Circulation: Arrhythmia and Electrophysiology

REVIEW

Unraveling Complexities in Genetically Elusive Long QT Syndrome

Babken Asatryan, MD, PhD; Brittney Murray, MS, CGC; Alessio Gasperetti, MD, PhD; Rebecca McClellan, MGC, CGC; Andreas S. Barth, MD, PhD

ABSTRACT: Genetic testing has become standard of care for patients with long QT syndrome (LQTS), providing diagnostic, prognostic, and therapeutic information for both probands and their family members. However, up to a quarter of patients with LQTS do not have identifiable Mendelian pathogenic variants in the currently known LQTS-associated genes. This absence of genetic confirmation, intriguingly, does not lessen the severity of LQTS, with the prognosis in these gene-elusive patients with unequivocal LQTS mirroring genotype-positive patients in the limited data available. Such a conundrum instigates an exploration into the causes of corrected QT interval (QTc) prolongation in these cases, unveiling a broad spectrum of potential scenarios and mechanisms. These include multiple environmental influences on QTc prolongation, exercise-induced repolarization abnormalities, and the profound implications of the constantly evolving nature of genetic testing and variant interpretation. In addition, the rapid advances in genetics have the potential to uncover new causal genes, and polygenic risk factors may aid in the diagnosis of high-risk patients. Navigating this multifaceted landscape requires a systematic approach and expert knowledge, integrating the dynamic nature of genetics and patient-specific influences for accurate diagnosis, management, and counseling of patients. The role of a subspecialized expert cardiogenetic clinic is paramount in evaluation to navigate this complexity. Amid these intricate aspects, this review outlines potential causes of gene-elusive LQTS. It also provides an outline for the evaluation of patients with negative and inconclusive genetic test results and underscores the need for ongoing adaptation and reassessment in our understanding of LQTS, as the complexities of gene-elusive LQTS are increasingly deciphered.

Key Words: arrhythmias, cardiac ■ death, sudden, cardiac ■ genetic testing ■ long QT syndrome ■ precision medicine

BACKGROUND ON GENETICALLY ELUSIVE LONG QT SYNDROME

Over the past 2 decades, significant advancements in high throughput gene sequencing technologies with the concomitant gradual decline of sequencing costs have contributed considerably toward our understanding of the genetic architecture of long QT syndrome (LQTS), a primary cardiac channelopathy that manifests with a prolonged QT interval on the ECG, propensity to torsades de pointes tachyarrhythmias, and sudden cardiac death (SCD).[1] An early diagnosis plays a crucial role in preventing LQTS-related SCD by enabling interventions such as avoiding QT-prolonging medications, implementing appropriate pharmacotherapy, and avoiding arrhythmia triggers.[2] The ClinGen reappraisal of the 17 LQTS-associated genes found definitive evidence for only 3 genes (*KCNQ1*, *KCNH2*, and *SCN5A*) for a causative role in congenital LQTS; another 4 genes (*CALM1*, *CALM2*, *CALM3*, and *TRDN*) were found to have strong or definitive evidence for causality in LQTS with atypical features, and *CACNA1C* showed moderate level evidence for causing LQTS (but definitive evidence for Timothy syndrome).[3] Genetic testing has evolved from a solely diagnostic tool to a vital measure for risk stratification, management, and family counseling in LQTS. The implications of genetically confirmed LQTS have been profoundly studied,[4] with clinical

Correspondence to: Babken Asatryan, MD, PhD, Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, 600 N Wolfe Str, Carnegie 568 Baltimore, MD 21287, Email basatryan@yahoo.com; basatry1@jhmi.edu; or Andreas S. Barth, MD, PhD, Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, 720 Rutland Ave, Ross 871 Baltimore, MD 21205, Email abarth3@jh.edu
For Sources of Funding and Disclosures, see page XXX.

Circulation: Arrhythmia and Electrophysiology is available at www.ahajournals.org/journal/circep

Nonstandard Abbreviations and Acronyms

LQTS	long QT syndrome
PRS	polygenic risk score
QTc	corrected QT interval
VUS	variant of uncertain significance

practice recommendations emphasizing genotype-specific prognostication and the selection of pharmacotherapy.[5] However, 11% to 25% of all patients with LQTS receive negative genetic test results. Notably, in a large multicenter study, genotype-negative patients with an LQTS risk score of ≥3.5 or with a resting corrected QT interval (QTc), ≥500 ms in repeated 12-lead ECGs, in the absence of a secondary cause for QT prolongation, showed a clinical course similar to those with genetically confirmed LQTS,[6] indicating that the lack of genetic confirmation in those with unequivocal LQTS phenotype does not diminish the severity of LQTS.[7] Despite its often-overlooked nature, negative genetic test results possess diverse connotations in different scenarios, which can evolve over time (Figure 1). Perplexity and inadequate comprehension regarding such outcomes are prevalent among both patients and the medical community.[8] It is, therefore, essential to consider several key aspects in these instances. In this review, we expose the intricate basis of QTc prolongation in those without identifiable Mendelian large-effect pathogenic and likely pathogenic variants and provide clinicians with key considerations for genotype-negative patients with LQTS (Figure 2).

EXPERT EVALUATION IN A CARDIOGENETIC CLINIC

Specialized clinical cardiovascular genetics programs play an indispensable role in the diagnosis and management of patients with LQTS (and beyond),[9] particularly, because the resting QTc interval may be normal or nondiagnostic in >50% of patients with genotype-positive LQTS while ~5% of healthy individuals may have a QTc interval within the abnormal range.[10] Given that genetic testing forms part of the diagnostic process, the latest international consensus documents heavily emphasize the importance of multidisciplinary expert teams to include an inherited arrhythmia expert and genetic counselor in providing cutting-edge care.[5,11]

The appropriate measurement of the QTc interval continues to be a challenge for many clinicians. The importance of an inherited arrhythmia expert was highlighted in a study by Viskin et al who demonstrated that <50% of general cardiologists measured the QTc correctly versus 96% of QT experts.[12] A recent study demonstrated that 16% of patients referred to a large LQTS referral center for second opinion were ultimately found to not have LQTS.[13] Inclusion of the U wave in the QTc is the most common reason for erroneous measurement, immediately leading to the clinical importance of a borderline QTc lengthening. A look at the T wave provides further information regarding repolarization and may especially be informative in those with borderline QTc or normal QTc despite the presence of a pathogenic or likely pathogenic variant in LQTS-associated genes.[14] Excluding false-positive findings such as due to the inclusion of U waves and inadequate rate correction caused by sinus tachycardia are routinely considered at specialized

