# Genetic Testing in Inherited Arrhythmia

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## COI Disclosure

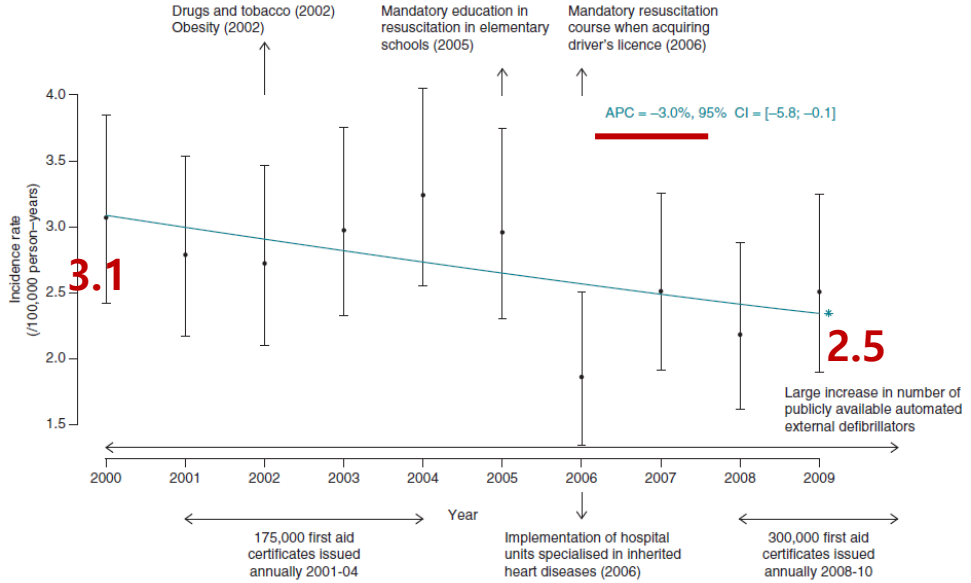
*Name of First Author:*

The authors have no financial conflicts of interest to disclose concerning the presentation

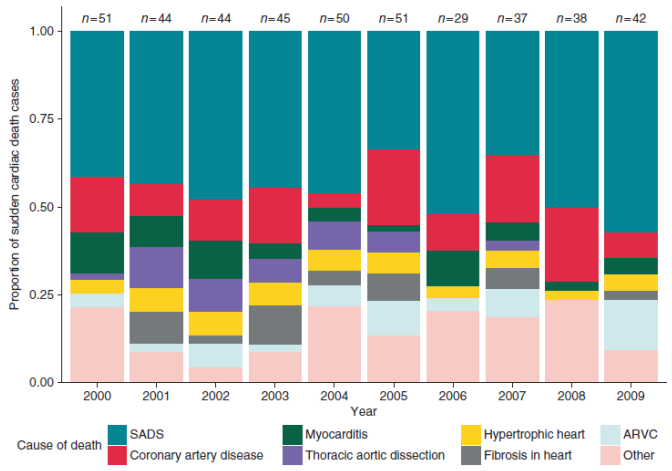
# Epidemiology of Sudden Cardiac Death

- Sudden cardiac death (SCD) accounts for approximately 50% of all cardiovascular deaths.

- Incidence of SCD is declining, but risk of SCD as proportion of the overall cardiovascular death may have increased.

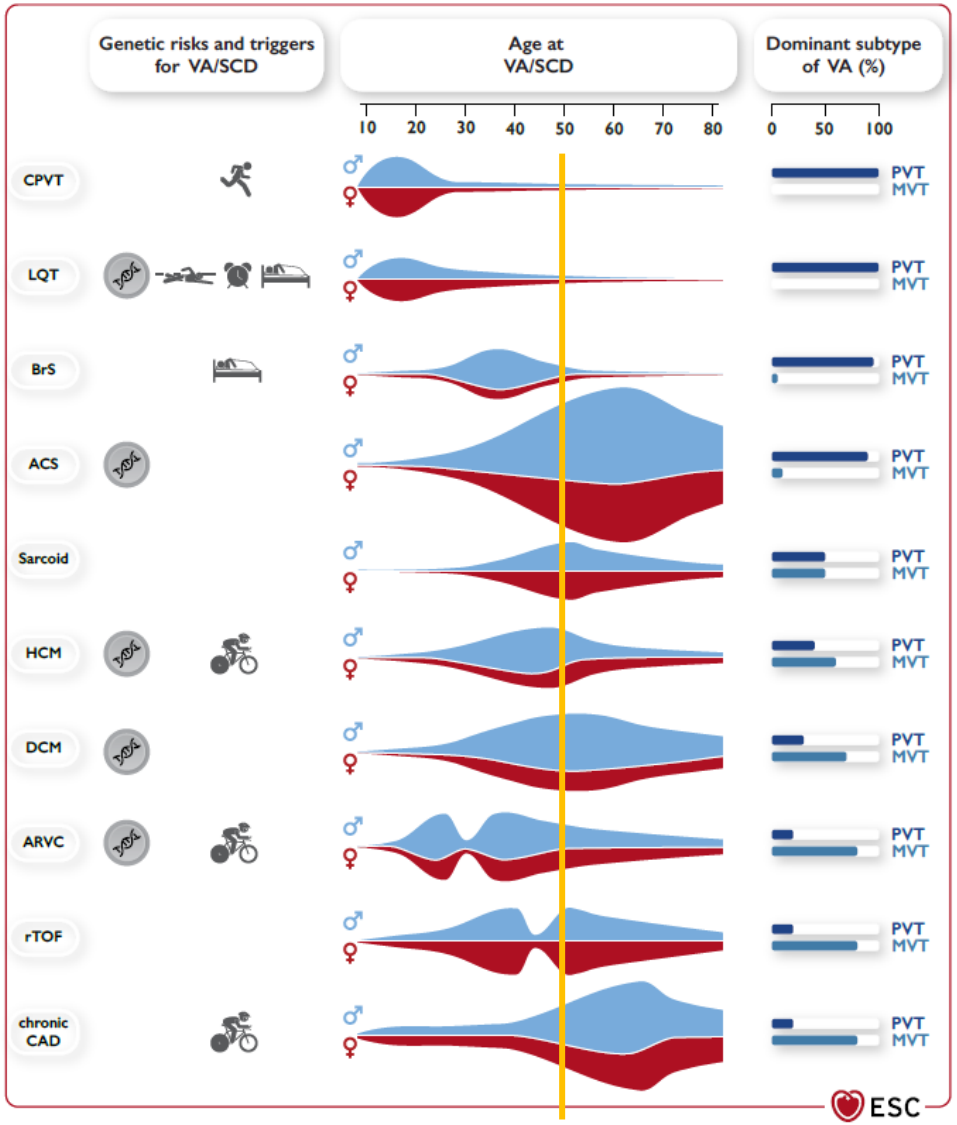



Data from Denmark (2000-2009)




Lynge et al. *Europace*.2019; 21,909-917.

