSY3(139); CHST15(131) |
| Flexible non-syn                             | 42          | 11.8%      | 2591   | 18.9%   | 0.00013             | 0.39            | 21      |                   |                                                 |
| GO IGG BINDING                                | Ultra-rare  | 5          | 1.4%   | 19      | 0.1%                | 0.00015         | 12      | FCGRT(2); UMOD(2); FCER1G(1) |
| (MTR)                                         |             |            |        |         |                     |                 |         |                   |                                                 |
| GO NEURON PROJECTION MEMBRANE                 | PTV         | 10         | 2.8%   | 102     | 0.7%                | 0.00015         | 36      | TRPV1(1)          |                                                 |
| Rare damaging                                 | 28          | 7.8%       | 477    | 3.5%    | 0.00018             | 0.48            | 15      | BAIAP3(8); SYNJ1(4); CCL3(3); COPB2(3); SLC1A3(3); CADPS(2); GABRA2(2); ABAT(1); GAD1(1); SNAP25(1) |
| MODULE 563                                    |             |            |        |         |                     |                 |         |                   |                                                 |
| Genefam 1487 CAP and C-type lectin domain    | Flexible non-syn (MTR) | 2 | 0.6% | 1 | 0% | 0.00019 | 0.48 | CLEC18A(1); CLEC18B(1) |
| containing                                     |             |            |        |         |                     |                 |         |                   |                                                 |
| Genefam 747 Signal regulatory                 | Recessive   | 3          | 0.8%   | 10      | 0.1%                | 0.00021         | 6       | SIRPBI(2); SIRPB2(1) |

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| GO Term                                      | Type       | p-value | q-value | FDR   | Fold Changes |
|----------------------------------------------|------------|---------|---------|-------|--------------|
| Proteins                                     |            |         |         |       |              |
| GO CHONDROITIN SULFATE                       | Flexible   | 0.00022 | 0.49    | 0.00022 |              |
| PROTEOGLYCAN BIOSYNTHETIC PROCESS            | non-syn    | 0.00022 | 0.49    | 0.00022 |              |
| GO FERROUS IRON BINDING                      | Ultra-rare | 0.00023 | 0.49    | 0.00023 |              |
| GO NUCLEAR INCLUSION BODY                    | Recessive  | 0.00024 | 0.49    | 0.00024 |              |
| GO PROTEIN METHYLTRANSFERASE ACTIVITY        | Recessive  | 0.00024 | 0.49    | 0.00024 |              |
| GO REGULATION OF CALCIUM ION TRANSPORT INTO CYTOSOL| Flexible | 0.00025 | 0.49    | 0.00025 |              |
| Genefam 1468 Glutaredoxin domain containing  | Flexible   | 0.00026 | 0.49    | 0.00026 |              |
| GO CARBOHYDRATE BINDING                      | Flexible   | 0.00026 | 0.49    | 0.00026 |              |