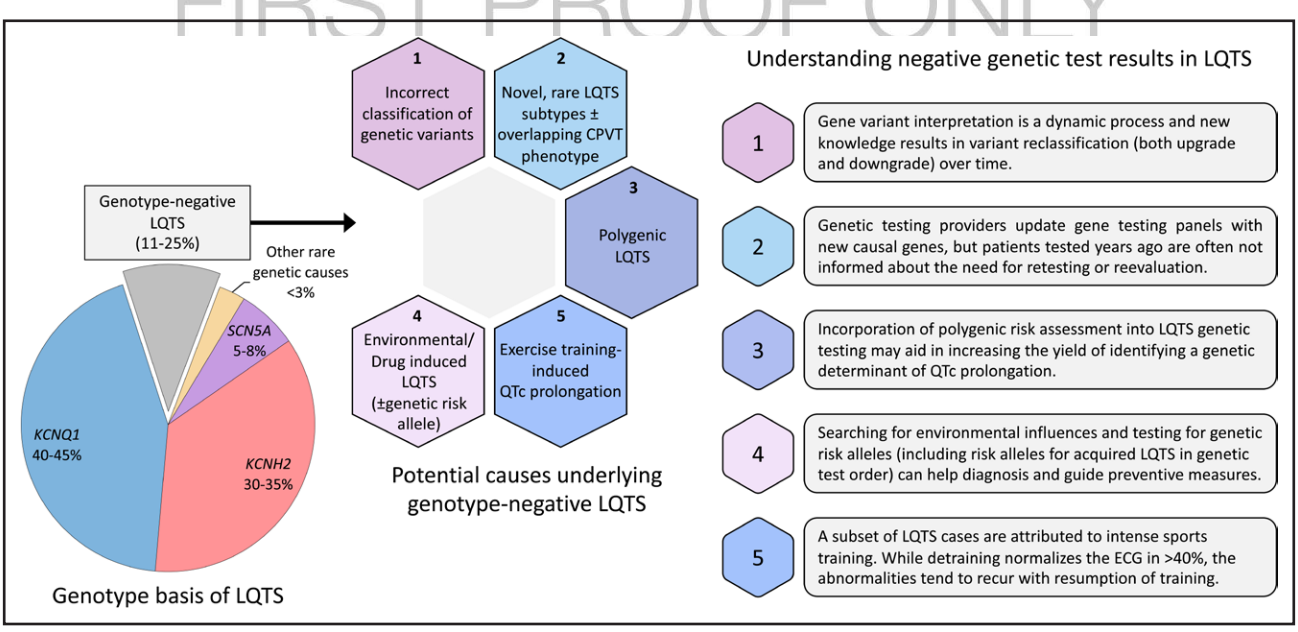

Figure 1. Potential causes implicated in genotype-negative long QT syndrome (LQTS).
CPVT indicates catecholaminergic polymorphic ventricular tachycardia.

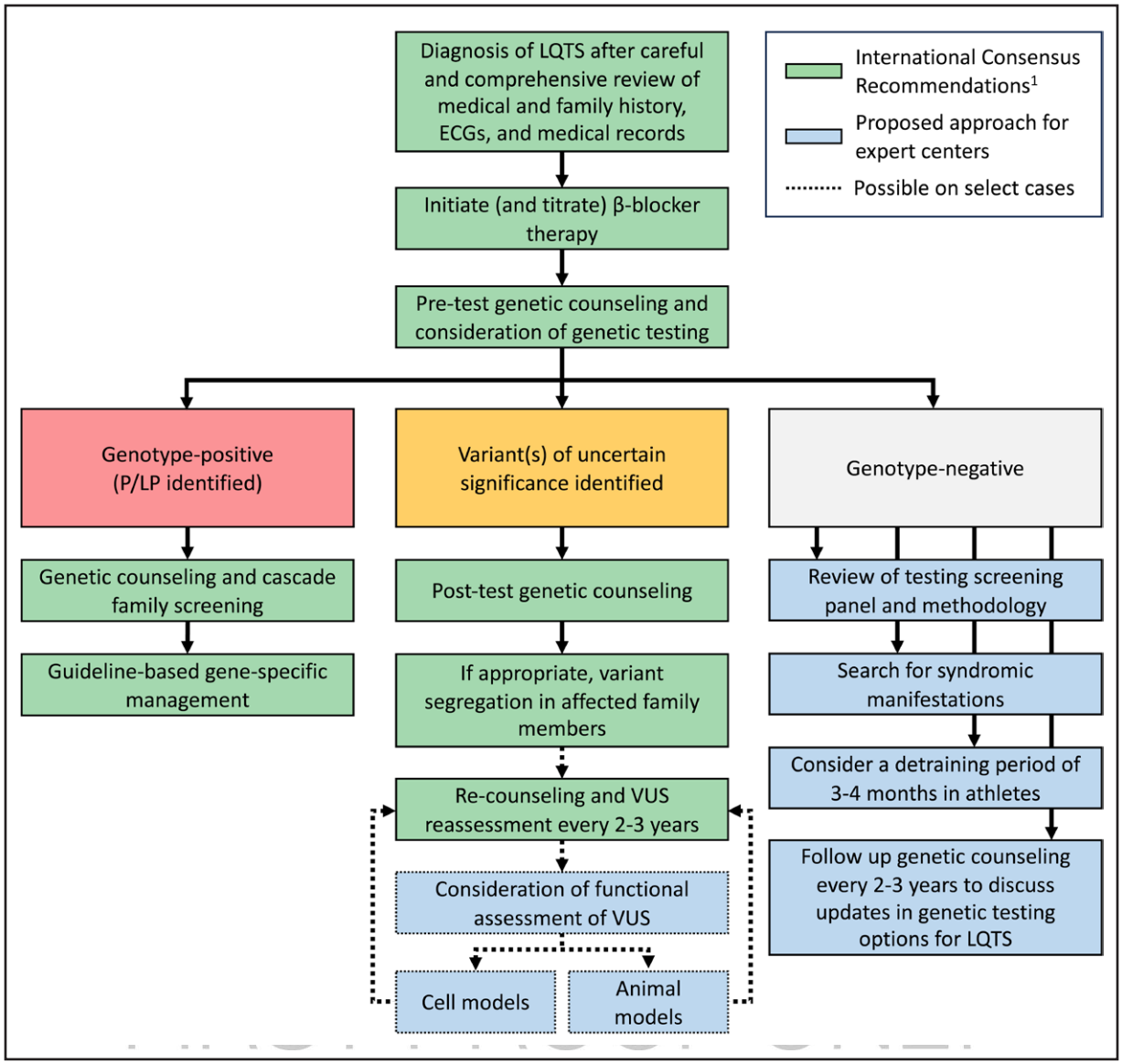

Figure 2. Proposed evaluation and management flow for patients with long QT syndrome (LQTS), with focus on patients with negative or inconclusive genetic test results.
VUS indicates variant of uncertain significance.
1Data derived from the study by Wilde et al.[5]

