Supplementary Table 1. Genes involved in cardiac disorders from the American College of Medical Genetics & Genomics (ACMG) genes (73). These are the (cardiac) genes recommended for reporting of secondary findings of LP/P variants.

|  |  |  |
| --- | --- | --- |
| **Gene** | **Locus** | **Disorder/s (Inheritance)** |
| *KCNQ1* | 11p15.5-p15.4 | Long-QT syndrome type 1 (AD); short QT syndrome type 2 (AD) |
| *KCNH2* | 7q36.1 | Long-QT syndrome type 2 (AD); short QT syndrome type 1 (AD) |
| *SCN5A* | 3p22.2 | Long QT syndrome type 3 (AD); Brugada Syndrome (AD); Dilated Cardiomyopathy (AD) |
| *TRDN* | 6q22.31 | Long QT syndrome (AR); Catecholaminergic polymorphic ventricular tachycardia (AR) |
| *CASQ2* | 1p13.1 | Catecholaminergic polymorphic ventricular tachycardia (AR) |
| *RYR2* | 1q43 | Catecholaminergic polymorphic ventricular tachycardia (AD) |
| *ACTC1* | 15q14 | Hypertrophic cardiomyopathy (AD) |
| *MYBPC3* | 11p11.2 | Hypertrophic cardiomyopathy (AD) |
| *MYH7* | 14q11.2 | Hypertrophic cardiomyopathy (AD) |
| *MYL2* | 12q24.11 | Hypertrophic cardiomyopathy (AD) |
| *MYL3* | 3p21.31 | Hypertrophic cardiomyopathy (AD) |
| *PRKAG2* | 7q36.1 | Hypertrophic cardiomyopathy (AD) |
| *TNNI3* | 19q13.42 | Hypertrophic cardiomyopathy (AD) |
| *TNNT2* | 1q32.1 | Hypertrophic cardiomyopathy (AD) |
| *TPM1* | 15q22.2 | Hypertrophic cardiomyopathy (AD) |
| *DSP* | 6p24.3 | Dilated cardiomyopathy (AD); Arrhythmogenic right ventricular cardiomyopathy (AD) |
| *FLNC* | 7q32.1 | Dilated cardiomyopathy (AD) |
| *LMNA* | 1q22 | Dilated cardiomyopathy (AD) |
| *MYH7* | 14q11.2 | Dilated cardiomyopathy (AD) |
| *SCN5A* | 3p22.2 | Dilated cardiomyopathy (AD) |
| *TNNT2* | 1q32.1 | Dilated cardiomyopathy (AD) |
| *TTN* | 2q31.2 | Dilated cardiomyopathy (truncating variants only) (AD) |
| *DSC2* | 18q12.1 | Arrhythmogenic right ventricular cardiomyopathy (AD) |
| *DSG2* | 18q12.1 | Arrhythmogenic right ventricular cardiomyopathy (AD) |
| *PKP2* | 12p11.21 | Arrhythmogenic right ventricular cardiomyopathy (AD) |
| *TMEM43* | 3p25.1 | Arrhythmogenic right ventricular cardiomyopathy (AD) |
| *GAA* | 17q25.3 | Pompe disease (AR) |
| *GLA* | Xq22.1 | Fabry disease (XL) |

Supplementary Table 2. Schwartz scoring system for the diagnosis of Long QT syndrome (1)

|  |  |
| --- | --- |
| **Criteria** | **Points** |
| Electrocardiographic findingsa | |
| QTca | |
| ≥480 ms | 3 |
| 460–479 ms | 2 |
| 450–459 (male) ms | 1 |
| QTcb 4th minute of recovery from exercise stress test ≥480 ms | 1 |
| Torsade de pointesc | 2 |
| T-wave alternans | 1 |
| Notched T-wave in three leads | 1 |
| Low heart rate for aged | 0.5 |
| Clinical history | |
| Syncopec | |
| With stress | 2 |
| Without stress | 1 |
| Congenital deafness | 0.5 |
| Family history | |
| Family members with definite LQTSe | 1 |
| Unexplained sudden cardiac death below age 30 among immediate family memberse | 0.5 |