VCAN(471); CSPG4(447); CHPF2(285); NCAN(241); XYLT1(193); CHSY1(175); CHPF(152); CSGALNACT1(144); BCAN(141); CHSY3(139); TH(3); FECH(2); HEPH(2); TET2(2); ALKBH3(1); CDO1(1); DNAJC24(1); PLOD1(1); SETD2(4); ASH1L(1); DOT1L(1); NSD1(1); PRDM16(1); PRDM2(1); SETD1A(1); WDR77(1); RYR2(508); HTT(252); CAPN3(214); ANK2(209); DMD(195); CACNA1C(159); PTK2B(135); PRKD1(115); NOS1(103); DIAPH1(102); GRXCR2(7); TXNRD1(7); GLRX2(4); GRXCR1(2); TXNRD3(2); GLRX3(1); PTGES2(1); PKD1(39); SIGLEC1(16); SI(14); FREM1(13);
| GO Term | Synonym | PTV or Rare Damaging | GeneID | Fold Change | FDR | Subcellular Localization | Prognostic Status |
|---------|---------|---------------------|--------|-------------|-----|--------------------------|------------------|
| **GO POSITIVE REGULATION OF CYCLIN DEPENDENT PROTEIN KINASE ACTIVITY** | syn | 35 | 9.8% | 671 | 4.9% | 0.00027 | 0.49 |
| | PKD1L3(13); MGAM(12); ACAN(11); PAM(11); PLA2R1(11); PRG4(11) | | | | | | |
| | PKD1(13); EGFR(3); SRC(3); STOX1(3); SPDYA(2); ADAM17(1); CCND2(1); CCNH(1); CCNT1(1); CDC6(1) | | | | | | |
| **GO RESPONSE TO OXYGEN LEVELS** | Flexible non-syn | 317 | 88.8% | 11535 | 84.1% | 0.00027 | 0.49 |
| | RYRI(21); ATM(16); ITPRI(12); NOS2(12); RYR2(12); PAM(11); COLIA1(10); HIF3A(10); PDGFRB(10); ALDH3A1(9) | | | | | | |
| **GO AXOLEmma** | PTV | 5 | 1.4% | 31 | 0.2% | 0.0003 | 0.51 |
| | MYO1D(2); ANK1(1); CNTNAP2(1); NRG1(1) | | | | | | |
| **MODULE 352** | Recessive | 5 | 1.4% | 28 | 0.2% | 0.0003 | 0.51 |
| | RANBP2(4); TPR(1) | | | | | | |
| **GO LYSOZYME ACTIVITY** | Flexible damaging | 9 | 2.5% | 96 | 0.7% | 0.0003 | 0.51 |
| | LYG2(3); LYZ(2); SPACA3(2); LYG1(1); LYZL4(1) | | | | | | |
| **GeneFam 1453 Condensin II** | Flexible non-syn (MTR) | 11 | 3.1% | 149 | 1.1% | 0.00031 | 0.51 |
| | NCAPD3(5); NCAPH2(4); SMC2(2); SMC4(1) | | | | | | |
| **ST GA12 PATHWAY** | Flexible non-syn | 73 | 20.4% | 1850 | 13.5% | 0.00032 | 0.51 |
| | PLD2(10); PLD1(9); RASAL1(8); EPHB2(7); PLD3(6); VAV1(5); F2(4); F2RL1(4); F2RL3(4); PTK2(4) | | | | | | |
| **Reactive SCFSKP2 Mediated Degradation of P27 P21** | Recessive | 4 | 1.1% | 21 | 0.2% | 0.00033 | 0.51 | CDKN1B(1); PSMB4(1); PSMF1(1); SKP2(1) | 56 |
| **GO Retinal Metabolic Process** | Flexible non-syn (MTR) | 18 | 5% | 256 | 1.9% | 0.00034 | 0.51 | CYP1B1(9); AKR1C3(3); AKR1C1(2); ALDH1A3(1); ALDH8A1(1); RPE65(1); SDR16C5(1) | 12 |
| **CTCTGGA MIR520A MIR525** | Flexible non-syn | 260 | 72.8% | 8745 | 63.7% | 0.00034 | 0.51 | BSN(22); THADA(18); NCOR2(17); NUMA1(17); CGN(13); DCHS1(13); SMG1(13); TSHZ1(10); ATRN(9); RAB11FIP1(9) | 158 |
| **GO Lymph Vessel Development** | Ultra-rare damaging (MTR) | 11 | 3.1% | 113 | 0.8% | 0.00036 | 0.51 | PKD1(6); FLT4(2); ACVR2B(1); FOXC1(1); HEGI(1) | 20 |
| **Reactive Innate Immune System** | Flexible damaging | 136 | 38.1% | 5946 | 43.3% | 0.00036 | 0.51 | CREBBP(262); EP300(219); NOD2(158); IFIHI(149); CR1(142); MASP1(136); NOD1(134); NLRX1(133); C3(123); CTSB(121) | 279 |
| **Genefam 1221 H/ACA Ribonucleoprotein Complex** | Rare damaging (MTR) | 4 | 1.1% | 19 | 0.1% | 0.00038 | 0.52 | DKC1(1); GAR1(1); NHP2(1); NOP10(1) | 4 |
| **GO DNA Methylation OR** | Ultra-rare | 26 | 7.3% | 454 | 3.3% | 0.00038 | 0.52 | EHMT2(3); MOV10LI(3); TRDMT1(3); ATRX(2) | 59 |
| DEMETHYLATION | damaging | BAZ2A(2); TET2(2); ALKBH3(1); ASZ1(1); DMAP1(1); DNMT3A(1) |
|---------------|----------|--------------------------------------------------|
| **DEPENDE** | Flexible non-syn | DNAH6(30); DNAH7(29); DNAH2(28); DNAH3(28); DNAH1(25); DNAH8(23); SPAG16(6); CCDC39(5); DNAAF2(4); RSPH9(4) |