cardiovascular genetics programs, where patients are often referred to for comprehensive evaluation. The latter must include review of all available prior ECGs to identify possible temporal variations in QTc and T-wave morphology, review of medications, and exclusion of hypothyroidism and electrolyte abnormalities by laboratory testing and underlying structural heart disease by echocardiography or cardiac magnetic resonance imaging, as appropriate. Notably, anterior T-wave inversion is observed in ≈20% of patients with LQTS, and expert knowledge is required to prevent diagnostic miscues.[15]

A detailed history should focus on the presence of symptoms in both the index patient and their family and include the presence of arrhythmogenic syncope and near-syncopal episodes, drowning or near drowning events, seizure disorders, recurrent miscarriage, stillbirths,[16] sudden infant death syndrome, cardiac arrests at young age without evidence of coronary disease and unprovoked motor vehicle accidents or other unexplained accident deaths, which may signal arrhythmogenic syncope. For example, a patient with no family history of LQTS or SCD and a single ECG demonstrating QTc prolongation (as can be seen after vasovagal syncope)[17] is less likely to have an underlying LQTS than a patient with multiple ECGs with prolonged QTc and positive family history of SCD. For their importance, these factors are incorporated in the commonly used Schwartz score. Moreover, it should be emphasized that recommendations for ECG screening of all first-degree family members apply in families with both genotype-positive and genotype-negative probands.

Provocation of QTc prolongation and T-wave changes may be critical to unmasking the diagnosis and useful in predicting genotype in patients with suspicion of LQTS.[10] LQTS provocation testing involves assessment of repolarization during and after exercise, in response to changes in heart rate or autonomic tone, with patients with LQTS displaying a maladaptive repolarization response. While other types of provocation tests have been proposed and used to varying degrees in LQTS diagnosis, exercise testing, when feasible, is the most effective form of provocation testing when considering diagnostic sensitivity and specificity, with advantages in establishing a diagnosis of LQTS in patients with an intermediate modified Schwartz score or borderline QTc interval.[10] Exercise testing is used for both diagnosis in patients suspected to have LQTS and evaluation of treatment efficacy during physical exercise in patients with confirmed LQTS. To enable maximal diagnostic precision, it is advisable to conduct initial provocation testing for diagnosis of LQTS off antiarrhythmic medications, particularly β-blockers, as these medications suppress adrenergic stimulation that is crucial to unmasking abnormal repolarization response, and can thereby ameliorate repolarization abnormalities.[10] The QTc interval at 4-minute recovery is the measure with the highest diagnostic value during exercise testing, with a QTc interval of ≥445 ms having a sensitivity of 90% and a specificity of 90% for LQTS, and a QTc interval of ≥480 ms having a sensitivity of 36% and a specificity of 100% for LQTS. The latter threshold is incorporated in the Schwartz score.[18] Additionally, sex-specific cutoffs (440 ms for males and 450 ms for females) and adapted measures in children (QTc, >460 ms at 7-minute recovery) were proposed.[10]

ENVIRONMENTALLY INDUCED QT PROLONGATION

Environmental factors can play a significant role in the development of QT prolongation, and a subset of genotype-negative patients with LQTS may in fact have an acquired, often underrecognized cause of QT prolongation. The ever-growing list of external triggers that are known to have arrhythmogenic QT-prolonging capabilities includes over 200 medications (most with noncardiac indications; as summarized in www.crediblemeds.org), electrolyte imbalances (particularly hypokalemia, hypomagnesemia, and hypocalcemia), hypothyroidism, but also myocardial healing from stress cardiomyopathy,[19,20] arrhythmogenic cardiac memory,[21] and certain foods/nutritional status (eg, anorexia nervosa, low-calorie-diet, alcohol intoxication, and grapefruit juice).[22,23] There is also robust data supporting the role of anti-Ro/SSA antibodies, often detected in patients with connective tissue diseases and Sjogren syndrome, in acquired LQTS and predisposition to TdP.[24,25] To complicate things further, QT prolongation precipitated by various environmental triggers is increasingly linked to the presence of genetic modifiers (eg, *KCNE1* variants),[3,26] thus a constellation of oligogenic/polygenic and environmental stimuli appears to contribute to complex pathophysiology. Careful consideration of such influences can help eliminate the offending cause and thereby the need for treatment in many patients.

When viewing this concept from the perspective of acquired LQTS, it is important to understand what factors should guide genetic testing in patients in whom acquired LQTS is suspected. Although in most acquired patients with LQTS, the QT interval normalizes after the elimination of the QTc-prolonging trigger, in some cases, it remains prolonged. Systematic genetic evaluation of a large cohort of probands with acquired LQTS revealed a pathogenic, LQTS-associated variant in 28% of cases, of which two-thirds were *KCNH2* variants.[27] Presence of ≥2 of the 3 predictors, defined as (1) young age at the time of exposure to proarrhythmic triggers (<40 versus ≥40 years), (2) prolonged baseline QTc measured in the absence of these factors (>440 versus ≤440 ms), and (3) a history of clinical symptoms, was shown to identify 97% of pathogenic LQTS variant carriers, indicating high clinical utility of this scoring system.[27]

EXERCISE TRAINING-INDUCED QTC PROLONGATION

Several studies have examined cardiac adaptations in elite athletes, but the reported prevalence of QT prolongation varies widely (0.4%–15%), depending on the specific population studied, the criteria used to define QT prolongation, and the intensity and duration of training.[28–30] It is important to note that these changes may represent adaptation within the constellation of athlete's heart remodeling and not necessarily translate into a higher risk of life-threatening ventricular arrhythmias.