LQTS SCORE: ≤1 point: low probability of LQTS. 1.5 to 3 points: intermediate probability of LQTS. ≥3.5 points high probability.

a In the absence of medications or disorders known to affect these electrocardiographic features.

b QTc calculated by Bazett’s formula where QTc. QT/SQR(RR).

c Mutually exclusive.

d Resting heart rate below the 2nd percentile for age.

e The same family member cannot be counted in A and B

Supplementary Table 3. Genes previously reported to be involved in Long QT syndrome (LQTS) (genes with limited or disputed evidence)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Gene** | **Locus** | **Syndrome** | **Protein (Functional Effect)** | **Frequency** | **ClinGen**  **Classification** |
| *ANKB* | 4q25-q27 | LQTS | NaV1.5 (↑) | <1% | Disputed |
| *CAV3* | 3p25 | LQTS | NaV1.5 (↑) | <1% | Limited |
| *SCN4B* | 11q23.3 | LQTS | NaV1.5 (↑) | <1% | Disputed |
| *AKAP9* | 7q21-q22 | LQTS | Ik (↓) | <1% | Disputed |
| *SNTA1* | 20q11.2 | LQTS | NaV1.5 (↑) | <1% | Disputed |
| *KCNJ5* | 11q24 | LQTS | Kir3.4 (↓) | <1% | Disputed |

Supplementary Table 4. Diagnostic score cards for the diagnosis of catecholaminergic polymorphic ventricular tachycardia (2)

|  |  |
| --- | --- |
| **Criteria** | **Points** |
| Symptoms | |
| Exercise/activity-associated ACA/SCA | 2 |
| Exercise/activity-associated syncope or generalized seizures | 1 |
| Exercise stress test or Holter monitoring during exertional activity (REQUIRES ≥1 exercise stress test/ambulatory Holter finding)\*† | |
| Inducible bidirectional ventricular tachycardia at HR >100 bpm | 4 |
| Inducible PVCs in bigeminy and bidirectional couplets at HR >100 bpm | 2 |
| Inducible PVCs at HR >100 bpm | 1 |
| Baseline HR QTc‡ | |
| QTc≤420 ms | 0.5 |
| 421<QTc<460 ms | 0 |
| QTc≥460 ms | −0.5 |
| CPVT genetic test | |
| Positive for ACMG-graded pathogenic variant | 4 |
| Positive for ACMG-graded likely pathogenic variant | 2 |
| Positive for a variant of uncertain significance | 0 |
| Negative CPVT genetic test (RYR2, CASQ2, TRDN, and CALM1-3) | −1 |
| Holter | |
| Ambulatory ventricular ectopy (>2% of total beats) | −1 |
| Imaging (TTE or cardiac MRI/CT) | |
| Evidence of ischemic or structural heart disease | −2 |
| Age | |
| ≥50 y of age at time of sentinel event | −1 |
| Family history\* | |
| First-degree relative with definite CPVT | 1.5 |
| Suspicious autopsy-negative SCD (exertional, near drowning, etc) in a first- or second-degree relative ≤45 y | 1 |
| Unexplained autopsy-negative SCD in a first- or second degree relative ≤age 45 y | 0.5 |

CPVT score (Requires an exercise stress test/ambulatory Holter finding): 3.5–12 points: high pretest probability of CPVT (definite/probable CPVT ≥90% likelihood); 2–3 points: intermediate pretest probability of CPVT (possible CPVT, ≈50% likelihood); 0.5–1.5 points: low pretest probability of CPVT (nondiagnostic); ≤0 points: no evidence of CPVT; No score: indeterminate

Supplementary Table 5. Genes previously reported to be involved in CPVT (genes with limited or disputed evidence)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Gene** | **Locus** | **Syndrome** | **Protein (Functional Effect)** | **Frequency** | **ClinGen**  **Classification** |
| *KCNJ2* | 17q24.3 | CPVT/AD, ATS | IK1 (↓) | <1% | Disputed |
| *SCN5A* | 3p22.2 | CPVT/AD | INa (↑), LQTS/BrS definite | <1% | Disputed |
| *PKP2* | 12p11.21 | CPVT/AD | ARVC definite | <1% | Disputed |
| *ANK2* | 4q25-q26 | CPVT/AD |  | <1% | Disputed |