# Disease-related SCD presentation




- <50 years :
  1. **Primary electrical diseases**
  2. Non-ischemic structural heart disease (SHD)

- >50 years : Chronic SHD
  1. Coronary artery disease (acute or chronic)
  2. Valvular heart disease
  3. Heart failure

2022 ESC Guidelines for the management of patients with VA and prevention of SCD

# Guidelines of genetic testing

- Genetic testing is routinely used in the evaluation of inherited cardiac syndromes, enabling the implementation of precision medicine and genetic cascade screening.

**2013**

**HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes**

Circulation: Genomic and Precision Medicine

**2020**

AHA SCIENTIFIC STATEMENT

Genetic Testing for Inherited Cardiovascular Diseases

A Scientific Statement From the American Heart Association

**2022**

ESC European Society of Cardiology

Europace (2022), **00**, 1–61
https://doi.org/10.1093/europace/euac030

POSITION PAPER

**European Heart Rhythm Association (EHRA)/ Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases**

**2022**

ESC European Society of Cardiology

European Heart Journal (2022) **00**, 1–130
https://doi.org/10.1093/eurheartj/ehac262

ESC GUIDELINES

**2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death**

# Interpretation of genetic variant

| | Benign | | Pathogenic | | | |
|---|---|---|---|---|---|---|
| | **Strong** | **Supporting** | **Supporting** | **Moderate** | **Strong** | **Very strong** |
| **Population data** | MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2 | | | Absent in population databases PM2 | Prevalence in affecteds statistically increased over controls PS4 | |
| **Computational and predictive data** | | Multiple lines of computational evidence suggest no impact on gene /gene product BP4<br><br>Missense in gene where only truncating cause disease BP1<br><br>Silent variant with non predicted splice impact BP7<br><br>In-frame indels in repeat w/out known function BP3 | Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3 | Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5<br><br>Protein length changing variant PM4 | Same amino acid change as an established pathogenic variant PS1 | Predicted null variant in a gene where LOF is a known mechanism of disease PVS1 |
| **Functional data** | Well-established functional studies show no deleterious effect BS3 | | Missense in gene with low rate of benign missense variants and path. missenses common PP2 | Mutational hot spot or well-studied functional domain without benign variation PM1 | Well-established functional studies show a deleterious effect PS3 | |
| **Segregation data** | Nonsegregation with disease BS4 | | Cosegregation with disease in multiple affected family members PP1 | Increased segregation data → | | |
| **De novo data** | | | | De novo (without paternity & maternity confirmed) PM6 | De novo (paternity and maternity confirmed) PS2 | |
| **Allelic data** | | Observed in *trans* with a dominant variant BP2<br><br>Observed in *cis* with a pathogenic variant BP2 | | For recessive disorders, detected in trans with a pathogenic variant PM3 | | |
| **Other database** | | Reputable source w/out shared data = benign BP6 | Reputable source = pathogenic PP5 | | | |
| **Other data** | | Found in case with an alternate cause BP5 | Patient's phenotype or FH highly specific for gene PP4 | | | |

**Level of certainty : 95%**

**Table 5** Rules for combining criteria to classify sequence variants

| | |
|---|---|
| Pathogenic | (i) 1 Very strong (PVS1) *AND*<br>(a) ≥1 Strong (PS1–PS4) *OR*<br>(b) ≥2 Moderate (PM1–PM6) *OR*<br>(c) 1 Moderate (PM1–PM6) and 1 supporting (PP1–PP5) *OR*<br>(d) ≥2 Supporting (PP1–PP5)<br>(ii) ≥2 Strong (PS1–PS4) *OR*<br>(iii) 1 Strong (PS1–PS4) *AND*<br>(a)≥3 Moderate (PM1–PM6) *OR*<br>(b)2 Moderate (PM1–PM6) *AND* ≥2 Supporting (PP1–PP5) *OR*<br>(c)1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5) |
| Likely pathogenic<br>**90%** | (i) 1 Very strong (PVS1) *AND* 1 moderate (PM1–PM6) *OR*<br>(ii) 1 Strong (PS1–PS4) *AND* 1–2 moderate (PM1–PM6) *OR*<br>(iii) 1 Strong (PS1–PS4) *AND* ≥2 supporting (PP1–PP5) *OR*<br>(iv) ≥3 Moderate (PM1–PM6) *OR*<br>(v) 2 Moderate (PM1–PM6) *AND* ≥2 supporting (PP1–PP5) *OR*<br>(vi) 1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5) |
| Benign<br>**95%** | (i) 1 Stand-alone (BA1) *OR*<br>(ii) ≥2 Strong (BS1–BS4) |
| Likely benign<br>**90%** | (i) 1 Strong (BS1–BS4) and 1 supporting (BP1–BP7) *OR*<br>(ii) ≥2 Supporting (BP1–BP7) |
| Uncertain significance | (i) Other criteria shown above are not met OR<br>(ii) the criteria for benign and pathogenic are contradictory |

Richards S et al. Genet Med. 2015 May;17(5):405-24.

# Genetic testing in Inherited Arrhythmia Syndrome

**Long QT syndrome (LQTS)**

**Brugada syndrome (BrS)**

**Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)**

**Short QT syndrome**

**Early repolarization syndrome**

**Idiopathic ventricular fibrillation (IVF)**

# ClinGen's Reappraisal of Gene Validity for Inherited Cardiac disease (Gene Curation Expert Panel)

**Clinical Validity Summary Matrix**

| GENE/DISEASE PAIR: | | | | |
|---|---|---|---|---|
| **Assertion criteria** | **Genetic Evidence (0-12 points)** | **Experimental Evidence (0-6 points)** | **Total Points (0-18)** | **Replication Over Time (Y/N)** |
| **Description** | Case-level, family segregation, or case-control data that support the gene-disease association | Gene-level experimental evidence that support the gene-disease association | Sum of Genetic & Experimental Evidence | > 2 publications with convincing evidence over time (>3 yrs) |
| **Assigned Points** | | | | |
| **CALCULATED CLASSIFICATION** | | **LIMITED** | **1-6** | |
| | | **MODERATE** | **7-11** | |
| | | **STRONG** | **12-18** | |
| | | **DEFINITIVE** | **12-18 & Replicated Over Time** | |
| **Valid contradictory evidence (Y/N)*** | **List references and describe evidence:** | | | |
| **CURATOR CLASSIFICATION** | | | | |
| **FINAL CLASSIFICATION** | | | | |