| **CIL** | PTV | ADORA2B(2); MTNR1A(2); NOS2(2); GUCA1B(1); NOS3(1); PDZD3(1) |
| **T** | Rare | ARRDC1(4); ARRDC4(3); ARRDC2(2); ARRDC3(1) |
| **GO Genefam 1311 Alpha arrestins** | Flexible | PLEC(22); BAIAP3(11); COL6A2(11); COL6A3(11); ITPR3(11); COL4A1(10); ITPR1(10); PPL(10); VWF(10); LAMA3(9) |
| **ARR** | 314 | SOX9(3); FSCN1(2); SMAD3(2); TGFβ2(2); CPB2(1) |
| **ON** | 10 | GLI3(3); CYLD(2); JAK3(2); PGLYRP3(2); DTX1(1); ERBB2(1); FBXO7(1); HLX(1); IHH(1); |
| Term                                                                 | Gene ID | MTR | Benjamini-Hochberg Corrected P-Value | Score | Fisher's Exact Test p-value |
|---------------------------------------------------------------------|---------|-----|-------------------------------------|-------|----------------------------|
| DIFFERENTIATION                                                      |         |     |                                     |       |                            |
| GO POSITIVE REGULATION OF LAMELLIPODIUM ASSEMBLY                     | Flexible non-syn (MTR) | 28  | 7.8%                                | 488   | 3.6%                       | 0.00042 | 0.52 | INHBA(1) |
|                                                                     |         |     |                                     |       |                            |
| GO POSITIVE REGULATION OF VASOCONSTRICTION                          | Recessive | 6   | 1.7%                                | 45    | 0.3%                       | 0.00043 | 0.52 | AVPR2(1); CD38(1); DBH(1); FGG(1); TBXA2R(1); TRPM4(1) |
| REACTOME GOLGI ASSOCIATED VESICLE BIOGENESIS                        | Rare damaging | 50  | 14%                                 | 1132  | 8.2%                       | 0.00044 | 0.52 | AP4E1(5); PUM1(5); DNAJC6(4); DNM2(4); IGF2R(4); AP1M2(3); GAK(3); TFRC(3); AP1B1(2); ARRB1(2) |
| REACTOME METABOLISM OF PORPHYRINS                                   | PTV     | 5   | 1.4%                                | 29    | 0.2%                       | 0.00045 | 0.52 | PPOX(2); BLVRB(1); FECH(1); HMBS(1) |
| MODULE 169                                                          | Ultra-rare damaging (MTR) | 28  | 7.8%                                | 443   | 3.2%                       | 0.00045 | 0.52 | MICAL2(3); CCL3(2); RGL3(2); SLC2A5(2); ABCC1(1); CACNA1A(1); CCL4(1); CR2(1); CREG1(1); CYBB(1) |
| GO REGULATION OF MRNA 3 END PROCESSING                              | Ultra-rare damaging | 14  | 3.9%                                | 183   | 1.3%                       | 0.00047 | 0.53 | CCNB1(3); AHCYL1(2); CNOT1(2); BARD1(1); CCNT1(1); CDC73(1); NCBP2(1); PAF1(1); RNF20(1); SUPT5H(1) |
| GO Category                        | Gene Name   | Total | RQ | Total | RQ | p-value | q-value |
|-----------------------------------|-------------|-------|----|-------|----|---------|---------|
| GO RNA SPLICING VIA ENDONUCLEOLYTIC CLEAVAGE AND LIGATION | Flexible non-syn | 42 | 11.8% | 850 | 6.2% | 0.00047 | 0.53 |
|  | CPSF1(12); DDX1(4); ERN1(4); ZBTB8OS(4); CLP1(3); TRPT1(3); TSEN2(3); TSEN54(3); CSTF2(2); TSEN34(2) | 16 |
| Genefam 857 Potassium calcium-activated channel subfamily M regulatory beta subunits | Flexible non-syn (MTR) | 6 | 1.7% | 48 | 0.3% | 0.00048 | 0.53 |
|  | KCNMB4(3); KCNMB1(1); KCNMB2(1); KCNMB3(1) | 4 |