Generally, QT prolongation is considered to be more prevalent in athletes engaged in endurance sports. Endurance athletes often present with marked sinus bradycardia due to sinus node remodeling and high vagal tone, which can lead to overestimation of the QT interval. Historically, Bazett formula is used to correct the QT interval at different heart rates, however, this formula performs poorly at the extreme of heart rates and tends to overestimate the QTc at slow heart rates. Thus, when LQTS is suspected in an athlete who presents with marked sinus bradycardia and a QTc, >470 ms in males or a QTc, >480 ms in females, the ECG should be repeated after exercise to raise the heart rate to 60 to 80 bpm thereby minimizing the risk of a false-positive LQTS diagnosis and avoiding a costly workup. As another option, an alternative formula for heart rate correction of the QT interval should be considered. In a cohort of 2484 elite soccer players, 6% to 15% of the athletes presented with prolonged QTc based on Bazett correction, while only 3% to

5% met the criteria using the Fridericia formula,[30] which shows less bias at extreme heart rates and might be preferred in such cases.[31]

Additionally, it is widely known that athletes can exhibit abnormalities in repolarization, mimicking the ECG abnormalities observed in LQTS. Dagradi et al demonstrated that certain athletes display significant QT interval prolongation and repolarization abnormalities, consistent with the diagnosis of LQTS.[32] Strikingly, the mean QTc of athletes with this entity of 492 ms was >99.9th percentile of QTc values of healthy controls and >80th percentile of QTc values recorded among patients with congenital LQTS.[7,33] Notably, among those who tested negative for LQTS-causing genetic variants, over 40% demonstrated normalization of their ECG after detraining, with tendency to reappear upon resumption of training. Therefore, although these individuals do not have congenital LQTS, they may have a form of acquired LQTS. A repeat QTc measurement after a detraining period of 3 to 4 months can help to identify asymptomatic individuals who show exercise-induced QTc prolongation yet do not have congenital LQTS.[32] Whether such predisposition to exercise training-induced QTc prolongation exists in athletes across different ethnicities, remains to be investigated.

CHALLENGES IN GENETIC TESTING

Interpreting Variants of Uncertain Significance

In most patients suspected to have LQTS, genetic testing is usually performed via a targeted LQTS panel with a limited set of high-evidence genes as a first step to reduce the number of variants of uncertain significance (VUS) that are typically seen in whole exome/genome sequencing. A VUS can trigger costly, stressful, and inappropriate diagnostic work-ups, and have negative implications for both the proband and family members.[34] The optimal strategy in subjects, who turn out negative in the first step, is much less defined, but increasingly, whole exome sequencing is being used. Variant assessment has significantly advanced over the past 2 decades and currently requires consideration of gene-disease mechanisms, ethnicity, allelic, functional, in silico, and segregation data.[35] Nonetheless, variant interpretation remains the major Achilles' heel of genetic testing with up to 50% of variants reclassified over a period of 5 years,[36] leading to both upgrades and downgrades in their clinical significance. Challenges in determining gene-disease associations for newly discovered or rarely implicated genes further obscure variant interpretation.[37] Given the dynamic nature of variant interpretation and limited data from studies on cardiac channelopathies,[38] the need for reevaluation of VUS is widely agreed upon by experts. However, the frequency of reevaluation needed to maximize the clinical yield is not clearly defined by professional societies. Data from noncardiovascular disease studies suggests that variant reevaluation at least every 2 years is appropriate,[39,40] but this is not performed routinely.

Although cascade sequencing of family members of affected probands with VUS is not routinely recommended, variant segregation analysis might be useful for variant interpretation in select families with multiple phenotypically affected members. Identification of multiple family members with LQTS phenotype who carry the VUS in question provides additional supporting data for the pathogenicity of the variant while the presence of phenotype in a family member who does not carry the same VUS provides evidence against the role of VUS in disease. Functional evaluation of variants that cosegregate with LQTS in large pedigrees can provide pathophysiological evidence for variant reclassification.[41] Determining the utility of segregation and identifying appropriate relatives for variant segregation is among the important goals of a posttest genetic counseling session.

Genetic Reevaluation/Retesting

In practice, the need and timeliness of genetic reevaluation should be guided by the current state of knowledge on the genetics of LQTS, as well as the extent of the gene panel and the sequencing methods (eg, inclusion of deletion/duplication testing) used at the initial testing. A previously observed shortfall in genetic testing, now long implemented in new genetic evaluations was the limited detection capabilities for atypical variants such as large deletions or duplications. Recognition of this limitation in LQTS led to the finding that ≈5% of patients with genetically elusive LQTS host large genomic rearrangements involving the canonical LQTS-susceptibility genes.[42] Thus, reflex genetic testing to investigate genomic rearrangements may be of clinical value in select gene-elusive patients with LQTS with strong phenotypes who were not initially evaluated for deletions and duplications.

Another possible reason for a missed genetic cause might be undetected variants in the known LQTS-associated genes, such as those in deep intronic or regulatory regions, which are largely not detectable as part of current LQTS gene panels. The possible role of such variants should be considered, particularly in probands with strong LQTS phenotype and families with multiple affected members. In a recent genome sequencing study of a multigenerational, previously genetically elusive LQTS pedigree with 6 affected family members, a novel deep intronic *KCNH2* variant (c.3331-316G>T) was identified.[43] The patient-derived, CRISPR/Cas9 gene variant-corrected, isogenic control-induced pluripotent stem cell-derived cardiomyocytes established that the deeply intronic variant created the frameshift variant p.S1112Pfs*171 in the *KCNH2*-encoded Kv11.1/hERG channel as the monogenetic basis for the familial LQT2. Thus, deep intronic variants within the 2 most common LQTS-susceptibility genes *KCNQ1* and *KCNH2*

should be considered in patients with seemingly genetically elusive LQTS.[43] Of note, 1 important reason for a false negative genetic test result when next-generation sequencing is used was pointed out by Millat et al[44] who noted the lack of coverage of specific regions of genes. Specifically, several exons of *KCNH2* were incompletely sequenced due to a high CG content. These limitations have been addressed with more recent methods and may not apply to all techniques currently used.

Considering the rapid developments in the field of genetics, regular updates, and clear communication between testing laboratories, health care providers, and patients are essential to facilitate appropriate clinical decision-making based on the most up-to-date variant classifications.