Strande et al. Am J Hum Genet. 2017. 1;100(6):895-906

**2018** Circulation

ORIGINAL RESEARCH ARTICLE

**Reappraisal of Reported Genes for Sudden Arrhythmic Death**

**Evidence-Based Evaluation of Gene Validity for Brugada Syndrome**

**2019** Circulation: Genomic and Precision Medicine

ORIGINAL ARTICLE

**Evaluating the Clinical Validity of Hypertrophic Cardiomyopathy Genes**

Circulation

**2020**

ORIGINAL RESEARCH ARTICLE

**An International, Multicentered, Evidence-Based Reappraisal of Genes Reported to Cause Congenital Long QT Syndrome**

**2021**

Circulation: Genomic and Precision Medicine

ORIGINAL ARTICLE

International Evidence Based Reappraisal of Genes Associated With Arrhythmogenic Right Ventricular Cardiomyopathy Using the Clinical Genome Resource Framework

Circulation

ORIGINAL RESEARCH ARTICLE

Evidence-Based Assessment of Genes in Dilated Cardiomyopathy

**2022**

ESC European Society of Cardiology

European Heart Journal (2022) **43**, 1500–1510
https://doi.org/10.1093/eurheartj/ehab687

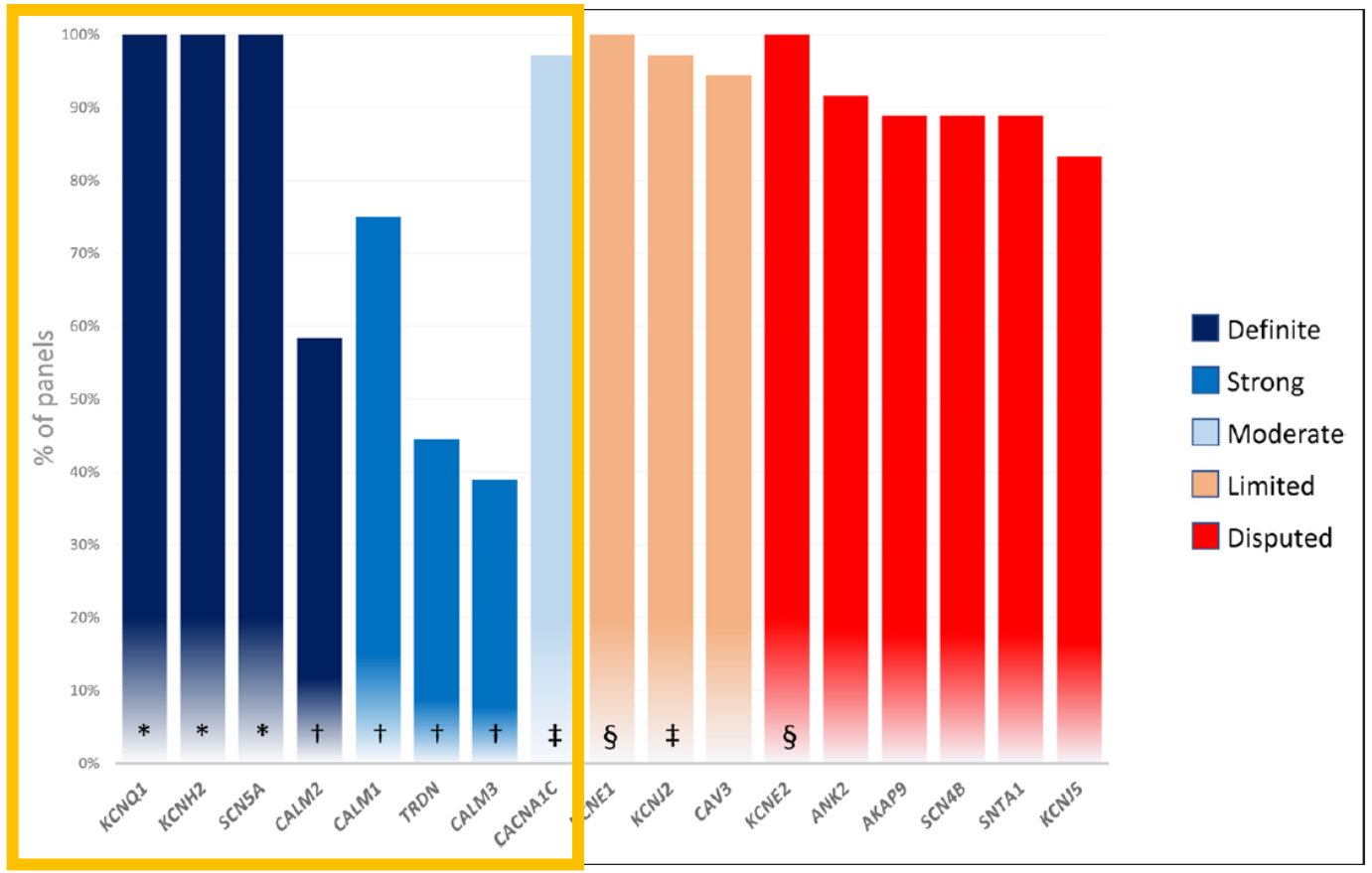
TRANSLATIONAL RESEARCH
*Genetics*

**Evaluation of gene validity for CPVT and short QT syndrome in sudden arrhythmic death**

# Long QT syndrome (LQTS)

Table 1. Reported Genes for Long QT Syndrome **(n=17)**

| Gene | Protein | HGNC ID | Chromosomal Location |
|---|---|---|---|
| *AKAP9* | A-kinase anchor protein 9 | 379 | 7q21.2 |
| *ANK2* | Ankyrin-2 | 493 | 4q25-q26 |
| *CACNA1C* | Calcium voltage-gated channel subunit alpha1 C | 1390 | 12p13.33 |
| *CALM1* | Calmodulin-1 | 1442 | 14q32.11 |
| *CALM2* | Calmodulin-2 | 1445 | 2p21 |
| *CALM3* | Calmodulin-3 | 1449 | 19q13.32 |
| *CAV3* | Caveolin-3 | 1529 | 3p25.3 |
| *KCNE1* | Potassium voltage-gated channel subfamily E regulatory subunit 1 | 6240 | 21q22.12 |
| *KCNE2* | Potassium voltage-gated channel subfamily E regulatory subunit 1 | 6242 | 21q22.11 |
| *KCNH2* | Potassium voltage-gated channel subfamily H member 2 | 6251 | 7q36.1 |
| *KCNJ2* | Potassium voltage-gated channel subfamily J member 2 | 6263 | 17q24.3 |
| *KCNJ5* | Potassium voltage-gated channel subfamily J member 5 | 6266 | 11q24.3 |
| *KCNQ1* | Potassium voltage-gated channel subfamily Q member 1 | 6294 | 11p15.5-p15.4 |
| *SCN4B* | Sodium voltage-gated channel beta subunit 4 | 10592 | 11q23.3 |
| *SCN5A* | Sodium voltage-gated channel alpha subunit 5 | 10593 | 3p22.2 |
| *SNTA1* | Syntrophin alpha 1 | 11167 | 20q11.21 |
| *TRDN* | Triadin | 12261 | 6q22.31 |




*Definitive evidence for typical LQTS.
†Strong or definitive evidence for LQTS with atypical features.

