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Genetic testing in heritable cardiac arrhythmia syndromes: differentiating pathogenic mutations from background genetic noise

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Abstract

Purpose of review—In this review, we summarize the basic principles governing rare variant interpretation in the heritable cardiac arrhythmia syndromes, focusing on recent advances that have led to disease-specific approaches to the interpretation of positive genetic testing results.

Recent findings—Elucidation of the genetic substrates underlying heritable cardiac arrhythmia syndromes has unearthed new arrhythmogenic mechanisms and given rise to a number of clinically meaningful genotype–phenotype correlations. As such, genetic testing for these disorders now carries important diagnostic, prognostic, and therapeutic implications. Recent large-scale systematic studies designed to explore the background genetic 'noise' rate associated with these genetic tests have provided important insights and enhanced how positive genetic testing results are interpreted for these potentially lethal, yet highly treatable, cardiovascular disorders.

Summary—Clinically available genetic tests for heritable cardiac arrhythmia syndromes allow the identification of potentially at-risk family members and contribute to the risk-stratification and selection of therapeutic interventions in affected individuals. The systematic evaluation of the 'signal-to-noise' ratio associated with these genetic tests has proven critical and essential to assessing the probability that a given variant represents a rare pathogenic mutation or an equally rare, yet innocuous, genetic bystander.

Keywords

Brugada syndrome; genetics; ion channels; long QT syndrome; sudden death

INTRODUCTION

Over the past decade, the discovery that mutations in the genes encoding key cardiac ion channel α-subunit and β-subunit as well as intracellular calcium-handling proteins serve as

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Conflicts of interest

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the primary genetic substrate for a spectrum of heritable cardiac arrhythmia syndromes or 'cardiac channelopathies', including long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and Brugada syndrome (BrS) [1–3], has broadened our mechanistic understanding of these sudden cardiac death (SCD)-predisposing genetic disorders. Furthermore, these discoveries have given rise to numerous clinically relevant genotype–phenotype correlations, spurring a number of professional societies to recommend the judicious use of clinical genetic testing for the purpose of identifying genetically predisposed individuals with concealed clinical phenotypes and guiding the genotype-specific risk-stratification and clinical management of individuals with clinically definitive disease [4,5,6■■,7■■].

However, as the availability and clinical use of genetic testing increases, so does the probability that rare 'variants of uncertain significance' (VUS), alterations in the normal sequence of a gene whose association with disease risk is unknown, will be identified in putative disease-susceptibility genes. As we enter an era of next-generation sequencing, the interpretation of genetic testing results, particularly when the clinical evidence for disease is insufficient or inconclusive, is bound to present an increasingly daunting challenge [8,9]. As with any clinical test, the proper interpretation of genetic testing results requires the careful consideration of all potential sources of both false-positive (e.g., background genetic noise or the frequency of genetic variations in a particular gene in a healthy population) and false-negative (e.g., high prevalence of concealed phenotypes due to incomplete penetrance) results (Fig. 1). Understanding the 'signal-to-noise' ratio associated with a given genetic test is particularly important in SCD-predisposing conditions in which the balancing act of distinguishing rare pathogenic mutations from equally rare, yet innocuous, genetic variants can have life-altering implications given that highly effective therapeutic interventions are available, but not entirely devoid of complications or comorbidities, particularly for invasive approaches.

In this review, we describe the basic principles governing rare variant interpretation, present evidence-based algorithms designed to aid in the interpretation of genetic testing results, and lastly detail the clinical utility of a properly interpreted positive genetic test in the diagnosis and clinical management of individuals with these potentially lethal, yet highly treatable, genetic disorders.