Novel LQTS Genes

The field of genetics is rapidly evolving, and new causal genes associated with genetic heart diseases are continuously being discovered. Cardiovascular disease panels are updated regularly, and newly identified genes are added. Therefore, the need for periodic retesting of patients with prior negative genetic test results should be routinely considered when new data becomes available. The emergence of novel clinical evidence such as data on newly diagnosed family members should also necessitate genetic counseling to discuss if retesting/reevaluation is appropriate. Patients with previous whole genome or whole exome sequencing might benefit from data reanalysis while those with limited gene panel testing might need to undergo additional testing. As of 2023, it would be reasonable to selectively retest genotype-negative LQTS patients tested before 2015 given the major changes in variant assessment criteria and the identification of novel causal genes in or after early-to-mid 2010s, such as *CALM1*, *CALM2*, *CALM3*, *TRDN*, and *TECRL*. Notably, patients with pathogenic variants in *CALM1-3* genes show either LQTS or catecholaminergic polymorphic ventricular tachycardia phenotypes, but certain patients may have coexistence of both LQTS and catecholaminergic polymorphic ventricular tachycardia.[3,45–47] In addition, pleiotropy in presentations, ranging from channelopathy to syndromic forms that may include cardiomyopathy, congenital heart disease, and primary neurological manifestations have been described. As medical knowledge and genetic testing technologies advance, many forms of currently considered elusive or unidentified genetic variants may become detectable in the future. Therefore, health care providers ordering genetic tests need to stay up to date with the latest research and advancements in genetic testing.

Polygenic Causes of LQTS

Recent evidence suggests that QTc duration is influenced by both rare and common variants in cardiac ion channel genes. Lahrouchi et al[6] demonstrated that polygenic risk score analyses based on common genetic variants that modulate the QT interval in the general population provide evidence for a polygenic architecture in gene-elusive patients with LQTS. Heritability analyses showed that ≈15% of the variance in overall LQTS susceptibility was attributable to common genetic variation, and the polygenic risk score was greater in patients who were genotype negative compared with those who were genotype positive.[6] In line with these findings, evaluation of the contributory role of PRS to QTc in patients with genetically confirmed LQTS showed that QTc-PRS explained <2% of the QTc variability in patients with LQT1, LQT2, or LQT3, while the contribution of PRS to QTc was 5-fold larger in the general population.[48] These findings argue for a polygenic basis of QTc prolongation (alongside the contribution of acquired risk factors) at least in some patients who have a sporadic presentation.[49] With growing opportunities to validate PRS in independent cohorts, polygenic determinants of QTc prolongation will likely be introduced to clinical care in the near future and help explain LQTS cases currently considered to be gene elusive.

Unfilled Gaps in Clinical Practice

Two groups of patients can be distinguished among those without genetic confirmation of LQTS—those with VUS, and those with completely negative genetic testing. Generally, the clinical gaps for these 2 subpopulations are similar, but patients with a VUS might benefit from variant reevaluation while those with negative test might require retesting at appropriate times. To date, most studies contributing to our understanding of genotype-elusive LQTS have focused on specific subdomains, and the overall contribution of each etiology/component, as described in previous sections of this review remains unknown. Accordingly, although the pathophysiological rationale for the effectiveness of β-blockers in reducing the risk of TdP and SCD is widely recognized, their effectiveness may vary across different etiologies. Additionally, there is a need for research studies that examine the efficacy of β-blockers in individuals with a genotype-elusive LQTS who possess a high LQTS PRS, as compared with those with medium or low PRS. Future studies shall also evaluate the spectrum of monogenic and polygenic modifiers in those with exercise training-induced QTc prolongation. Finally, we expect that increasing use of whole exome/genome sequencing studies in large genotype-negative LQTS pedigrees—which are exceedingly rare with the current application of genetic testing—will enable the identification of novel causal genes in those considered to be genotype-elusive with current gene panel testing, thereby enabling precision care in affected families.

Future Directions for the Field

Over the past decade, several advances started reshaping the field of genomics and molecular medicine. Specifically, many efforts have been directed toward improving gene variant interpretation practices. For example, many automatic tools have been developed to aid in variant interpretation, including tools that perform guidelines-based pathogenicity assessment using a software/web tool,[50] and algorithms that convert the sequence variant interpretation recommendation in a probabilistic framework,[51] and data-driven approaches. The latter include machine-learning models trained to distinguish pathogenic from benign variations,[52,53] or a combination of these methods.[54] Although prior models have not been robustly tested in inherited cardiovascular diseases, there is a clear need to develop machine-learning models that can help in variant prioritizing and interpretation. Additionally, functional genomics methods are increasingly used to uncover patterns that aid in variant calling.[55,56] Combining functional imaging with artificial intelligence-based methods of variant assessment has the potential to reduce the VUS burden.

Patient-specific induced pluripotent stem cell models can be utilized to investigate the pathogenesis of LQTS in vitro, and test drug efficacy and toxicity in a disease-specific context.[1,57] In addition, induced pluripotent stem cell and their isogenic controls are a reliable electrophysiological model for comprehensive variant characterization that can aid pathogenicity assessment in patients with LQTS with VUS. Modeling LQTS and testing new drugs using patient-specific induced pluripotent stem cell cardiomyocytes could be an important step forward in the realm of personalized care in LQTS.

Other promising avenues for patients with genotype-elusive LQTS include the development of clinically applicable PRS that would aid in risk stratification and management, and selective use of whole exome/genome sequencing in gene-elusive LQTS families for novel gene discovery. Newly implicated genes should, however, be interpreted with caution, as more than half of the genes reported as causing LQTS have been shown to have limited or disputed evidence to support their disease causation.[3]

As the field of inherited heart diseases is developing rapidly, optimized use of these tools considering risks, benefits, and costs, will continuously help decipher the spectrum of etiologies associated with genotype-elusive LQTS and help reduce the VUS burden, thereby fostering precision medicine in patients with LQTS and families.

CONCLUSIONS

Patients with LQTS may be gene-elusive for a variety of reasons, including environmental influences, strenuous physical activity, polygenic risk factors, previously unknown or unrecognized genetic causes, and the ever-evolving nature of gene variant interpretation. The emergence of new knowledge opens additional avenues to elucidate the causes of LQTS/QTc prolongation in patients with negative genetic test results, making expert evaluation and regular follow-up critical. This presents patients and physicians with a unique opportunity to confirm or refute diagnosis, explore the foundations of LQTS beyond the boundaries of current standard-of-care practices, and derive meaningful clinical implications.