Adler et al. Circulation. 2020;141:418-428

# Long QT syndrome (LQTS)

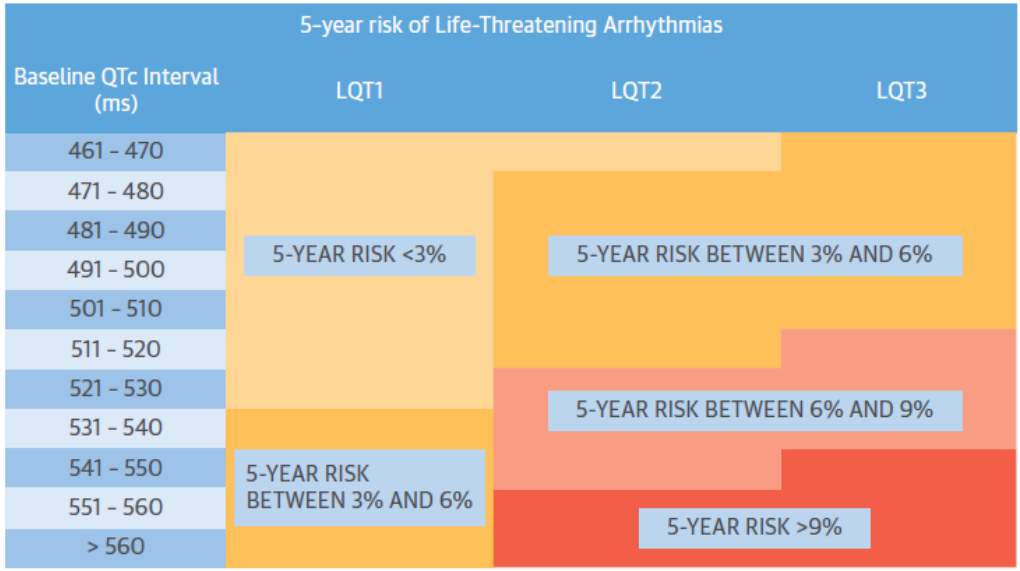
- Genetic testing in LQTS also has prognostic and therapeutic value in addition to diagnostic evidence.

| Disease | Diagnostic | Prognostic | Therapeutic |
|---|---|---|---|
| **Arrhythmia syndromes** | | | |
| Long QT syndrome | +++ | +++ | +++ |
| CPVT | +++ | + | + |
| Brugada syndrome | + | + | + |
| Progressive cardiac conduction disease | + | + | + |
| Short QT syndrome | + | + | + |
| Sinus node disease | – | + | – |
| Atrial fibrillation | – | + | – |
| Early repolarization syndrome | – | – | – |

**Table 10 Modified long QT syndrome diagnostic score**[243]

| Findings | | | Points |
|---|---|---|---|
| ECG | QTc | ≥480 ms | 3.5 |
| | | =460–479 ms | 2 |
| | | =450–459 ms (in males) | 1 |
| | | ≥480 ms during 4th minute of recovery from exercise stress test | 1 |
| | *Torsade de pointes* | | 2 |
| | T wave alternans | | 1 |
| | Notched T wave in 3 leads | | 1 |
| | Low heart rate for age | | 0.5 |
| Clinical history | Syncope | With stress | 2 |
| | | Without stress | 1 |
| Family history | Family member(s) with definite LQTS | | 1 |
| | Unexplained SCD at age <30 years in first-degree family | | 0.5 |
| Genetic finding | Pathogenic mutation | | 3.5 |

ECG, electrocardiogram; LQTS, long QT syndrome; SCD, sudden cardiac death.
Diagnosis of LQTS with a score >3.




KCNQ1 → Sympathetic denervation effective
KCH2 → Preserve K level (PO potassium)
SCN5A (GOF) → Sodium current blockers (Mexiletine)

2022 ESC Guidelines for the management of patients with VA and prevention of SCD

2022 EHRA/HRS/APHRS/LAHRS Expert Consensus Statement

Mazzanti, A. et al. J Am Coll Cardiol.2018;71(15):1663-71.

# Guideline Recommendations: LQTS

| Recommendations | Consensus statement instruction | Ref. |
|---|---|---|
| Molecular genetic testing for definitive disease associated genes (currently *KCNQ1, KCNH2, SCN5A, CALM1, CALM2*, and *CALM3*) should be offered to all index patients with a high probability diagnosis of LQTS, based on examination of the patient's clinical history, family history, and ECG characteristics obtained at baseline, during ECG Holter recording and exercise stress test (Schwartz Score ≥ 3.5, Supplementary *Table S2*).[a] |  | 20 |
| Analysis of specific genes should be offered to patients with a specific diagnosis as follows: *KCNQ1 and KCNE1* in patients with Jervell and Lange-Nielsen syndrome, *CACNA1C* in Timothy syndrome, *KCNJ2* in Andersen–Tawil syndrome, and *TRDN* in patients suspected to have triadin knockout syndrome. |  | 20,89–93 |
| An analysis of *CACNA1C* and *KCNE1* may be performed in all index patients in whom a cardiologist has established a diagnosis of LQTS with a high probability, based on examination of the patient's clinical history, family history, and ECG characteristics obtained at baseline, during ECG Holter recording and exercise stress test (Schwartz Score ≥ 3.5).[a] |  | |
| Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causing variant. |  | |
| Predictive genetic testing in related children is recommended from birth onward (any age). |  | |