General principles of rare variant interpretation

Due to the presence of variable/incomplete disease penetrance and the existence of background genetic noise (Fig. 1), the interpretation of genetic testing should, with the exception of certain well-established disease-causative mutations, always be viewed as probabilistic, rather than deterministic/binary, in nature. When interpreted in the context of the overall clinical picture by experienced personnel (e.g., molecular/genetic cardiologists, clinical/cardiovascular geneticists, or genetic counselors), there are several criteria that can be used to support labeling a given variant as a 'potentially disease-causative mutation'. These criteria often include, but are not necessarily limited to, cosegregation of the variant with disease; absence or extreme rarity of the variant in control cohorts or publicly available exome/genome datasets; nonsense, frameshift, or insertion/deletion mutations that lead to truncated protein products; localization of nonsynonymous single nucleotide variants (nsSNVs) to highly conserved amino acid residues/key functional domains and/or result in radical amino acid substitutions (i.e., phylogenetic/physicochemical properties); and evidence of perturbed ion channel function through in-vitro functional studies [10,11]. Although these criteria are quite helpful, it is important to remember that satisfying any one of these particular criteria does not necessarily equate to a designation as a definite, pathogenic mutation. In fact, in-silico tools like Sorting Intolerant from Tolerant (SIFT), PolyPhen2, and so on, that assess a variant's likelihood of pathogenicity based on

phylogenetic and/or physicochemical properties, must be used with great caution because in isolation their false-positive rate can be quite high, especially when applied to LQTS genetic testing [12].

When these general principles fail to provide sufficient cumulative evidence to label a given variant as 'pathogenic/disease-causative', the variant should be deemed a VUS until additional information (e.g., disease-specific considerations, functional studies, etc.) to either confirm or deny its pathogenicity can be obtained. Importantly, the presence of a VUS should never be used to establish a diagnosis in the index case or for confirmatory genetic testing of potentially at-risk relatives.

Long QT syndrome

Congenital LQTS is a genetically heterogeneous disorder of myocardial repolarization with an estimated prevalence as high as one in 2000 persons [13]. Clinically, LQTS is objectively characterized by a prolonged heart rate-corrected QT interval (QTc) that exceeds the 99th percentile values for otherwise healthy men (> 470 ms) and women (> 480 ms) on 12-lead ECG and an increased risk of syncope, seizures, and sudden death secondary to *torsades de pointes*, the characteristic form of polymorphic ventricular fibrillation observed in LQTS [14]. However, the clinical diagnosis of LQTS is often clouded by the genetic phenomena of incomplete penetrance and variable expressivity [15–17], as evidenced by the 10–40% of genotype-positive individuals who fail to display overt QT prolongation on resting ECG [15,18].

At present, mutations in 13 distinct LQTS-susceptibility genes have been implicated in the pathogenesis of the disorder (Table 1 [19–47]). However, 60–75% of clinically definitive LQTS patients harbor a mutation in one of three major LQTS-susceptibility genes: the *KCNQ1*-encoded Kv7.1 potassium channel (LQT1, 30–35%), the *KCNH2*-encoded Kv11.1/hERG potassium channel (LQT2, 25–30%), or the *SCN5A*-encoded Nav1.5 sodium channel (LQT3, 5–10%) [24,48]. Inclusion of the remaining 10 minor LQTS-susceptibility genes increases the genetic yield by less than 5%, but also increases the likelihood of encountering a false-positive. Additionally, reflex testing for copy number variations/larger genomic rearrangements in *KCNQ1* and *KCNH2* is available and may increase the overall yield to approximately 80–85% [49,50]. At minimum, all clinically available genetic tests include the three major LQTS-susceptibility genes, and the expected yield of targeted (LQT1–3) and comprehensive (LQT1–LQT13) genetic testing in index cases with unequivocal evidence of disease is summarized in Table 2 [7■■,18].

Recent studies have demonstrated that approximately 4% of ostensibly healthy white individuals and 6–8% of black individuals harbor a rare, amino acid-altering genetic variant in one of the three major LQTS-susceptibility genes (*KCNQ1, KCNH2,* or *SCN5A*) [51]. Coupling the established rate of innocuous background genetic variation with large compendia of rare variants identified in clinically definite LQTS cases has allowed the calculation of a so-called signal-to-noise ratio associated with targeted genetic testing (Table 2) and yielded a number of observations that have improved how the presence of a VUS in a major LQTS-susceptibility gene should be interpreted.