ARTICLE INFORMATION

Affiliation

Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD.

Sources of Funding

Dr Asatryan is supported by a postdoctoral research fellowship grant from the Gottfried und Julia Bangerter-Rhyner-Stiftung (Switzerland) and the 2022 Research Fellowship for aspiring electrophysiologists from the Swiss Heart Rhythm Foundation. Dr Barth is supported by the Lovin' Every Day Foundation.

Disclosures

None.

REFERENCES

1. Schwartz PJ. 1970-2020: 50 years of research on the long QT syndrome-from almost zero knowledge to precision medicine. *Eur Heart J*. 2021;42:1063–1072. doi: 10.1093/eurheartj/ehaa769
2. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, Denjoy I, Guicheney P, Breithardt G, Keating MT, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation*. 2001;103:89–95. doi: 10.1161/01.cir.103.1.89
3. Adler A, Novelli V, Amin AS, Abiusi E, Care M, Nannenberg EA, Feilotter H, Amenta S, Mazza D, Bikker H, et al. An international, multicentered, evidence-based reappraisal of genes reported to cause congenital long QT syndrome. *Circulation*. 2020;141:418–428. doi: 10.1161/CIRCULATIONAHA.119.043132
4. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, et al. Risk stratification in the long-QT syndrome. *N Engl J Med*. 2003;348:1866–1874. doi: 10.1056/NEJMoa022147
5. Wilde AAM, Semsarian C, Marquez MF, Sepehri Shamloo A, Ackerman MJ, Ashley EA, Sternick EB, Barajas-Martinez H, Behr ER, Bezzina CR, et al; Document Reviewers. 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. *Heart Rhythm*. 2022;19:e1–e60. doi: 10.1016/j.hrthm.2022.03.1225
6. Lahrouchi N, Tadros R, Crotti L, Mizusawa Y, Postema PG, Beekman L, Walsh R, Hasegawa K, Barc J, Ernsting M, et al. Transethnic genome-wide association study provides insights in the genetic architecture and heritability of long QT syndrome. *Circulation*. 2020;142:324–338. doi: 10.1161/CIRCULATIONAHA.120.045956
7. Viskin S. Important developments in long QT syndrome: not only for arrhythmia specialists. *Circulation*. 2020;142:2416–2419. doi: 10.1161/CIRCULATIONAHA.120.051434
8. Predham S, Hathaway J, Hulait G, Arbour L, Lehman A. Patient recall, interpretation, and perspective of an inconclusive long QT syndrome genetic test result. *J Genet Couns*. 2017;26:150–158. doi: 10.1007/s10897-016-9991-4
9. Ahmad F, McNally EM, Ackerman MJ, Baty LC, Day SM, Kullo IJ, Madueme PC, Maron MS, Martinez MW, Salberg L, et al. Establishment of specialized clinical cardiovascular genetics programs: recognizing the need and meeting standards: a scientific statement from the

