JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 12, NO. 2, 2026

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Phenotype-Enhanced Classification of Genetic Variants in Long QT Syndrome, Type 2

Arthur A.M. Wilde, MD, PhD,[a] Alexander J.A. Groffen, PhD[b]

For most inherited arrhythmia syndromes genetic testing has become standard of care.[1] Over the years, the assessment of pathogenicity of unknown variants in disease entities, including the congenital long QT syndrome (LQTS), has undergone a shift from a purely phenotype-driven process (through linkage studies aiming for sound agreement between genotypic and phenotypic affected individuals) to a process with dominant genotypic characteristics where variant classification is based on allele frequency in control populations, predictions of amino acid substitutions, and many other tools under continuous development for increased accuracy. In 2015, the introduction of American College of Medical Genetics and Genomics (ACMG)/Association for Molecular Pathology guidelines have outlined criteria for such tools and proposed a relative weight for them, providing a framework for cross-laboratory consistency in variant classification.[2] Since then, various recommendations from ClinGen working groups for variant classification have further refined the use of ACMG criteria, generally moving towards a more cautious approach in classification. Furthermore, a scoring system was devised to align ACMG classification to the statistical likelihood of variant pathogenicity following Bayesian models.[3]

According to the 5-class ACMG model, variants with a 10% to 90% risk of being pathogenic are designated variants of unknown significance (VUS) (class 3). Although the availability of this class has scientific merits, reported VUS have limited clinical actionability and cause confusion in patients and families because carrier and noncarrier family members will generally receive similar follow-up. By contrast, (likely) pathogenic (class 4/5) variants provide a (likely) diagnosis of LQTS and enable choices for clinical follow-up and (gene-)specific treatment. Family members can receive genetic counseling and be screened presymptomatically, followed by appropriate treatment of genetically affected individuals, and noncarriers can be dismissed. From this viewpoint, VUS are considered a burden rather than a boon. Solving this problem in LQTS is a pressing issue as treatment choices also depend on the underlying genotype. Current guidelines aim to limit the yield of VUS findings by narrowing down the differential diagnosis in a full cardiological work-up including an exercise test, followed by targeted testing of only relevant genes.[1]

In a patient with an electrocardiogram highly suspicious for LQTS2, suppose that genetic testing returns 2 VUS with similar ACMG criteria: 1 in KCNQ1 and 1 in KCNH2. Obviously, the VUS in KCNH2 is more suspicious, but the generic ACMG criteria offer limited means to incorporate this feature into the classification. A smart attempt to solve this issue is to integrate aspects of the phenotype into the ACMG classification (ie, phenotype-enhanced ACMG variant adjudication [PE-ACMG]). This method has been shown to be valuable in LQTS type 1 (LQTS1) and catecholaminergic polymorphic ventricular tachycardia.[4,5] Of critical importance in applying PE-ACMG is the presence of unique genotype-specific elements in the phenotype under study. By identifying these

From the [a]Department of Clinical Cardiology, Amsterdam University Medical Centre (location AMC), Amsterdam, the Netherlands; and the [b]Department of Human Genetics, Amsterdam University Medical Centre (location VUmc), Amsterdam, the Netherlands.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2405-500X/$36.00 https://doi.org/10.1016/j.jacep.2025.11.019

"phenotype defining features" in catecholaminergic polymorphic ventricular tachycardia and LQTS1, the VUS burden could reliably be reduced from 47% to 7% and from 39% to 21%, respectively.[4,5]

In this issue of *JACC: Clinical Electrophysiology*, the Mayo Clinic (Rochester, Minnesota) and Auxologico Institute (Milan, Italy) propose a PE-ACMG method for LQTS2 based on the presence of 2 LQTS2-defining characteristics: biphasic/notched T waves and auditory stimuli or emotional stress as the triggering factor, allowing a reduction in the VUS burden from 33% to just 4%.[6]

The presence of unique genotype-specific elements is critical when applying this method. The trigger (auditory stimuli or emotional stress) is such an element, although in early series, an auditory trigger was also present in up to 7% of LQTS3 patients.[7] The ST-segment morphology, that is, biphasic/notched T waves, has a sensitivity/specificity for correct genotype classification of 83%/94%.[8] Hence, both elements have a high, but not perfect, predictive value. More importantly, both elements are not always present, as is also clear from the present series. The trigger was only present in 10% of patients with a VUS (n = 13/140) (Table 1 of their paper) and biphasic/notched T waves were present in 47% of patients (n = 66/140). It is unclear how the patients with a "phenotype-defining feature" and the patients without are divided among the 69 families, but the observed high reduction in VUS burden clearly does require at least 1 of these features in almost each family. However, the reduction of VUS also includes 11 VUS that were "downgraded" to a benign variant based on a low Schwartz score (≤1) and no LQTS2-defining features. Based on the prevalence of the genotype-specific features, the step to downgrade the VUS to a benign variant seems somewhat hazardous, although the low Schwartz score a priori leads to a low likelihood of the presence of LQTS, and one may actually wonder why a genetic test was performed in these individuals in the first place.