Specifically, certain mutation types (e.g., radical/truncating) and missense mutation localizing to specific topological structure-function domains of the Kv11.1/hERG, Kv7.1, and Nav1.5 channels (e.g., pore/transmembrane regions) carry a high (>95%) estimated predictive value (EPV), suggesting that, when identified in a case with high clinical probability for the contemplated clinical diagnosis, these mutations carry a high genetic probability of being disease-causative [51]. Collectively, this body of evidence has been

used to synthesize a topology-driven algorithm designed to aid in the probabilistic interpretation of positive LQTS genetic testing results (Fig. 2a).

Based on current Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA) guidelines, comprehensive or targeted LQTS genetic testing is recommended for any individual with a strong clinical suspicion of LQTS based on clinical/family history and electrocardiographic phenotype or an asymptomatic individual with unexplained QT prolongation (> 480 before puberty and > 500 after puberty) [7■■]. Mutation-specific testing/cascade screening is recommended for the relatives of genotype-positive LQTS index patients, even for family members with negative clinical/electrocardiographic phenotypes [7■■]. Although genetic testing is not needed to establish a diagnosis of LQTS in the setting of a robust clinical phenotype, genotype is one of many factors to consider when assessing the risk of SCD and selecting appropriate therapeutic interventions [52]. Specifically, genotype has proven particularly useful in predicting the efficacy of β-blocker pharmacotherapy as β-blockade has been shown to be extremely protective in LQT1 patients and moderately protective in LQT2 patients [53]. In contrast, targeting the pathogenic late sodium current with a combination of a β-blocker (propranolol) and possibly mexiletine, flecainide, or ranolazine represents the preferred pharmacotherapy option for LQT3 patients [54,55]. Nevertheless, it should be stressed that all risk-stratification/management decisions, particularly prophylactic implantable cardioverter defibrillator (ICD) implantation in LQT3 patients, require the careful consideration of the patient's entire clinical picture, which includes both genetic and nongenetic risk factors such as 15 years of age or less, female sex, and QTc more than 500 ms.

Catecholaminergic ventricular tachycardia

CPVT is a genetic disease of intracellular calcium handling that affects an estimated one in 7000 to one in 10 000 individuals and is associated with an increased risk of syncope and SCD secondary to adrenergically mediated ventricular arrhythmias [56–58]. In general, CPVT is associated with a normal resting ECG and diagnosed on the basis of clinical history and the induction of significant ventricular ectopy, including the diagnostic hallmark of bidirectional or polymorphic ventricular tachycardia, during exercise or catecholamine stress testing [58,59]. In contrast to other cardiac channelopathies, the penetrance and expressivity of CPVT appears to be much higher, with an overall disease penetrance reported to be approximately 80% [60,61■] and a positive family history of SCD present in up to 60% of families harboring mutations in *RYR2* [56].

At present, mutations in three distinct CPVT-susceptibility genes have been associated with the pathogenesis of CPVT (Table 1). Approximately 60–65% of CPVT index cases harbor a mutation in the *RYR2*-encoded ryanodine receptor 2/intracellular calcium release channel (CPVT1), whereas mutations in the minor genes (*CASQ2*/CPVT2 and *KCNJ2*/CPVT3) are identified in fewer than 5% of cases [56,57,62]. The overall yield and signal-to-noise ratio of CPVT genetic testing are summarized in Table 2.

At present, over 100 CPVT1-causative mutations have been reported and these mutations tend to localize to three specific clusters/regions of the RyR2 protein. The fact that nearly all of the known CPVT1 mutations localize to only 45 exons of the massive and hypomorphic 105-exon-containing *RYR2* gene has led several groups to propose targeted/tiered screening approaches [57]. However, the identification of CPVT1-causative mutations that reside outside these ‘hotspot’ exons has led to some concern that targeted/tiered screening may be suboptimal [34]. As such, no consensus or clear definition of the most appropriate strategy for *RYR2* screening currently exists.