American heart association. *Circ Genom Precis Med*. 2019;12:e000054. doi: 10.1161/HCG.0000000000000054
10. Abrahams T, Davies B, Laksman Z, Sy RW, Postema PG, Wilde AAM, Krahn AD, Han HC. Provocation testing in congenital long QT syndrome: a practical guide. *Heart Rhythm*. 2023;20:1570–1582. doi: 10.1016/j.hrthm.2023.07.059
11. Stiles MK, Wilde AAM, Abrams DJ, Ackerman MJ, Albert CM, Behr ER, Chugh SS, Cornel MC, Gardner K, Ingles J, et al. 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. *Heart Rhythm*. 2021;18:e1–e50. doi: 10.1016/j.hrthm.2020.10.010
12. Viskin S, Rosovski U, Sands AJ, Chen E, Kistler PM, Kalman JM, Rodriguez Chavez L, Iturralde Torres P, Cruz FF, Centurion OA, et al. Inaccurate electrocardiographic interpretation of long QT: the majority of physicians cannot recognize a long QT when they see one. *Heart Rhythm*. 2005;2:569–574. doi: 10.1016/j.hrthm.2005.02.011
13. Bains S, Neves R, Bos JM, Giudicessi JR, MacIntyre C, Ackerman MJ. Phenotypes of overdiagnosed long QT syndrome. *J Am Coll Cardiol*. 2023;81:477–486. doi: 10.1016/j.jacc.2022.11.036
14. Wilde AAM, Schwartz PJ. Long QT syndrome, a diagnosis that warrants expert opinion and expert centers. *J Am Coll Cardiol*. 2023;81:487–489. doi: 10.1016/j.jacc.2022.11.037
15. Lane CM, Bos JM, Rohatgi RK, Ackerman MJ. Beyond the length and look of repolarization: defining the non-QTc electrocardiographic profiles of patients with congenital long QT syndrome. *Heart Rhythm*. 2018;15:1413–1419. doi: 10.1016/j.hrthm.2018.04.033
16. Crotti L, Tester DJ, White WM, Bartos DC, Insolia R, Besana A, Kunic JD, Will ML, Velasco EJ, Bair JJ, et al. Long QT syndrome-associated mutations in intrauterine fetal death. *JAMA*. 2013;309:1473–1482. doi: 10.1001/jama.2013.3219
17. Sucu M, Ozer O, Davutoglu V, Ercan S, Yuce M, Coskun FY. Relationship between neurocardiogenic syncope and ventricular repolarization. *Pacing Clin Electrophysiol*. 2015;38:625–629. doi: 10.1111/pace.12599
18. Schwartz PJ, Crotti L. QTc behavior during exercise and genetic testing for the long-QT syndrome. *Circulation*. 2011;124:2181–2184. doi: 10.1161/CIRCULATIONAHA.111.062182
19. Halkin A, Roth A, Lurie I, Fish R, Belhassen B, Viskin S. Pause-dependent torsade de pointes following acute myocardial infarction: a variant of the acquired long QT syndrome. *J Am Coll Cardiol*. 2001;38:1168–1174. doi: 10.1016/s0735-1097(01)01468-1
20. Madias C, Fitzgibbons TP, Alsheikh-Ali AA, Bouchard JL, Kalsmith B, Garlitski AC, Tighe DA, Estes NA 3rd, Aurigemma GP, Link MS. Acquired long QT syndrome from stress cardiomyopathy is associated with ventricular arrhythmias and torsades de pointes. *Heart Rhythm*. 2011;8:555–561. doi: 10.1016/j.hrthm.2010.12.012
21. Viskin S, Chorin E, Schwartz AL, Kukla P, Rosso R. Arrhythmogenic effects of cardiac memory. *Circulation*. 2022;146:1170–1181. doi: 10.1161/CIRCULATIONAHA.122.061259
22. Chorin E, Hochstadt A, Granot Y, Khoury S, Schwartz AL, Margolis G, Barashi R, Viskin D, Ghantous E, Schnapper M, et al. Grapefruit juice prolongs the QT interval of healthy volunteers and patients with long QT syndrome. *Heart Rhythm*. 2019;16:1141–1148. doi: 10.1016/j.hrthm.2019.04.039
23. Havakuk O, Schwartz AL, Rosso R, Viskin S. Editorial commentary: a question on proarrhythmic food: Is grapefruit "the forbidden fruit" for patients with long QT syndrome? *Trends Cardiovasc Med*. 2020;30:313–314. doi: 10.1016/j.tcm.2020.05.007
24. Yue Y, Castrichini M, Srivastava U, Fabris F, Shah K, Li Z, Qu Y, El-Sherif N, Zhou Z, January C, et al. Pathogenesis of the novel autoimmune-associated long-QT syndrome. *Circulation*. 2015;132:230–240. doi: 10.1161/CIRCULATIONAHA.115.009800
25. Lazzerini PE, Cevenini G, Qu YS, Fabris F, El-Sherif N, Acampa M, Cartocci A, Laghi-Pasini F, Capecchi PL, Boutjdir M, et al. Risk of QTc interval prolongation associated with circulating anti-Ro/SSA antibodies among US veterans: an observational cohort study. *J Am Heart Assoc*. 2021;10:e018735. doi: 10.1161/JAHA.120.018735
26. Wada Y, Yang T, Shaffer CM, Daniel LL, Glazer AM, Davogustto GE, Lowery BD, Farber-Eger EH, Wells QS, Roden DM. Common ancestry-specific ion channel variants predispose to drug-induced arrhythmias. *Circulation*. 2022;145:299–308. doi: 10.1161/CIRCULATIONAHA.121.054883
27. Itoh H, Crotti L, Aiba T, Spazzolini C, Denjoy I, Fressart V, Hayashi K, Nakajima T, Ohno S, Makiyama T, et al. The genetics underlying acquired long QT syndrome: impact for genetic screening. *Eur Heart J*. 2016;37:1456–1464. doi: 10.1093/eurheartj/ehv695
28. Basavarajaiah S, Wilson M, Whyte G, Shah A, Behr E, Sharma S. Prevalence and significance of an isolated long QT interval in elite athletes. *Eur Heart J*. 2007;28:2944–2949. doi: 10.1093/eurheartj/ehm404
29. Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. *JAMA*. 2006;296:1593–1601. doi: 10.1001/jama.296.13.1593
30. Huttin O, Selton-Suty C, Venner C, Vilain JB, Rochecongar P, Aliot E. Electrocardiographic patterns and long-term training-induced time changes in 2484 elite football players. *Arch Cardiovasc Dis*. 2018;111:380–388. doi: 10.1016/j.acvd.2017.10.005
31. Pickham D, Hsu D, Soofi M, Goldberg JM, Saini D, Hadley D, Perez M, Froelicher VF. Optimizing QT interval measurement for the preparticipation screening of young athletes. *Med Sci Sports Exerc*. 2016;48:1745–1750. doi: 10.1249/MSS.0000000000000962
32. Dagradi F, Spazzolini C, Castelletti S, Pedrazzini M, Kotta MC, Crotti L, Schwartz PJ. Exercise training-induced repolarization abnormalities masquerading as congenital long QT syndrome. *Circulation*. 2020;142:2405–2415. doi: 10.1161/CIRCULATIONAHA.120.048916
33. Vink AS, Neumann B, Lieve KVV, Sinner MF, Hofman N, El Kadi S, Schoenmaker MHA, Slaghekke HMJ, de Jong J, Clur SB, et al. Determination and interpretation of the QT interval. *Circulation*. 2018;138:2345–2358. doi: 10.1161/CIRCULATIONAHA.118.033943
34. Landstrom AP, Chahal AA, Ackerman MJ, Cresci S, Milewicz DM, Morris AA, Sarquella-Brugada G, Semsarian C, Shah SH, Sturm AC; American Heart Association Data Science and Precision Medicine Committee of the Council on Genomic and Precision Medicine and Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Hypertension; Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Council on Peripheral Vascular Disease; and Stroke Council. Interpreting incidentally identified variants in genes associated with heritable cardiovascular disease: a scientific statement from the American Heart Association. *Circ Genom Precis Med*. 2023;16:e000092. doi: 10.1161/HCG.0000000000000092
35. Josephs KS, Roberts AM, Theotokis P, Walsh R, Ostrowski PJ, Edwards M, Fleming A, Thaxton C, Roberts JD, Care M, et al. Beyond gene-disease validity: capturing structured data on inheritance, allelic-requirement, disease-relevant variant classes, and disease mechanism for inherited cardiac conditions. *medRxiv*. 2023:2023.2004.2003.23287612. doi: 10.1101/2023.04.03.23287612
36. Campuzano O, Sarquella-Brugada G, Fernandez-Falgueras A, Coll M, Iglesias A, Ferrer-Costa C, Cesar S, Arbelo E, Garcia-Alvarez A, Jorda P, et al. Reanalysis and reclassification of rare genetic variants associated with inherited arrhythmogenic syndromes. *EBioMedicine*. 2020;54:102732. doi: 10.1016/j.ebiom.2020.102732
37. Hosseini SM, Kim R, Udupa S, Costain G, Jobling R, Liston E, Jamal SM, Szybowska M, Morel CF, Bowdin S, et al; National Institutes of Health Clinical Genome Resource Consortium. Reappraisal of reported genes for sudden arrhythmic death: evidence-based evaluation of gene validity for Brugada syndrome. *Circulation*. 2018;138:1195–1205. doi: 10.1161/CIRCULATIONAHA.118.035070
38. Rosamilia MB, Lu IM, Landstrom AP. Pathogenicity assignment of variants in genes associated with cardiac channelopathies evolve toward diagnostic uncertainty. *Circ Genom Precis Med*. 2022;15:e003491. doi: 10.1161/CIRCGEN.121.003491
39. Mersch J, Brown N, Pirzadeh-Miller S, Mundt E, Cox HC, Brown K, Aston M, Esterling L, Manley S, Ross T. Prevalence of variant reclassification following hereditary cancer genetic testing. *JAMA*. 2018;320:1266–1274. doi: 10.1001/jama.2018.13152
40. SoRelle JA, Thodeson DM, Arnold S, Gotway G, Park JY. Clinical utility of reinterpreting previously reported genomic epilepsy test results for pediatric patients. *JAMA Pediatr*. 2019;173:e182302. doi: 10.1001/jamapediatrics.2018.2302
41. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, et al; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American college of medical genetics and genomics and the association for molecular pathology. *Genet Med*. 2015;17:405–424. doi: 10.1038/gim.2015.30
42. Tester DJ, Benton AJ, Train L, Deal B, Baudhuin LM, Ackerman MJ. Prevalence and spectrum of large deletions or duplications in the major long QT syndrome-susceptibility genes and implications for long QT syndrome genetic testing. *Am J Cardiol*. 2010;106:1124–1128. doi: 10.1016/j.amjcard.2010.06.022
43. Tobert KE, Tester DJ, Zhou W, Haglund-Turnquist CM, Giudicessi JR, Ackerman MJ. Genome sequencing in a genetically elusive