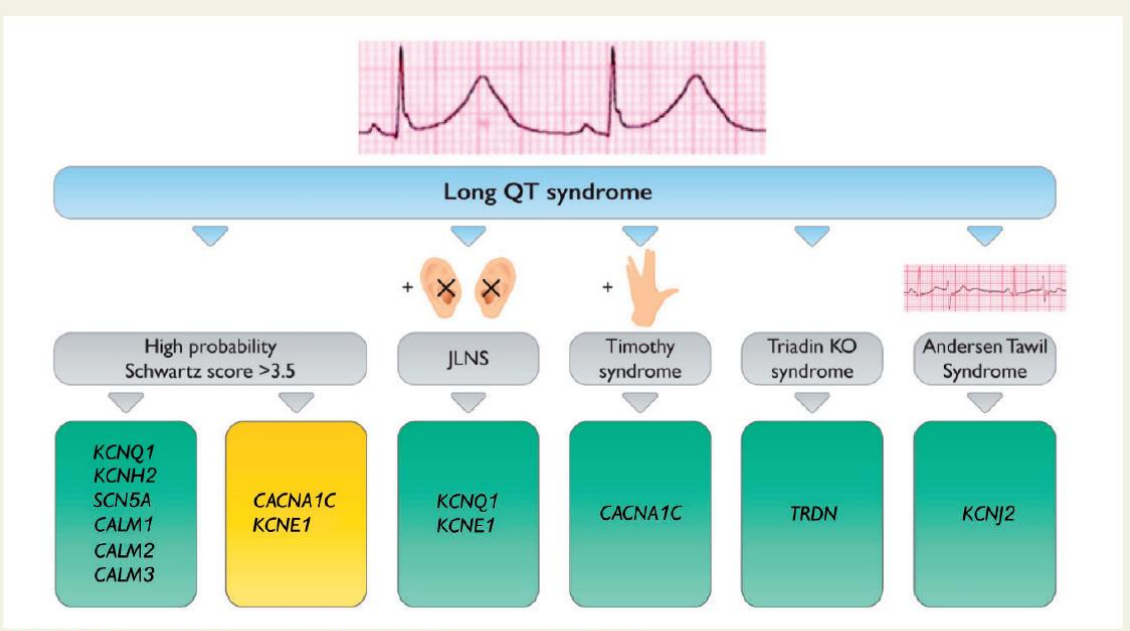



**Figure 3** Clinical algorithm for genetic testing and family screening in long-QT syndrome.

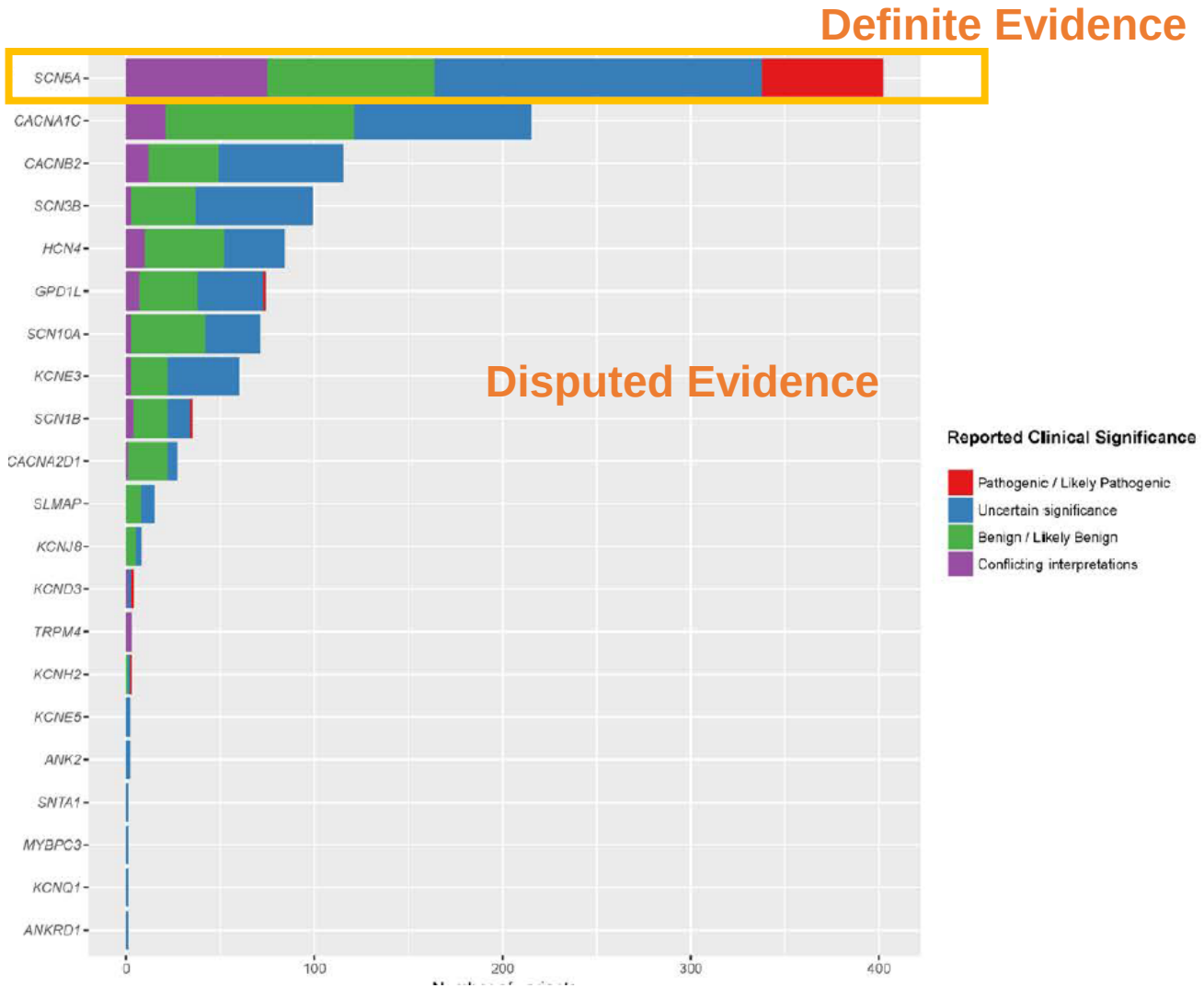
2022 EHRA/HRS/APHRS/LAHRS Expert Consensus Statement