Given the relative paucity of background genetic variation in *RYR2*, particularly within hotspot exons, no additional CPVT-specific criteria for the interpretation of a positive genetic test currently exist. Based on current HRS/EHRA guidelines, CPVT genetic testing is recommended for any individual with a strong clinical suspicion of CPVT based on history and electrocardiographic phenotype observed during exercise/catecholamine provocation testing for the primary purpose of identifying the underlying CPVT-causative mutation needed to facilitate the recommended mutation-specific screening of all potentially at-risk first-degree and second-degree relatives, including newborns/infants given the known association between CPVT and sudden infant death syndrome [7■■]. Genotype presently has no bearing on the risk-stratification or selection of management strategies in patients with CPVT.

Brugada syndrome

BrS is a rare heritable cardiac arrhythmia syndrome with an estimated prevalence of five in 10 000 individuals of European descent, but may be more prevalent in those of Asian descent [63]. Clinically, BrS is characterized by the presence of coved-type ST-segment elevation and inverted T-waves (type 1 BrS ECG pattern) in the right precordial leads (V_1–V_3) and an increased risk of syncope and SCD secondary to re-entrant ventricular tachycardia/ventricular fibrillation [64,65]. BrS predominantly affects post-pubertal men between 20 and 50 years of age with SCD generally occurring during sleep [66]. Due to the transient and dynamic nature of BrS ECG pattern, sodium channel blockers (e.g., flecainide, procainamide, and ajmaline) may precipitate a type 1 BrS ECG pattern in order to clarify the diagnosis in patients with suspected disease [63]. In comparison to other cardiac channelopathies, overall disease penetrance in BrS appears to be quite low, as evidenced by the observation that on average only 16% (range 12.5–50%) of SCN5A mutation-positive individuals across 52 BrS families featured spontaneous/sodium channel blocked-induced ST-segment elevation and/or a history of cardiac events [67].

Over the past 20 years, mutations in at least 11 distinct BrS-susceptibility genes have been identified (Table 1). Loss-of-function mutations in the *SCN5A*-encoded Nav1.5 sodium channel represent the most common genetic substrate (BrS1), accounting for approximately 15–30% of all BrS cases [67–69]. An additional 10–15% of BrS cases, particularly individuals with ST-segment elevation and a shortened QT interval (< 330 ms for men and < 340 ms for women), may be linked to perturbation of the L-type calcium channel (Table 1) [37,44]. However, recent evidence suggests that, in the absence of concomitant ST-segment elevation and short QT interval, a BrS2 through BrS11 genotype is collectively observed in fewer than 5% of cases [70■]. However, it should be noted that this observation might also be cohort-specific.

Due to the combined rarity of the minor BrS genotypes, only BrS1 (*SCN5A*) targeted BrS genetic testing has been deemed to be clinically useful at the present time [6■■,7■■] and the expected genetic yield/signal-to-noise ratio associated with targeted testing is summarized in Table 2. Although no studies that specifically address the issue of *SCN5A* variant interpretation in BrS exist, evidence derived from the study of a large international compendium of BrS-associated *SCN5A* mutations [71] and the systematic assessment of mutations in the 12 BrS-susceptibility genes in a large unrelated cohort of BrS patients [70■] have yielded several important observations/genotype–phenotype correlations that may aid in the interpretation of BrS genetic testing results. An algorithm synthesized from this body of evidence is outlined in Fig. 2b.