AD: autosomal dominant; ARVC: arrhythmogenic right ventricular cardiomyopathy; ATS: Andersen-Tawil syndrome; BrS: Brugada syndrome. LQTS: long QT syndrome

Supplementary Table 6: Modified Shanghai scoring system for the diagnosis of BrS (3)

|  |  |
| --- | --- |
| **Criteria** | **Points** |
| I. ECG (at least 1 ECG criterium is required for diagnosis)  Only award points once for highest score within this category. |  |
| Spontaneous type 1 Brugada ECG pattern at nominal or high leads | 3.5 |
| Fever-induced type 1 Brugada ECG pattern at nominal or high leads | 3 |
| Sodium-channel blocker-induced Brugada type I ECG pattern at nominal or high leads\* | 2 |
| II. Clinical history  Only award points once for highest score within this category |  |
| Unexplained cardiac arrest or documented VF/polymorphic VT | 3 |
| Nocturnal agonal respirations | 2 |
| Suspected arrhythmic syncope | 2 |
| Syncope of unclear mechanism/unclear etiology | 1 |
| Atrial fibrillation/flutter in patients <30 years without alternative etiology | 0.5 |
| II. Family history (first or second degree relative)  Only award points once for highest score within this category |  |
| Definite BrS | 2 |
| Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) | 1 |
| Unexplained SCD <45 years with negative autopsy | 0.5 |
| IV. Genetic test result |  |
| Pathogenic or likely pathogenic genetic variant in *SCN5A\*\** | 0.5 |

Score: >3.5 points required for probable/definite Brugada syndrome (BrS); 2-3 points for possible BrS; <2 points is considered nondiagnostic.

\*: In the original criteria, only a type 2 or 3 ECG that converts to type 1 qualifies. We suggest to generalize to drug-induced type 1, regardless of the baseline ECG. (e.g. a survivor of VF with a normal baseline ECG but a drug-induced type I should meet diagnostic criteria for definite BrS).

\*\*: In the original criteria, the phrasing was “Probable pathogenic mutation in BrS susceptibility gene”. We suggest to use the ACMG/AMP nomenclature and restrict to SCN5A.

Supplementary Table 7. Genes previously reported to be involved in Brugada syndrome (genes with limited or disputed evidence)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Gene** | **Locus** | **Syndrome** | **Protein (Functional Effect)** | **Frequency** | **ClinGen**  **Classification** |
| *GPD1L* | *3p22.3* | BrS | INa (↓) | <1% | *Disputed* |
| *CACNA1C* | *12p13.33* | BrS | ICa-L (↓) | <1% | *Disputed* |
| *CACNB2* | *10p12.31-33* | BrS | ICa-L (↓) | <1% | *Disputed* |
| *SCN1B* | *19q13.11* | BrS | INa (↓) | <1% | *Disputed* |
| *KCNE3* | *11q13.4* | BrS | ITO (↑) | <1% | *Disputed* |
| *SCN3B* | *11q24.1* | BrS | INa (↓) | <1% | *Disputed* |
| *HCN4* | *15q24.1* | BrS | IF | <1% | *Disputed* |
| *KCND3* | *1p13.2* | BrS | ITO (↑) | <1% | *Disputed* |
| *ABCC9* | *12p12.1* | BrS | IK-ATP (↑) | <1% | *Disputed* |
| *ANK2* | *4q25-26* | BrS | INa (↓) | <1% | *Disputed* |
| *CACNA2D1* | *7q21.11* | BrS | ICa-L (↓) | <1% | *Disputed* |
| *FGF12* | *3q28-29* | BrS | INa (↓) | <1% | *NA* |
| *KCNE5* | *Xq23* | BrS | ITO (↑) | <1% | *Disputed* |
| *KCNH2* | *7q35-36* | BrS | IKr (↑) | <1% | *Disputed* |
| *KCNJ8* | *12p12.1* | BrS | IK-ATP (↑) | <1% | *Disputed* |
| *PKP2* | *12p11.21* | BrS | INa (↓) | <1% | *Disputed* |
| *RANGRF* | *17p13.1* | BrS | INa (↓) | <1% | *Disputed* |
| *RRAD* | *16q22.1* | BrS | INa (↓) | <1% | *NA* |
| *SCN10A* | *3p22.2* | BrS | INa (↓) | <1% | *Disputed* |
| *SCN2B* | *11q23.3* | BrS | INa (↓) | <1% | *Disputed* |
| *SEMA3A* | *7q21.11* | BrS | ITO (↑) | <1% | *NA* |
| *SLMAP* | *3p14.3* | BrS | INa (↓) | <1% | *Disputed* |
| *TRPM4* | *19q13.33* | BrS | ? | <1% | *Disputed* |