| Genefam 663 N-terminal EF-hand calcium binding proteins | Flexible damaging | 10 | 2.8% | 109 | 0.8% | 0.00048 | 0.53 |
|  | NECAB2(9); NECAB3(1) | 3 |
| GO INTRAS DNA DAMAGE CHECKPOINT | Ultra-rare damaging | 9 | 2.5% | 86 | 0.6% | 0.00049 | 0.53 |
|  | MSH2(4); HUS1(2); MDC1(2); XPC(1) | 12 |
| GO REGULATION OF MUSCLE CONTRACTION | Flexible non-syn | 212 | 59.4% | 8814 | 64.2% | 0.0005 | 0.53 |
|  | RYR2(568); ANK2(514); DMD(514); SCN10A(482); DSP(431); PLCE1(304); SCN5A(289); DOCK5(276); MYBPC3(272); ACTN3(261) | 147 |
| GO RENAL SYSTEM PROCESS | Rare damaging (MTR) | 17 | 4.8% | 1306 | 9.5% | 0.00051 | 0.53 |
|  | KCNMA1(60); WFS1(54); KCNQ1(41); PCSK5(37); ADCY4(36); SLC4A5(36); ADCY5(30); HNF1A(32); ADCY7(31); SULF2(30) | 102 |
| KEGG CYSTEINE AND | Ultra-rare | 18 | 5% | 281 | 2% | 0.00051 | 0.53 |
|  | TRDMT1(3); AHCY(2); AHCYLI(2); ADI1(1); | 34 |
| Condition                                | Type         | Gene Count | P Value | q Value | Gene List                                                                                       |
|------------------------------------------|--------------|------------|---------|---------|-----------------------------------------------------------------------------------------------|
| **METHIONINE METABOLISM**                | damaging     | 4          | 0.00051 | 0.53    | CDO1(1); DNMT3A(1); DNMT3B(1); DNMT3L(1); GOT1(1); GOT2(1)                                    |
| **GO LYSINE N M ETHYLTRANSFERASE ACTIVITY** | Rare         | 53         | 14.8%   | 8.6%    | ASH1L(6); EHMT2(5); NSD1(5); SETD1A(5); IRF4(3); PRDM2(3); PRDM6(3); SETD2(3); EZH2(2); MEN1(2) |
|                                           | damaging     | 53         | 14.8%   | 8.6%    | IRF4(3); PRDM2(3); PRDM6(3); SETD2(3); EZH2(2); MEN1(2)                                        |
| **MODULE 440**                           | Ultra-rare   | 14         | 3.9%    | 1.3%    | CPS1(3); GAMT(2); PYCR1(2); ACY1(1); ARG1(1); ASS1(1); CKM(1); CKMT1B(1); DIO1(1); OAT(1)     |
|                                           | damaging     | 53         | 14.8%   | 8.6%    | ASS1(1); CKM(1); CKMT1B(1); DIO1(1); OAT(1)                                                  |
| **GO POSITIVE REGULATION OF CHROMOSOME SEGREGATION** | Rare         | 20         | 5.6%    | 2.3%    | CCNB1(3); RB1(3); RCC2(3); SIRT2(3); SMC6(3); CDC6(1); ESPL1(1); GORASP1(1); PLK1(1); SMC5(1) |
|                                           | damaging     | 53         | 14.8%   | 8.6%    | CCNB1(3); RB1(3); RCC2(3); SIRT2(3); SMC6(3); CDC6(1); ESPL1(1); GORASP1(1); PLK1(1); SMC5(1) |
| **REACTOME CYCLIN E ASSOCIATED EVENTS DURING G1 S TRANSITION** | Recessive   | 4          | 1.1%    | 0.2%    | CDKN1B(1); PSMB4(1); PSMF1(1); SKP2(1)                                                        |
| **GO REGULATION OF BONE DEVELOPMENT**    | PTV          | 8          | 2.2%    | 0.5%    | GLI3(2); LTF(2); TJP2(2); POR(1); SLC9B2(1)                                                  |
|                                           | Ultra-rare   | 43         | 12%     | 6.4%    | SEC24B(4); AP3D1(3); AP3M2(3); AP4E1(3); AP1B1(2); AP1M2(2); EGFR(2); IGF2R(2);               |
|                                           | damaging     | 53         | 14.8%   | 8.6%    | SEC24B(4); AP3D1(3); AP3M2(3); AP4E1(3); AP1B1(2); AP1M2(2); EGFR(2); IGF2R(2);               |