Based on current HRS/EHRA guidelines, genetic testing for *SCN5A* alone is useful for most individuals with a strong clinical suspicion of BrS based on clinical/family history and or electrocardiographic phenotype with the primary goal of identifying a BrS-causative

mutation in the index case that would facilitate the recommended mutation-specific screening of appropriate relatives [6■■,7■■,70■]. Phenotype-guided genetic analysis of *CACNA1C, CACNB2,* and *CACNA2D1* may be useful in BrS patients who also feature a short QT interval [70■]. However, like CPVT, no clear prognostic or therapeutic implications are associated with positive genetic testing results.

Other heritable cardiac arrhythmia syndromes

Genetic testing for cardiac channelopathies such as short QT syndrome (SQTS), familial atrial fibrillation (FAF), and cardiac conduction disease (CCD) less frequently encountered in clinical practice is available. However, the lower contribution of known disease-susceptibility genes to the pathogenesis of these disorders currently limits the clinical utility of these tests. As such, few insights exist to guide the interpretation of SQTS, FAF, or CCD genetic testing results.

CONCLUSION

Given that clinical genetic testing should be viewed as probabilistic rather than deterministic in nature, the accurate interpretation of genetic testing results requires careful consideration of both genetic and clinical factors. The elucidation of the spectrum of healthy genetic variation inherent in channelopathy-susceptibility genes that comprises the background genetic noise associated with clinical genetic testing for these disorders has provided important insights that now guide the interpretation of positive genetic test results. With the recent completion of large-scale exome/genome sequencing projects (e.g., 1000 Genomes Project), we are beginning to realize that the prevalence of functionally relevant genetic variation within putative channelopathy-susceptibility genes may be higher than previously anticipated. Cautious scrutiny of this evolving compendium of human genetic variation in health coupled with the use of next-generation sequencing technology to thoroughly explore the genetic architecture underlying the heritable cardiac arrhythmia syndromes promises to provide clinically meaningful insights that will improve the interpretation of positive genetic testing results in the future for these potentially lethal, yet highly treatable, genetic disorders.

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KEY POINTS

- Clinical genetic testing for heritable cardiac arrhythmia syndromes must be viewed as probabilistic, rather than deterministic, and always interpreted in the context of a patient's entire clinical picture.
- Rare variant interpretation is a balancing act that requires careful consideration of both the prevalence of genotype-positive individuals with concealed clinical phenotypes secondary to incomplete penetrance and variable expressivity and the estimated one in 25 otherwise healthy individuals expected to harbor a rare, and most likely innocuous, background genetic variant within one of the three major channelopathysusceptibility genes.
- Radical/truncating mutations and missense mutations residing within critical structure-function domains (e.g., transmembrane/pore) of the cardiac ion channels encoded by the one major BrS-susceptibility and three major LQTS-susceptibility gene(s) are probably pathogenic when identified in patients with a robust clinical phenotype.
- The judicious use and proper interpretation of clinical genetic tests offer the potential to identify potentially at-risk relatives, contribute to risk-stratification, and guide the selection of appropriate therapeutic interventions.

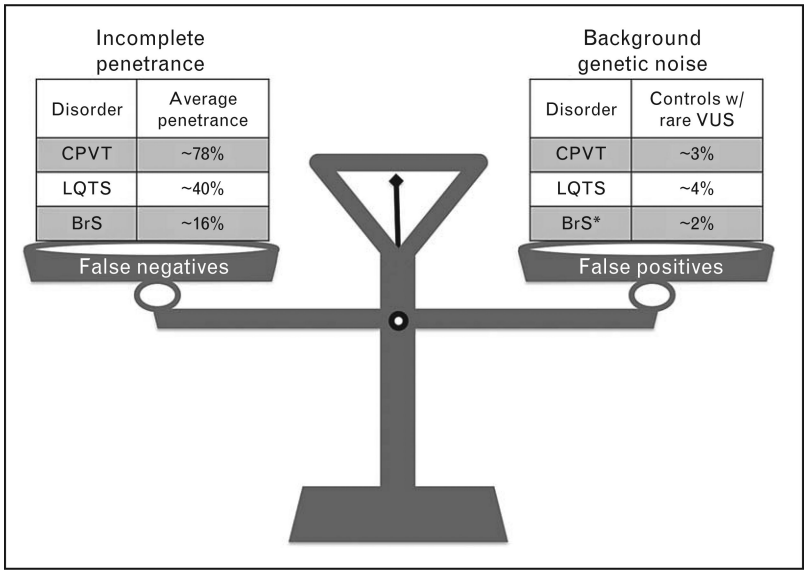

FIGURE 1.