Supplementary Table 8. Genes previously reported to be involved in progressive cardiac conduction defect (PCCD/CCD) (genes with limited or disputed evidence)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Gene** | **Locus** | **Syndrome** | **Protein (Functional Effect)** | **Frequency** | **ClinGen**  **Classification** |
| *GJA5* | *1q21.2* | *ASS, AFib* | *Connexin 40*  *Loss-of-function* | <1% | *NA/minor gene* |
| *SCN1B* | *19q13.11* | *AFib, febrile seizures / Dravet syndrome (infantile epileptic encephalopathy,* | *Na channel β1 subunit (Naβ1)*  *Loss-of-function* | <1% | *NA/minor gene* |

Supplementary Table 9. Diagnostic score cards for short QT syndrome (4)

|  |  |
| --- | --- |
| **Criteria** | **Points** |
| Electrocardiograma | |
| QTc <370 ms | 1 |
| QTc <350 ms | 2 |
| QTc <330 ms | 3 |
| J point-T peak intervalb <120 ms | 1 |
| Clinical historyc\* | |
| History of sudden cardiac arrest | 2 |
| Documented polymorphic VT or VF | 2 |
| Unexplained syncope | 1 |
| Atrial fibrillation | 1 |
| Family historyd\* | |
| First- or second-degree relative with high-probability SQTS | 2 |
| First- or second-degree relative with autopsy-negative SCD | 1 |
| Sudden infant death syndrome | 1 |
| Genotype\* | |
| Genotype positive | 2 |
| Mutation of undetermined significance in a culprit gene | 1 |

SQTS score: High-probability SQTS: ≥4 points, intermediate-probability SQTS: 3 points, low-probability SQTS:≤2 points.

a Electrocardiogram: must be recorded in the absence of modifiers known to shorten the QT.

b Jpoint-Tpeak interval must be measured in the precordial lead with the greatest amplitude T-wave.

c Clinical history: events must occur in the absence of an identifiable etiology, including structural heart disease. Points can only be received for 1 of cardiac arrest, documented polymorphic VT, or unexplained syncope.

d Family history: points can only be received once in this section.

\*A minimum of 1 point must be obtained in the electrocardiographic section in order to obtain additional points.

Supplementary Table 10. Genes previously reported to be involved in short QT syndrome (genes with limited or disputed evidence)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Gene** | **Locus** | **Syndrome** | **Protein (Functional Effect)** | **Frequency** | **ClinGen**  **Classification** |
| *CACNA1C* | 12p13.3 | SQTS/AD | ICa-L (↓) | <1% | Disputed |
| *CACNB2* | [10p12.33-p12.31](https://www.omim.org/geneMap/10/79?start=-3&limit=10&highlight=79) | SQTS/AD | ICa-L  (↓) | <1% | Disputed |
| *CACNA2D1* | [7q21.11](https://www.omim.org/geneMap/7/352?start=-3&limit=10&highlight=352) | SQTS/AD | ICa-L  (↓) | () | Disputed |

Functional effect: (↓) loss-of-function or (↑) gain-of-function at the cellular in vitro level.