multigenerational long QT syndrome pedigree identifies a novel LQT2-causative deeply intronic KCNH2 variant. *Heart Rhythm*. 2022;19:998–1007. doi: 10.1016/j.hrthm.2022.02.004
44. Millat G, Chanavat V, Rousson R. Evaluation of a new high-throughput next-generation sequencing method based on a custom AmpliSeq library and ion torrent PGM sequencing for the rapid detection of genetic variations in long QT syndrome. *Mol Diagn Ther*. 2014;18:533–539. doi: 10.1007/s40291-014-0099-y
45. Crotti L, Spazzolini C, Tester DJ, Ghidoni A, Baruteau AE, Beckmann BM, Behr ER, Bennett JS, Bezzina CR, Bhuiyan ZA, et al. Calmodulin mutations and life-threatening cardiac arrhythmias: insights from the international calmodulinopathy Registry. *Eur Heart J*. 2019;40:2964–2975. doi: 10.1093/eurheartj/ehz311
46. Crotti L, Spazzolini C, Nyegaard M, Overgaard MT, Kotta MC, Dagradi F, Sala L, Aiba T, Ayers MD, Baban A, et al. Clinical presentation of calmodulin mutations: the international calmodulinopathy registry. *Eur Heart J*. 2023;44:3357–3370. doi: 10.1093/eurheartj/ehad418
47. Webster G, Aburawi EH, Chaix MA, Chandler S, Foo R, Islam A, Kammeraad JAE, Rioux JD, Al-Gazali L, Sayeed MZ, et al. Life-threatening arrhythmias with autosomal recessive TECRL variants. *Europace*. 2021;23:781–788. doi: 10.1093/europace/euaa376
48. Turkowski KL, Dotzler SM, Tester DJ, Giudicessi JR, Bos JM, Speziale AD, Vollenweider JM, Ackerman MJ. Corrected QT interval-polygenic risk score and its contribution to type 1, type 2, and type 3 long-QT syndrome in probands and genotype-positive family members. *Circ Genom Precis Med*. 2020;13:e002922. doi: 10.1161/CIRCGEN.120.002922
49. Cerrone M, Remme CA, Tadros R, Bezzina CR, Delmar M. Beyond the one gene-one disease paradigm: complex genetics and pleiotropy in inheritable cardiac disorders. *Circulation*. 2019;140:595–610. doi: 10.1161/CIRCULATIONAHA.118.035954
50. Nicora G, Limongelli I, Gambelli P, Memmi M, Malovini A, Mazzanti A, Napolitano C, Priori S, Bellazzi R. CardioVAI. An automatic implementation of ACMG-AMP variant interpretation guidelines in the diagnosis of cardiovascular diseases. *Hum Mutat*. 2018;39:1835–1846. doi: 10.1002/humu.23665
51. Tavtigian SV, Greenblatt MS, Harrison SM, Nussbaum RL, Prabhu SA, Boucher KM, Biesecker LG; ClinGen Sequence Variant Interpretation Working Group (ClinGen SVI). Modeling the ACMG/AMP variant classification guidelines as a Bayesian classification framework. *Genet Med*. 2018;20:1054–1060. doi: 10.1038/gim.2017.210
52. Lai C, Zimmer AD, O'Connor R, Kim S, Chan R, van den Akker J, Zhou AY, Topper S, Mishne G. LEAP. Using machine learning to support variant classification in a clinical setting. *Hum Mutat*. 2020;41:1079–1090. doi: 10.1002/humu.24011
53. Li Q, Zhao K, Bustamante CD, Ma X, Wong WH. Xrare: a machine learning method jointly modeling phenotypes and genetic evidence for rare disease diagnosis. *Genet Med*. 2019;21:2126–2134. doi: 10.1038/s41436-019-0439-8
54. Nicora G, Zucca S, Limongelli I, Bellazzi R, Magni P. A machine learning approach based on ACMG/AMP guidelines for genomic variant classification and prioritization. *Sci Rep*. 2022;12:2517. doi: 10.1038/s41598-022-06547-3
55. Floyd BJ, Weile J, Kannankeril PJ, Glazer AM, Reuter CM, MacRae CA, Ashley EA, Roden DM, Roth FP, Parikh VN. Proactive variant effect mapping aids diagnosis in pediatric cardiac arrest. *Circ Genom Precis Med*. 2023;16:e003792. doi: 10.1161/CIRCGEN.122.003792
56. Glazer AM, Davogustto G, Shaffer CM, Vanoye CG, Desai RR, Farber-Eger EH, Dikilitas O, Shang N, Pacheco JA, Yang T, et al; eMERGE Network. Arrhythmia variant associations and reclassifications in the eMERGE-III sequencing study. *Circulation*. 2022;145:877–891. doi: 10.1161/CIRCULATIONAHA.121.055562
57. Yu Y, Deschenes I, Zhao MT. Precision medicine for long QT syndrome: patient-specific iPSCs take the lead. *Expert Rev Mol Med*. 2023;25:e5. doi: 10.1017/erm.2022.43