The balancing act involved in the interpretation of heritable cardiac arrhythmia syndrome genetic testing results. Careful consideration of potential sources of false positives (e.g., background genetic noise) and false negatives (e.g., prevalence of concealed phenotypes due to incomplete penetrance) along with the patient's entire clinical picture is necessary to effectively interpret reportedly positive long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and Brugada syndrome (BrS) genetic testing results. * indicates that the BrS background noise rate of 2% is just with respect to *SCN5A*-associated BrS1 in whites. The background noise rate would be much higher when considering BrS1-11 in total and in minorities.

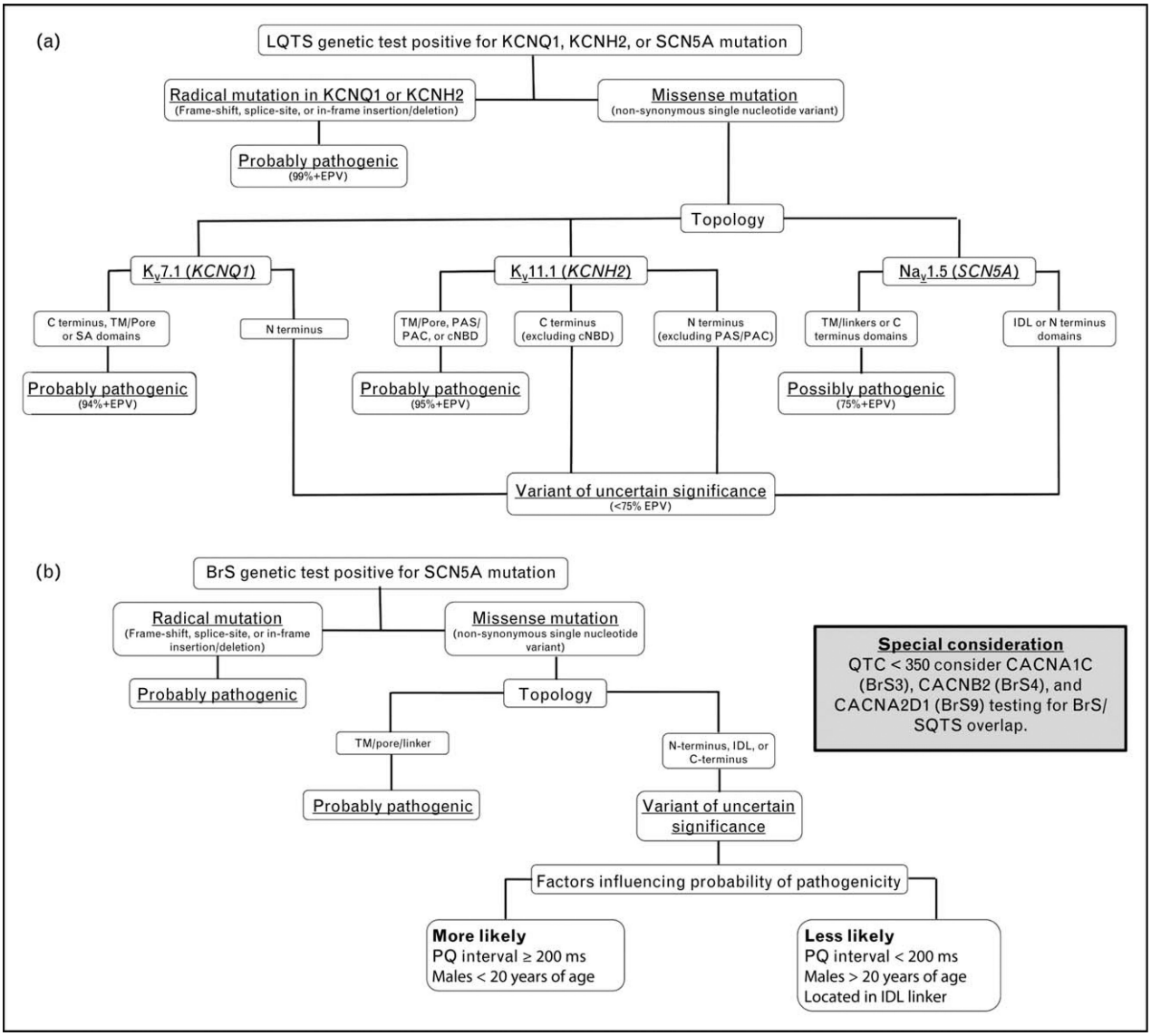

FIGURE 2.

Evidence-based algorithms designed to aid in the interpretation of positive long QT syndrome and Brugada syndrome genetic testing results. (a) Algorithm for interpreting a positive long QT syndrome (LQTS) genetic test. Radical mutations that significantly alter/truncate Kv7.1 or Kv11.1, such as insertions/deletions, alteration of intronic/exonic splice site boundaries, and nonsense mutations, are probably LQTS-associated. Those rare, absent in controls, nonsynonymous single nucleotide variants (nsSNVs; missense mutations) that localize to Kv7.1 (TM/pore, SA, or C terminal domains), Kv11.1 (TM/Pore, PAS/PAC, or cNBD), or