The use of PE-ACMG has clear value for prioritizing variants, but has to be used with caution. First, the consistency between PE-ACMG classification and a recent high-throughput functional study of KCNH2 variants is imperfect. In a recent study, Multiplex Assay of Variant Effect (MAVE) was performed in which 187,96 variants were studied for cell surface trafficking, and 533 variants by patch clamp analysis.[9] The concordance rate between the present phenotype-based classification and these measurements was only 60% (29/48). Now, it is true that "the clinical utility and scalability of applying these in vitro assays for novel variant assessment remains uncertain," but lack of consistency between functional data, generally regarded as a very important aspect of pathogenicity and an important contributor to the ACMG criteria, and phenotypic data certainly is a concern.

Second, a pitfall of PE-ACMG classification exists in cases where a causative variant may be missed. Consider a LQTS2 patient with a causative deep-intronic variant (eg, causing aberrant splicing and constituting a null allele) combined with a functionally normal allele with a neutral rare missense variant. In many whole exome sequencing-based or targeted gene panels, the deep intronic variant may remain undetected. Using phenotype-enhanced classification, the clinical significance of the missense variant may be overestimated. If considered pathogenic, a consequence would be that all family members heterozygous for the missense variant would be (mis)diagnosed with LQTS given that a class 5 variant in KCNH2 contributes 3.5 points in the modified diagnostic Schwartz score.[10] Admittedly this example is not very likely to occur in practice, but it illustrates a risk and argues for the use of weighted ACMG criteria (such as PS5 as proposed in Table 2 of their paper) rather than an immediate upgrade to class 4/5.

In conclusion, the phenotype-enhanced method proposed by Neves and colleagues provides a new tool to incorporate LQTS2-specific phenotypic features in ACMG-based classification of KCNH2 variants. When applied with caution, LQTS patients may benefit from a reduced number of VUS with a concomitant increase of clinical actionability of genetic testing. It is to be expected that future studies in larger patient cohorts will provide further insight in the optimal weight (supporting, moderate or strong) that should be attributed to PE-ACMG criteria.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Arthur A.M. Wilde, Department of Clinical Cardiology, Amsterdam University Medical Centre, B2.239, Meibergdreef 9, P.O. Box 22700, Amsterdam 1100DE, the Netherlands. E-mail: a.a.wilde@UMC.UVA.NL.

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 12, NO. 2, 2026
FEBRUARY 2026:360–362

REFERENCES

1. Wilde AAM, Semsarian C, Marquez MF, et al. 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.

2. Richards S, Aziz N, Bale S, et al. 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.

3. Tavtigian SV, Harrison SM, Boucher KM, Biesecker LG. Fitting a naturally scaled point system to the ACMG/AMP variant classification guidelines. *Hum Mutat*. 2020;41:1734–1737.

4. Bains S, Dotzler SM, Krijger C, et al. A phenotype-enhanced variant classification framework to decrease the burden of missense variants of uncertain significance in type 1 long QT syndrome. *Heart Rhythm*. 2022;19:435–442.

5. Giudicessi JR, Lieve KVV, Rohatgi RK, et al. Assessment and validation of a phenotype-enhanced variant classification framework to promote or demote RYR2 missense variants of uncertain significance. *Circ Genom Precis Med*. 2019;12:e002510.

6. Neves R, Crotti L, Bains S, et al. A phenotype-enhanced variant classification framework to decrease the burden of variants of uncertain significance in type 2 long QT syndrome. *JACC Clin Electrophysiol*. 2026;12(2):350–359.

7. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation*. 2001;103:89–95.

8. Zhang L, Timothy KW, Vincent GM, et al. Spectrum of ST-T-wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. *Circulation*. 2000;102:2849–2855.

9. O'Neill MJ, Ng CA, Aizawa T, et al. Multiplexed assays of variant effect and automated patch clamping improve KCNH2-LQTS variant classification and cardiac event risk stratification. *Circulation*. 2024;150:1869–1881.

10. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2022;43:3997–4126.

KEY WORDS genetic testing, long QT syndrome, phenotype, variant of uncertain significance