BrS: Brugada Syndrome; SQTS: Short QT Syndrome

Supplementary Table 11. Genes previously reported to be involved in sinus node disease (genes with limited or disputed evidence)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ***Gene*** | **Locus** | **Syndrome** | **Protein (Functional Effect)** | **Frequency** | **ClinGen**  **Classification** |
| *ANK2* | 4q25-q26 | SND, AFib | Scaffolding adaptor protein AnkB  (Loss-of-function) | () | NA/minor gene |
| *KCNJ3* | 2q24.1 | SND, AFib | G-protein gated inwardly rectifying K+ (GIRK) channel 3 (Kv3.1)  (Gain-of-function, IK,ACh↑) | () | NA/minor gene |
| *MYH6* | 14q11.2 | [ASD3], SND; Island founder variant (0.38%) | Myosin heavy chain 6 | () | NA/minor gene |

Frequency: (): mutation rate unknown and/or single reports. NA: not available.

Other Phenotypes: […], phenotype associated with gene, but unlinked with SND.

ClinGen: Clinical Genome Resource of NCBI; https://clinicalgenome.orgAFib: atrial fibrillation; ASD: atrial septal defect; SND: sinus node dysfunction

Supplementary Table **12.** Genes previously reported to be involved in early repolarization syndrome (genes with limited or disputed evidence)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Gene** | **Locus** | **Syndrome** | **Protein (Functional Effect)** | **Frequency** | **ClinGen**  **Classification** |
| *SCN5A* | 3p22.2 | BrS/AD | Loss of INa1.5 channel function | 1-10% | N/A, minor gene |
| *KCND3* |  |  | Increase in transient outward current (ITo) | <1% | N/A, minor gene |
| *ABCC9* |  |  | Increase in ATP-sensitive potassium current (IK-ATP) | <1% | N/A, minor gene |
| *CACNA1C* | 12p13.3 | SQTS/AD | Loss of function L-type calcium channel (ICa-L-type) | <1% | N/A, minor gene |
| *CACNA2D1* | *7q21.11* | BrS | Loss of function L-type calcium channel (ICa-L-type) | <1% | N/A, minor gene |
| *CACNB2* | *10p12.31-33* | BrS | Loss of function L-type calcium channel (ICa-L-type) | <1% | N/A, minor gene |
| *KCNJ8* | *12p12.1* | BrS | Increase in ATP-sensitive potassium current (IK-ATP) | <1% | N/A, minor gene |
| *SCN10A* | *3p22.2* | BrS | Loss of INa1.5 channel function | 1-10% | N/A, minor gene |

Gene Category: refers to mutation detection rate (28); core genes: major (>10%) or minor (1-10%); rare gene (<1%);

AD: autosomal dominant; BrS: Brugada syndrome; SQTS: Short QT syndrome

Supplementary Table 13**.** Genes previously reported to be involved in Hypertrophic Cardiomyopathy (genes with limited or disputed evidence)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Gene** | **Locus** | **Syndrome** | **Protein (Functional Effect)** | **Frequency** | **ClinGen**  **Classification** |
| *TTN* | 2q31.2 | familial HCM, ACM, DCM | loss-of-function | <1% | Limited |
| *KLF10* | 8q22.3 | familial HCM | loss-of-function | <1% | Limited |
| *MYPN* | 10q21.3 | familial HCM, DCM, skeletal myopathy | interaction with nebulette and alpha actin | <1% | Limited |
| *ANKRD1* | 10q23.31 | familial HCM, DCM, sensori-neural hearing impairment | gain-of-function | <1% | Limited |
| *MYLK2* | 20q11.21 | familial HCM | gain-of-function | <1% | Limited |
| *MYOZ2* | 4q26 | familial HCM | interaction of calcineurin to alpha actin | <1% | Limited |
| *NEXN* | 1p31.1 | familial HCM, DCM | interaction with alpha actin | <1% | Limited |
| *VCL* | 10q22.2 | familial HCM, DCM | loss-of-function | <1% | Limited |
| *TRIM63* | 1p36.11 | familial HCM | unknown | <1% | Limited |
| *RYR2* | 1q43 | familial HCM, ACM, CPVT | loss-of function of Ca++ release | <1% | Limited |
| *MYH6* | 14q11.2 | familial HCM | loss-of-function | <1% | Limited |
| *OBSCN* | 1q42.13 | familial HCM | loss-of-function | <1% | Limited |
| *PDLIM3* | 4q35.1 | familial HCM , DCM | unknown | <1% | Limited |
| *TCAP* | 17q12 | familial HCM, limb-girdle MD | loss-of-function impairs sarcomere assembly | <1% | Limited |
| *MYOM1* | 18p11.31 | familial HCM | unknown | <1% | Limited |
| *CALR3* | 19p13.11 | familial HCM | loss-of-function | <1% | Limited |