# Brugada syndrome (BrS)

**(n=21)**

Table 1. Reported Genes for Brugada Syndrome

| Gene Symbol | Gene Name |
|---|---|
| ABCC9 | ATP binding cassette subfamily C member 9 |
| ANK2 | Ankyrin 2 |
| CACNA1C | Calcium voltage-gated channel subunit alpha1 C |
| CACNA2D1 | Calcium voltage-gated channel auxiliary subunit alpha2delta 1 |
| CACNB2 | Calcium voltage-gated channel auxiliary subunit beta 2 |
| FGF12 | Fibroblast growth factor 12 |
| GPD1L | Glycerol-3-phosphate dehydrogenase 1 like |
| HCN4 | Hyperpolarization activated cyclic nucleotide-gated potassium channel 4 |
| KCND3 | Potassium voltage-gated channel subfamily D member 3 |
| KCNE3 | Potassium voltage-gated channel subfamily E regulatory subunit 3 |
| KCNE5 | Potassium voltage-gated channel subfamily E regulatory subunit 5 |
| KCNH2 | Potassium voltage-gated channel subfamily H member 2 |
| KCNJ8 | Potassium voltage-gated channel subfamily J member 8 |
| RANGRF | RAN guanine nucleotide release factor |
| PKP2 | Plakophilin 2 |
| SCN10A | Sodium voltage-gated channel alpha subunit 10 |
| SCN1B | Sodium voltage-gated channel beta subunit 1 |
| SCN2B | Sodium voltage-gated channel beta subunit 2 |
| SCN3B | Sodium voltage-gated channel beta subunit 3 |
| SCN5A | Sodium voltage-gated channel alpha subunit 5 |
| SEMA3A | Semaphorin 3A |
| SLMAP | Sarcolemma-associated protein |
| TRPM4 | Transient receptor potential cation channel subfamily M member 4 |




Hossini et al, Circulation. 2018;138:1195-1205

# Guideline Recommendations: BrS

| Recommendation | Consensus statement instruction | Ref. |
|---|---|---|
| Genetic testing with sequencing of *SCN5A* is recommended for an index case diagnosed with BrS with a type I ECG in standard or high precordial leads occurring either (i) spontaneously, or (ii) induced by sodium-channel blockade in presence of supporting clinical features or family history. |  | 21,171 |
| Rare variants in genes with a disputed or refuted gene-disease clinical validity should not be reported routinely[a] for BrS genetic testing in a diagnostic setting. |  | 21 |
| Targeted sequencing of variant(s) of unknown significance in *SCN5A* with a population allele frequency $<1 \times 10^{-5}$ identified in an index case can be considered concurrently with phenotyping for family members, following genetic counselling, to assess variant pathogenicity through co-segregation analysis. |  | |
| Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causative variant. |  | |
| Predictive genetic testing (of pathogenic *SCN5A* variants) in related children is recommended from birth onward (any age). |  | |

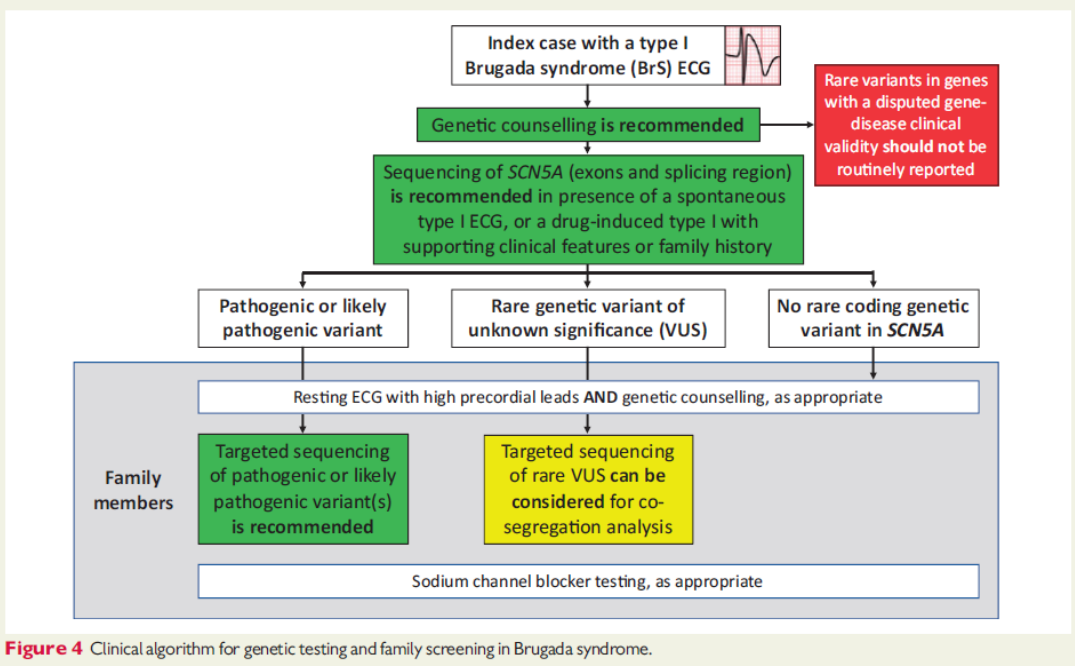



**Figure 4** Clinical algorithm for genetic testing and family screening in Brugada syndrome.

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# Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

**Table I** Classification of evidence for genes reported as causing catecholaminergic polymorphic ventricular tachycardia

(n=11)

| Gene | Protein | HGNC ID | Chromosomal location | Inheritance | Presence on GTR panels, *n* = 12 (%) | Scoring classification | Final expert classification | Other arrhythmia conditions with valid gene–disease relationship |
|---|---|---|---|---|---|---|---|---|
| *RYR2* | Ryanodine receptor 2 | 10484 | 1q43 | AD | 100% | *Definitive* | *Definitive* | — |
| *CASQ2* | Calsequestrin-2 | 1513 | 1p13.1 | AR | 100% | *Definitive* | *Definitive* | — |
| | | | | AD | | *Moderate* | *Moderate* | |
| *TRDN* | Triadin | 12261 | 6q22.31 | AR | 92% | *Definitive* | *Definitive* | LQTS |
| *TECRL* | Trans-2,3-enoyl-CoA reductase like | 27365 | 4q13.1 | AR | 25% | *Definitive* | *Definitive* | — |
| *CALM1* | Calmodulin-1 | 1442 | 14q32.11 | AD | 92% | *Moderate* | *Moderate*[a] | LQTS |
| *CALM2* | Calmodulin-2 | 1445 | 2p21 | AD | 58% | *Moderate* | *Moderate*[a] | LQTS |
| *CALM3* | Calmodulin-3 | 1449 | 19q13.32 | AD | 67% | *Limited* | *Moderate*[a] | LQTS |
| *KCNJ2* | Potassium voltage-gated channel subfamily J member 2 | 6263 | 17q24.3 | AD | 92% | *Limited* | *Disputed* | Andersen–Tawil syndrome, SQTS |
| *SCN5A* | Sodium voltage-gated channel alpha subunit 5 | 10593 | 3p22.2 | AD | 25% | *Limited* | *Disputed* | LQTS, BrS |
| *PKP2* | Plakophilin-2 | 9024 | 12p11.21 | AD | 0% | *Limited* | *Disputed* | ARVC |
| *ANK2* | Ankyrin-2 | 493 | 4q25-q26 | AD | 75% | *Limited* | *Disputed* | — |