Nav1.5 (TM/pore/linker or C terminus) are probably or possibly pathogenic. Variants outside these topological structure-function domains are deemed to be variants of uncertain significance (VUS), unless additional evidence is present (e.g., cosegregation with disease, LQTS-like electrophysiological phenotype, etc.). cNBD, cyclic nucleotide binding domain; EPV, estimated predictive value; IDL, interdomain linker; PAC, per-arnt-sim C-terminal associated; PAS, per-arnt-sim; SA, subunit assembly; TM, transmembrane. (b) Algorithm for interpreting a positive Brugada syndrome (BrS) genetic test. Radical mutations that significantly alter/truncate Nav1.5 protein structure, such as insertions/

deletions, alteration of intronic/exonic splice site boundaries, and nonsense mutations, are probably pathogenic. Those rare, absent in controls, nsSNVs (missense mutations) that localize to the Nav1.5 TM/pore/linker are probably pathogenic. Variants outside this topological structure-function domain, particularly those residing in the first interdomain linker (IDL), are of uncertain disease relevance. When such a VUS is identified in an individual with a PQ interval at least 200 ms or a male less than 20 years of age, its probability of pathogenicity increases but not sufficiently so to be declared a BrS1-associated mutation without additional evidence. IDL, interdomain linker; TM, transmembrane domain.