| Condition                                | Gene Expression | P-Value | AOD | Z-score | NM | Annotation Details |
|------------------------------------------|-----------------|---------|-----|---------|----|--------------------|
| WTGAAAT UNKNOWN                          | Ultra-rare      | 160     | 44.8% | 6532    | 0.00058 | SEC23A(2); SEC24C(2); ZFHX3(127); SYNE1(106); DST(75); LAMA5(71); CSMD3(68); ITPR3(64); COL7A1(62); NBEAL1(60); ANK2(56); MYH3(53) |
| GO BLOC 1 COMPLEX                        | Rare            | 8       | 2.2% | 79      | 0.00059 | BCAS4(2); PI4K2A(2); BLOC1S1(1); DTPB1(1); SNAP25(1); SNAP47(1) |
| MODULE 539                                | PTV             | 7       | 2%   | 62      | 0.00061 | PPOX(2); CP(1); FECH(1); GYPA(1); GYPC(1); HMBS(1) |
| GO NERVE DEVELOPMENT                      | Flexible        | 121     | 33.9% | 3417    | 0.00062 | UNC13B(8); ERBB3(7); AFG3L2(6); ATP8B1(6); NAV2(6); NRP1(6); SULF1(6); CHRN2(5); GLI3(5); PLXNA3(5) |
| GO POSITIVE REGULATION OF MRNA 3 END PROCESSING | Ultra-rare     | 7       | 2%   | 55      | 0.00065 | CNOT1(2); CCNB1(1); CDC73(1); NCBP2(1); PAF1(1); TNRC6C(1) |
| GO HISTONE LYSINE N METHYLTRANSFERASE ACTIVITY | Recessive    | 10      | 2.8% | 113     | 0.00065 | SETD2(4); ASH1L(1); DOT1L(1); NSD1(1); PRDM16(1); PRDM2(1); SETD1A(1) |
| GO Category                      | Type of Alteration | P-value | Fold Change | Impact | Functional Terms                                                                                     | Count |
|----------------------------------|--------------------|---------|-------------|--------|-----------------------------------------------------------------------------------------------------|-------|
| GO DNA ALKYLATION                | Ultra-rare damaging | 0.00065 | 0.57        | 23     | EHMT2(3); MOV10L1(3); TRD1(3); ATRX(2); BAZ2A(2); ASZ1(1); DMAP1(1); DNMT3A(1); DNMT3B(1); DNMT3L(1) | 45    |
| GO TRANSCYTOSIS                  | Ultra-rare damaging | 0.00067 | 0.57        | 7      | FCGRT(2); TG(2); USO1(2); SRC(1)                                                                     | 11    |
| GO RETINOL METABOLIC PROCESS     | Flexible non-syn (MTR) | 0.00067 | 0.57        | 34     | CYP1B1(9); AKR1C3(3); DHRS3(3); PLB1(3); RDH12(3); RETSAT(3); AWAT2(2); DGAT1(2); DGAT2(2); RDH13(2) | 29    |
| GO REGULATION OF PODOSOME ASSEMBLY | PTV or rare damaging | 0.00069 | 0.57        | 19     | KIF9(3); MAPK9(3); SRC(3); BLK(2); FSCN1(2); HCK(2); LCP1(2); ARHGEF5(1); CAPG(1); GSN(1)          | 14    |
| GO CCR CHEMOKINE RECEPTOR BINDING | Rare damaging (MTR)  | 0.00071 | 0.59        | 9      | CCL3(3); CCL17(2); CCL4(1); CCR2(1); CX3CL1(1); JAK1(1)                                             | 35    |
| GO PEPTIDYL LYSINE DIMETHYLATION | Recessive           | 0.00073 | 0.59        | 5      | SETD2(4); ASHIL(1)                                                                                 | 12    |
| GO PURINE NUCLEOTIDE             | Flexible non-syn    | 0.00073 | 0.59        | 38     | ABC11(11); SLC35B3(8); CALHM1(5)                                                                    | 11    |