Walsh et al. Euro Heart J. 2022. 43, 1500-1510

# Guideline Recommendations: CPVT

| Recommendation | Consensus statement instruction | Ref. |
|---|---|---|
| In any patient satisfying the diagnostic criteria for CPVT (such as Class 1 clinical diagnosis[a] or CPVT diagnostic score >3.5[b]), molecular genetic testing is recommended for the currently established definite/strong evidence CPVT-susceptibility genes: *RYR2, CASQ2, CALM1-3, TRDN*, and *TECRL*. |  | 91,141–145 |
| In phenotype-positive CPVT patients (definition: see rec. 1) who are negative for those established CPVT-susceptibility genes, genetic testing may be considered for CPVT phenocopies resulting from pathogenic variants in the *KCNJ2, SCN5A*, and *PKP2* genes. |  | 17,146–148 |
| In patients with a modest phenotype for CPVT (i.e. CPVT diagnostic score ≥ 2 but < 3.5[b]), genetic testing may be considered for the established definite/strong evidence CPVT-susceptibility genes: *RYR2, CASQ2, CALM1-3, TRDN*, and *TECRL*. |  | 17,91,141–145 |
| Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causative variant. |  | 149,150 |
| Predictive genetic testing in related children at risk of inheriting a P/LP variant is recommended from birth onward (any age). |  | |

**Table 7** Genes implicated in catecholamine polymorphic ventricular tachycardia (CPVT)

| Gene | Locus | Phenotype—syndrome | Protein (functional effect) | Frequency | ClinGen classification |
|---|---|---|---|---|---|
| *RyR2* | 1q43 | CPVT/AD | RyR2 (↑); inappropriate $Ca^{2+}$ release from the SR | 60–70% | Definite |
| *CASQ2* | 1p13.1 | CPVT/AR | Inappropriate $Ca^{2+}$ release from the SR | ±5% | Definite |
| *CASQ2* | 1p13.1 | CPVT/AD | Inappropriate $Ca^{2+}$ release from the SR | ±5% | Moderate |
| *CALM 1–3* | 14q32.11<br>2p21<br>19q13.32 | CPVT/AD | ↑ RyR2 binding affinity resulting in inappropriate $Ca^{2+}$ release from the SR | <1% | Strong |
| *TECRL*[a] | 4q13.1 | CPVT/AR | Altered $Ca^{2+}$ homeostasis, possibly linked to fatty acid/lipid metabolism | <1% | Definite |
| *TRDN*[a] | 6q22.31 | CPVT/AR | ↓ expression leading to remodelling of the cardiac dyad/calcium release unit | <1% | Definite |
| *KCNJ2* | 17q24.3 | ATS/AD | Loss-of-$I_{K1}$ channel function | <1% | Definite |

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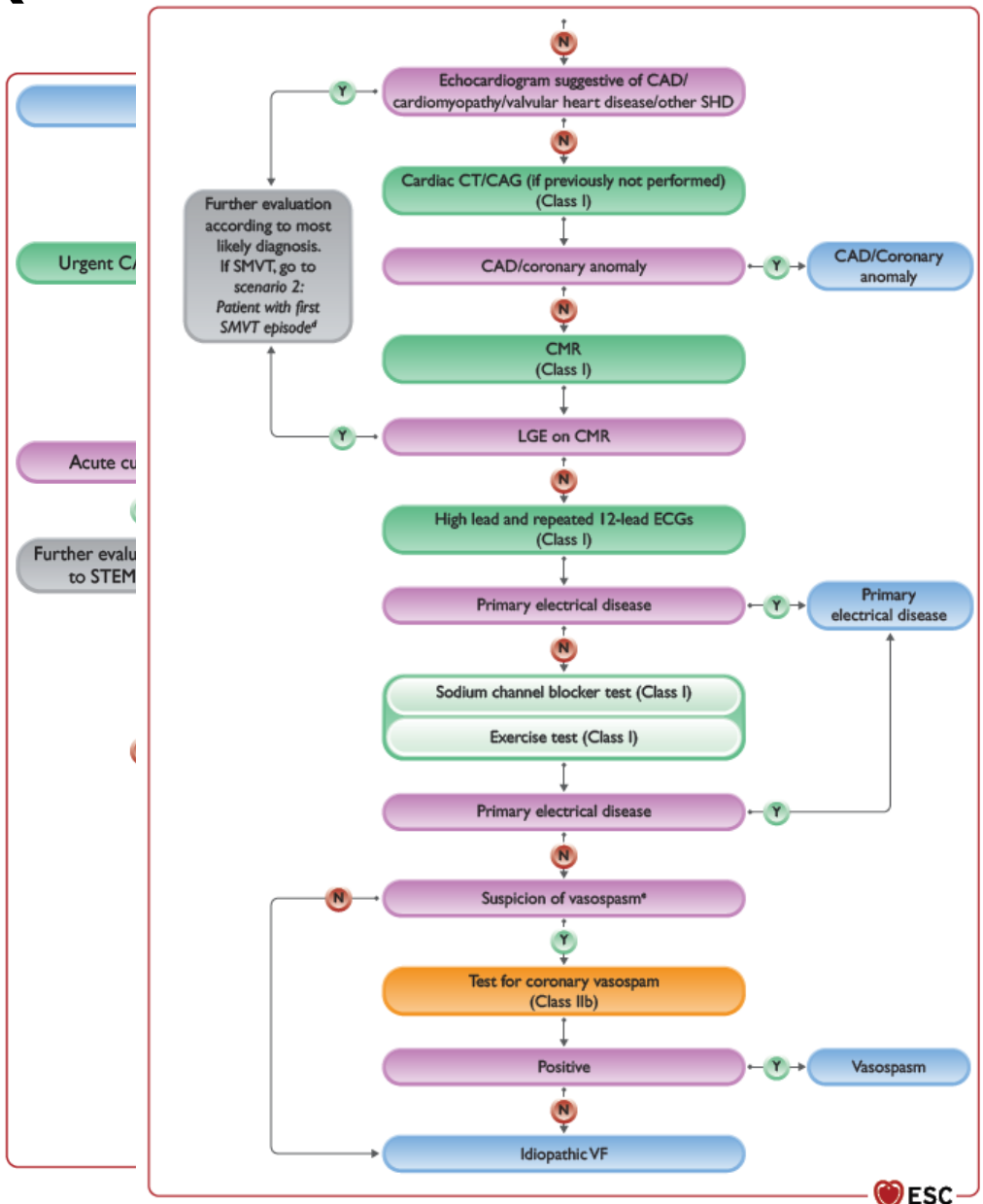
# Idiopathic Ventricular Fibrillation (IVF)

- IVF is a diagnosis of exclusion, after extensive evaluation of cardiac & non-cardiac cause of VF arrest.