Table 1

Genetic basis of cardiac channelopathies

Gene (genotype)	Locus	Protein	Frequency	Ref.
LQTS				
KCNQ1 (LQT1)[a]	11p15.5	Kv7.1	30–35%	[19]
KCNH2 (LQT2)[a]	7q35-46	Kv11.1	25–30%	[20]
SCN5A (LQT3)[a]	3p21-p24	Nav1.5	5–10%	[21]
ANKB (LQT4)[a]	4q25-q27	Ankyrin B	Rare	[22]
KCNE1 (LQT5)[a]	21q22.1	MinK	Rare	[23]
KCNE2 (LQT6)[a]	21q22.1	MiRP1	Rare	[24]
KCNJ2 (LQT7/ATS1)[a]	17q23	Kir2.1	Rare	[25]
CACNA1C (LQT8/TS1)[a]	12p13.3	Cav1.2	Rare	[26]
CAV3 (LQT9)[a]	3p25	Caveolin 3	Rare	[27]
SCN4B (LQT10)[a]	11q23.3	Nav1.5 β4-subunit	Rare	[28]
AKKAP9 (LQT11)[a]	7q21-q22	Yotiao	Rare	[29]
SNTA1 (LQT12)[a]	20q11.2	Syntrophin-α1	Rare	[30]
KCNJ5 (LQT13)	11q24	Kir3.4	Rare	[31]
CPVT				
RYR2 (CPVT1)[a]	1q42.1-43	Ryanodine receptor 2	50–60%	[32]
CASQ2 (CPVT2)[a]	1p13.3-p11	Calsequestrin 2	1–2%	[33]
KCNJ2 (CPVT3)[a]	17q23	Kir2.1	10%	[34]
BrS				
SCN5A (BrS1)[a]	3p21-p24	Nav1.5	20–30%	[35]
GPD1L (BrS2)[a]	3q22.3	Glycerol-3-phosphate dehydrogenase 1-like	Rare	[36]
CACNA1C (BrS3)[a]	12p13.3	Cav1.2	6.6%	[37]
CACNB2 (BrS4)[a]	10p12	Cav1.2 β2-subunit	Rare	[38]
SCN1B (BrS5)[a]	19q13.1	Nav1.5 β1-subunit	Rare	[39]
KCNE3 (BrS6)[a]	11q13.4	MiRP2	Rare	[40]
SCN3B (BrS7)[a]	11q24.1	Nav1.5 β3-subunit	Rare	[41]
KCNJ8 (BrS8)[a]	12p12.1	Kir6.1	2%	[42,43]
CACNA2D1 (BrS9)	7q21-q22	Cav1.2 α2/δ1-subunit	Rare	[44]
KCND3 (BrS10)[a]	1p13.2	Kv4.3	Rare	[45,46]
MOG1 (BrS11)	17p13.1	Mog1	Rare	[47]

Rare is defined as contributing to fewer than 1% of cases. Although tentative disease subtypes are provided in parenthesis, we strongly recommend annotating only common disease subtypes numerically. For rare genetic subtypes, we suggest that a descriptor such as SNTA1-LQTS instead of

LQT12 is preferable, as no consensus exists on the numerical nomenclature for many minor subtypes. ATS, Andersen–Tawil syndrome; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; LQTS, long QT syndrome; TS, Timothy syndrome.

[a]Commercial genetic testing for these genes is available from at least one company.

Table 2

Clinical impact and considerations for genetic testing in cardiac channelopathy index cases

	Epidemiologic considerations		Clinical impact			Practical considerations	
Disorder	**Prevalence**	**Annual event rate**	**Diagnostic**	**Prognostic**	**Therapeutic**	**Yield of genetic test**[a]	**Signal-to-noise ratio**[b]
LQTS	1 : 2000	0.3–0.6%	Strong	Strong	Moderate	75% (80%)	19 : 1
CPVT	1 : 7000	3.1%	Strong	Weak	Negligible	60% (70%)	20 : 1
BrS	5 : 10000	1.4%	Moderate	Weak	Negligible	20% (30%)	10 : 1

BrS, Brugada syndrome; CPVT, catecholaminergic ventricular tachycardia; LQTS, long QT syndrome.

The clinical impact and practical consideration sections are reproduced in part from [7■■].

[a]Yield of genetic test represents published/unpublished estimates derived from unrelated cases with robust clinical phenotypes. The first number represents the yield of the targeted major susceptibility-gene screen for whites, whereas numbers in parentheses represent the total yield of all known disease-susceptibility genes included in commercially available panels for whites. There is currently insufficient evidence to derive genetic yields for minority populations.

[b]The signal-to-noise ratio is calculated by dividing the yield in cases by the background rate of variants of uncertain significance (VUS) in controls.