| Category                                      | Description                          | Gene ID(s)                  | Allele Type | N  | %   | Fold | p-Value | Effect |
|-----------------------------------------------|---------------------------------------|-----------------------------|-------------|----|------|------|---------|--------|
| TRANSPORT                                     | syn                                   |                             |             |    |      |      |         |        |
| GO MEMBRANE                                   | Ultra-rare damaging                   | SLC25A23, SLC25A6, SLC25A24, SLC35B2, GJA1, GJB1, SLC25A17 |             |    |      |      |         |        |
| HYPERPOLARIZATION                             | Ultra-rare damaging                   | CFTR, KCNQ3, KCNA5, PRKCZ  |             |    |      |      |         |        |
| REACTOME CELL SURFACE                        | Rare damaging                         | SLC16A3, SRC, CD48, FN1, ITGAM |             |    |      |      |         |        |
| INTERACTIONS AT THE VASCULAR WALL             | Rare                                  | OLRI, PLCG1, PPIL2, SLC7A5  |             |    |      |      |         |        |
| VASCULAR WALL (MTR)                           | Rare                                  | COL1A1                      |             |    |      |      |         |        |
| Genefam 1377 Haloacid dehalogenase             | PTV or rare damaging                  | LHPP, HDHD2, NANP, HDHD3    |             |    |      |      |         |        |
| like hydrolase domain containing              |                                       | HDHD5                       |             |    |      |      |         |        |
| PID INTEGRIN5 PATHWAY                         | Recessive                             | FBN1, FN1, ITGA4, ITGB7     |             |    |      |      |         |        |
| GO NEGATIVE REGULATION OF IMMUNE RESPONSE     | Recessive                             | COL3A1, MASP1, CR1, FOXF1   |             |    |      |      |         |        |
| GENFAM 662 NBPF members                       | Recessive                             | IL1RL1, IRAK3, JAK3, NMI    |             |    |      |      |         |        |
| GO REGULATION OF HISTONE METHYLATION          | Recessive                             | MTHFR, BCOR, TET1, BRCA1    |             |    |      |      |         |        |
| GENFAM 11202180301                            | Recessive                             | JARID2, KDM4A, NSD1, RNF20  |             |    |      |      |         |        |
| AAAGGAT MIR501                                | Recessive                             | CELSR2, WDFY3, ALS2, ATP6V1H |             |    |      |      |         |        |
| Gene Family | Type | Mutations | MAF | HWE p-value | Frequency of Disease | Associated Genes |
|-------------|------|-----------|-----|-------------|---------------------|------------------|
| CAMTA1(1); KIF1C(1); PHC1(1); SCN3A(1); SYNC(1); ZIC4(1) | | | | | | |
| Genefam 89 Zinc fingers RANBP2-type | Recessive | 6 | 1.7% | 0.00091 | 0.6 | RANBP2(4); ZRANB1(1); ZRANB2(1) |
| SIRNA EIF4GI UP | | 24 | 6.7% | 0.00091 | 0.6 | THADA(3); LAP3(2); MAGEF1(2); NCAPD2(2); PYGL(2); ASAHI1(1); ASS1(1); CORO1B(1); ECI1(1); FCAR(1) |