ACM: arrhythmogenic cardiomyopathy, CPVT: catecholaminergic polymorphic ventricular tachycardia; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; MD: muscular dystrophy

Supplementary Table 14.Genes previously reported to be involved in dilated cardiomyopathy (genes with limited or disputed evidence)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Gene** | **Locus** | **Phenotype** | **Protein** | **Frequency** | **ClinGen**  **Classification** |
| *MYBPC3* | 11p11.2 | HCM, DCM, ARVC/ACM | Myosin binding protein C | ~1% | Limited |
| *MYL2* | 12q24.11 | HCM, DCM | Regulatory myosin light chain | <1% | Limited |
| *MYH6* | 14q11.2 | HCM, DCM | alpha-myosin heavy chain | <1% | Limited |
| *MYPN* | 10q21.3 | Myopathy, DCM, HCM | Myopalladin | <1% | Limited |
| *NEBL* | 10p12.31 | DCM | Nebulette | <1% | Limited |
| *CSRP3* | 11p15.1 | DCM | Cysteine and glycine rich protein 3 | <1% | Limited |
| *CTF1* | 16p11.2 | DCM | Cardiotrophin 1 | <1% | Limited |
| *DTNA* | 18q12.1 | DCM | Dystrobrevin alpha | <1% | Limited |
| *TCAP* | 17q12 | DCM, HCM | Telethonin | <1% | Limited |
| *LDB3* | 11p15.1 | DCM | LIM domain binding 3 | <1% | Limited |
| *SGCD* | 5q33.2-q33.3 | Myopathy, DCM | Delta-sarcoglycan | <1% | Limited |
| *DSG2* | 18q12.1 | ARVC, DCM | Desmoglein 2 | <1% | Limited |
| *NKX2-5* | 5q35.1 | DCM | Homeobox protein Nkx-2.5 | <1% | Limited |
| *ABCC9* | 12p12.1 | DCM | ATP binding cassette subfamily C member 9 | <1% | Limited |
| *PRDM16* | 1p36 | DCM | PR domain zinc finger protein 16 | <1% | Limited |
| *ANKRD1* | 10q23.31 | DCM, HCM | Ankyrin repeat domain 1 | <1% | Limited |
| *PLEKHM2* | 1p36.21 | DCM | Pleckstrin homology domain-containing protein M2 | <1% | Limited |
| *GATAD1* | 7q21.2 | DCM | GATA zinc finger domain containing 1 | <1% | Limited |
| *PSEN2* | 1q42.13 | DCM | Presenilin 2 | <1% | Limited |
| *ILK* | 11p15.4 | DCM | Integrin linked kinase | <1% | Limited |
| *LAMA4* | 6q21 | DCM | Laminin subunit alpha 4 | <1% | Limited |
| *EYA4* | 6q23.2 | Deafness, DCM | EYA transcriptional coactivator and phosphatase 4 | <1% | Limited |
| *OBSCN* | 1q42.13 | DCM | Obscurin | <1% | Limited |
| *TBX20* | 7p14.2 | DCM | T-box transcription factor 20 | <1% | Limited |
| *TNNI3K* | 1p31.1 | DCM | TNNI3 interacting kinase | <1% | Limited |
| *mtDNA* |  | Myopathy, MERFF, MELAS, etc | Mitochondrial genes | <1% | N/A, rare gene |
| *DMD* | [Xp21.2-p21.1](https://www.omim.org/geneMap/X/144?start=-3&limit=10&highlight=144) | Myopathy, DCM | Dystrophin | <1% | N/A, rare gene |
| *TAZ* | Xp28 | DCM | Tafazzin | <1% | N/A, rare gene |
| *MYL3* | 3p21.31 | HCM, (ARVC/ACM, DCM) | Myosin light chain 3 | <1% | Disputed |
| *PKP2* | 12p11.21 | ARVC/ACM | Plakophilin 2 | <1% | Disputed |
| *PSEN1* | 14q24.2 |  | presenilin 1 | <1% | Disputed |
| *PDLIM3* | 4q35.1 | (HCM) | PDZ and LIM domain 3 | <1% | Disputed |