- Prevalence of IVF is decreasing, due to improved diagnostic testing (i.e post-mortem genetic analysis).
  - 8-10% in VF arrest




2022 ESC Guidelines for the management of patients with VA and prevention of SCD

# Idiopathic Ventricular Fibrillation (IVF)

- Genetic background of IVF may be quite heterogenous, due to possibility of unrecognized cardiomyopathy and channelopathy.

- There may be genetic background of ‘true’ IVF.

**Table 3** **IVF genes and their suspected mechanism(s)**

| Genes | Suspected mechanism(s) | Observed phenotype |
|---|---|---|
| *CALM1* | Dysregulated binding of Calmodulin (CaM) to ion channels with different consequences on ion channel function (altered calcium-sensitive gating, channel assembly, and cell surface expression) and related disturbances in excitability, excitation–contraction coupling and refractoriness | Modest QTc prolongation |
| *IRX3*-encoded Iroquois homeobox gene family transcription factor | Attenuation of IRX3 transfection up-regulated SCN5A and connexin-40 mRNA, resulting in functional perturbation in the His-Purkinje system | Short-coupled TdP/PVC-triggered VF |
| *RYR2*-encoded cardiac calcium release channel | Suppression-of-function mutation reduces $Ca^{2+}$ release and leads to gradual $Ca^{2+}$ overload in the sarcoplasmic reticulum and prolonged release leading to early afterdepolarizations | Short-coupled TdP/PVC-triggered VF |
| Promoter haplotype in the *DPP6* gene locus on chromosome 7 | Increased DPP6 mRNA levels as consequence of mutations in regulatory sequences of the gene, leading to altered inactivation kinetics of native transient current (*I*to) channel complex | Short-coupled TdP/PVC-triggered VF |

Conte et al. Europace. 2021. 23, 4-10

# Guideline Recommendations: IVF

## Post-mortem

When a SCD remains unexplained despite an autopsy and toxicology, post-mortem genetic testing in the deceased individual targeted to channelopathy genes should be performed when the circumstances and/or family history support a primary electrical disease.

When a SCD <50 years old remains unexplained despite an autopsy, toxicology and channelopathy gene panel testing, post-mortem genetic testing in the deceased individual may be extended to a wider panel including cardiomyopathy genes.

## Survivors

In selected UCA survivors with idiopathic VF, genetic testing for founder variants,[a] where relevant, should be considered.

In UCA survivors, genetic testing of channelopathy and cardiomyopathy genes may be considered.

## Decedents

In a decedent with unexplained SCD or an UCA survivor, hypothesis-free (post-mortem) genetic testing using exome or genome sequencing should not be performed.

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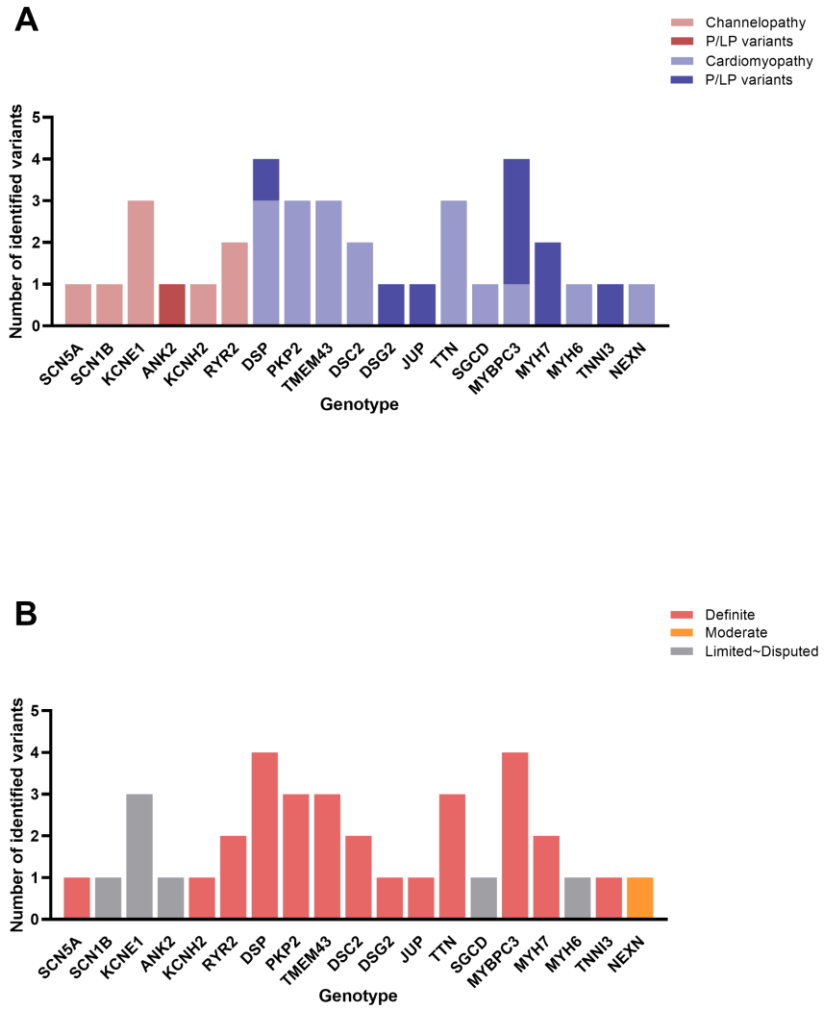
# Difficulties in non-definite phenotypes

- Genetic  sequencing in patients that lack relevant phenotype is not recommended.
- It increases the number of VUSs without significant increase of P/LP variants.
- Increase of VUS leads to the chance of picking up secondary or incidental findings that are not relevant to the disease in question.

## Genetic testing in Korean IVF probands




Musunru et al. Circ Genom Precis Med. 2020

Jeong et al. Not published

# Take Home Message

- Advances in genetic sequencing techniques have enabled an in-depth evaluation of inherited cardiovascular disease.

- Genetic variants previously described as “pathogenic” were too common in populations to be disease causing, which led to reappraisal of gene validity.

- Index Patients
  - For clinical use, genetic testing with genes of strong to definite evidence is suitable.
- Family Members
  - Targeted genetic sequencing is recommended in family members, if index patient is detected with disease-causing variant.