| SIRNA EIF4GI UP | PTV | 24 | 6.7% | 0.00091 | 0.6 | THADA(3); LAP3(2); MAGEF1(2); NCAPD2(2); PYGL(2); ASAHI1(1); ASS1(1); CORO1B(1); ECI1(1); FCAR(1) |
| GO NEPHRON TUBULE FORMATION | Flexible non-syn | 36 | 10.1% | 0.00091 | 0.6 | PAX8(5); WNT9B(5); SOX8(4); HNF1B(3); OSR1(3); PAX2(3); SIX1(3); SOX9(3); GREM1(2); HES5(2) |
| GO NEPHRON TUBULE FORMATION | | 36 | 10.1% | 0.00091 | 0.6 | PAX8(5); WNT9B(5); SOX8(4); HNF1B(3); OSR1(3); PAX2(3); SIX1(3); SOX9(3); GREM1(2); HES5(2) |
| REACTOME TRANS GOLGI NETWORK VESICLE BUDDING | Rare damaging | 54 | 15.1% | 0.00091 | 0.6 | AP4E1(5); PUM1(5); DNAJC6(4); DNMI2(4); AP4E1(5); PUM1(5); DNAJC6(4); DNMI2(4); IGF2R(4); AP1M2(3); GAK(3); TFRC(3); AP1B1(2); ARRB1(2) |
| REACTOME TRANS GOLGI NETWORK VESICLE BUDDING | | 54 | 15.1% | 0.00091 | 0.6 | AP4E1(5); PUM1(5); DNAJC6(4); DNMI2(4); AP4E1(5); PUM1(5); DNAJC6(4); DNMI2(4); IGF2R(4); AP1M2(3); GAK(3); TFRC(3); AP1B1(2); ARRB1(2) |
| NFKAPPA 01 | Flexible non-syn (MTR) | 169 | 47.3% | 0.00095 | 0.6 | ASH1L(5); NLK(5); UBE4B(5); BMP2K(4); ERN1(4); NFA5T(4); NIPBL(4); PRX(4); STON2(4); UACA(4) |
| NFKAPPA 01 | | 169 | 47.3% | 0.00095 | 0.6 | ASH1L(5); NLK(5); UBE4B(5); BMP2K(4); ERN1(4); NFA5T(4); NIPBL(4); PRX(4); STON2(4); UACA(4) |
| PID RANBP2 PATHWAY | Recessive | 4 | 1.1% | 0.00096 | 0.6 | RANBP2(4) |
| GO MRNA SPlice SITE SELECTION | PTV or rare damaging | 27 | 7.6% | 493 | 3.6% | 0.00097 | 0.6 | SETX(8); NOL3(5); RBMXL1(5); SF3A1(2); SFSWAP(2); ISY1(1); LUC7L2(1); LUC7L3(1); PRPF39(1); SF1(1) |
|-------------------------------|---------------------|----|------|----|------|---------|-----|--------------------------------------------------|
| GO NEGATIVE REGULATION OF HEMOPOIESIS | Ultra-rare damaging | 41 | 11.5% | 831 | 6.1% | 0.00097 | 0.6 | GLI3(3); CCL3(2); CYLD(2); HES5(2); JAK3(2); LTF(2); NOTCH1(2); PGLYRP3(2); TJP2(2); CDC73(1) |
| BIOCARTA AHSP PATHWAY | Recessive | 2 | 0.6% | 4 | 0% | 0.00098 | 0.61 | ALAS2(1); FECH(1) |
| GO HISTONE METHYLTRANSFERASE ACTIVITY | Recessive | 10 | 2.8% | 119 | 0.9% | 0.001 | 0.63 | SETD2(4); ASH1L(1); DOT1L(1); NSD1(1); PRDM16(1); PRDM2(1); SETD1A(1) |
| GO RESPONSE TO DRUG | Flexible non-syn | 337 | 94.4% | 12729 | 92.8% | 0.001 | 0.63 | COL18A1(18); CENPF(17); NPC1L1(15); APC(14); MCM7(12); NOS2(12); ATR(11); PAM(11); SCN11A(11); CAD(10) |

**Supplementary Table 9: Gene-Set Enrichment Analysis (Megagene) Results.** Capped at p < 0.001, for each gene, only the model with the lowest p value is shown.
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Supplementary Appendix: Author Contributions

K.C., S.P., J.A., C.H., N.S. N. B. and D.A. conceived of and designed the study; A.B., T.W., S.H., D.P., A.A., A.W., N.S., and D.A. acquired and processed the University of Leicester clinical samples; S.H., S.E.I, I.T., L.M., D.W.M., S.D., D.F., R.M.G., and E.G. acquired and processed the Victor Chang Institute clinical samples; K.C., A.B., J.A., T.W., S.H., and D.A. performed the review of clinical phenotypes among putative molecular diagnoses; K.C.; Q.W., D.V., S.H.L and S.D. performed the bioinformatic processing; K.C. performed the statistical analyses with support from A.B., D.V., and S.P.; K.C., A.B., J.A., T.W., S.P., C.H., and D.A. interpreted the results and drafted the manuscript and all authors critically revised the manuscript for important intellectual content.