ACM: arrhythmogenic cardiomyopathy, CPVT: catecholaminergic polymorphic ventricular tachycardia; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; MD: muscular dystrophy

Supplementary Table 15**.** Genes previously reported to be involved in arrhythmogenic cardiomyopathy (genes with limited or disputed evidence)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Gene** | **Locus** | **Phenotype / Syndrome** | **Protein (Cellular complex)** | **Frequency** | **ClinGen**  **Classification** |
| *CTNNA3* | 10q21.3 | ARVC/ACM | Catenin alpha-3 (area composita) | <1% | Limited |
| *CDH2* | 18q12.1 | ARVC/ACM | Cadherin-2 (area composita) | <1% | Limited\* |
| *LMNA* | 1q22 | DCM. Prominent conduction system abnormalities and atrial arrhythmias common. Exceptional ARVC/ACM | Lamin A/C (nuclear envelope) | <1% | Limited |
| *SCN5A* | 3p22.2 | DCM. Exceptional ARVC/ACM | Sodium channel protein type 5 subunit alpha (ion channel) | <1% | Limited |
| *TJP1* | 15q13.1 | ARVC/ACM and DCM | Tight junction protein 1 (area composita) | <1% | Limited |
| *ACTC1* | 15q14 | HCM. LVNC. DCM | Actin alpha cardiac muscle 1 (sarcomere) | - | Disputed |
| *LDB3* | 10q23.2 | ARVC/ACM | LIM domain-binding protein 3 (sarcomere) | - | Disputed |
| *MYBPC3* | 11p11.2 | HCM. LVNC. DCM | Myosin binding protein C3 (sarcomere) | - | Disputed |
| *MYH7* | 14q11.2 | HCM. DCM. LVNC | Myosin heavy chain 7 (sarcomere) | - | Disputed |
| *MYL2* | 12q24.11 | HCM | Myosin light chain 2 (sarcomere) | - | Disputed |
| *MYL3* | 3p21.31 | HCM | Myosin light chain 3 (sarcomere) | - | Disputed |
| *TGFB3* | 14q24.3 | ARVC/ACM. LDS | Transforming growth factor, beta 3 (signalling pathways) | - | Disputed |
| *TP63* | 3q28 | ARVC/ACM | Tumor protein p63 (transcription factors) | - | Disputed |
| *TTN* | 2q31.2 | DCM. ARVC/ACM | Titin (sarcomere related) | - | Disputed |
| *RYR2* | 1q43 | CPVT | Ryanodine receptor 2 (sarcoplasmic reticulum; calcium handling) | - | Refuted |

ARVC: arrhythmogenic right ventricular cardiomyopathy, CPVT: catecholaminergic polymorphic ventricular tachycardia; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; LDS: Loeys-Dietz syndrome; LVNC: left ventricular noncompaction cardiomyopathy; MD: muscular dystrophy

\*:new evidence supports CDH2 as a disease gene in a small subset of ACM patients

**References**

1. Schwartz PJ, Crotti L. QTc behavior during exercise and genetic testing for the long-QT syndrome. Circulation. 2011;124(20):2181-4.

2. Giudicessi JR, Lieve KVV, Rohatgi RK, Koca F, Tester DJ, van der Werf C, et al. Assessment and Validation of a Phenotype-Enhanced Variant Classification Framework to Promote or Demote RYR2 Missense Variants of Uncertain Significance. Circ Genom Precis Med. 2019;12(5):e002510.

3. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, et al. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. Europace. 2017;19(4):665-94.

4. Gollob MH, Redpath CJ, Roberts JD. The short QT syndrome: proposed diagnostic criteria. Journal of the American College of Cardiology. 2011;57(7):802-12.