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ORIGINAL RESEARCH

CLINICAL ELECTROPHYSIOLOGY

A Phenotype-Enhanced Variant Classification Framework to Decrease the Burden of Variants of Uncertain Significance in Type 2 Long QT Syndrome

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ABSTRACT

BACKGROUND Pathogenic/likely pathogenic variants in the *KCNH2*-encoded Kv11.1 potassium channel cause type 2 long QT syndrome (LQT2). Despite the updated 2015 American College of Medical Genetics (ACMG) variant interpretation guidelines, the burden of KCNH2 variants of uncertain significance (VUS) in patients evaluated for long QT syndrome (LQTS) remains ~30%. Previously, we developed and validated phenotype-enhanced (PE) ACMG variant adjudication for type 1 long QT syndrome.

OBJECTIVES The purpose of this study was to determine whether a PE-ACMG variant classification approach can reduce the VUS burden in patients with clinically suspected LQT2.

METHODS Retrospective analysis was performed on 209 unique missense variants within *KCNH2* from 2 LQTS specialty centers. Each variant was categorized based on the classification on the initial genetic test reports. Subsequently, all VUS were re-adjudicated with the use of a PE-ACMG framework that incorporates the patient's phenotype using the LQTS clinical diagnostic Schwartz score plus 2 LQT2-defining features: 1) biphasic/notches T waves; and 2) LQTS-triggered events during emotional stress or auditory stimuli.

RESULTS In total, 69/209 (33%) unique KCNH2 variants were classified as VUS based on their initial genetic test report. Mean Schwartz score for patients with a VUS was 3.6, and 41 patients (29%) had a score over 3.5. After PE-ACMG adjudication, 31/69 variants (45%) were upgraded to pathogenic, 18 (26%) to likely pathogenic, and 11 (16%) were downgraded to benign variants. Only 9 of 69 variants (13%) remained VUS. Overall, the VUS burden decreased from 69 of 209 (33%) to 9/209 (4%; $P < 0.0001$).

CONCLUSIONS Phenotype-guided variant adjudication significantly decreased the VUS burden of LQT2 case-derived KCNH2 missense variants from 2 LQTS specialty centers. There is clear value in incorporating LQT2-specific phenotype/clinical data to aid in the interpretation of *KCNH2* missense variants identified during LQTS genetic testing, thereby facilitating prompt initiation of LQT2-guided therapy and cascade testing of appropriate relatives. (JACC Clin Electrophysiol. 2026;12:350-359) © 2026 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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Since the early 2000s, clinicians have used genetic testing to aid in the diagnosis and management of patients with genetic heart diseases (GHDs). Today, we are in an era when genetic testing for GHDs is widely accessible and strongly recommended—earning a Class I indication in the most recent clinical guidelines.[1,2] However, one of the greatest ongoing challenges in the field remains the high prevalence of variants of uncertain significance (VUS). Identifying a VUS creates a diagnostic dilemma for patients, families, and clinicians, because it is unclear whether the variant is disease causing or merely represents benign "genetic noise."

To address this issue, the American College of Medical Genetics and Genomics (ACMG) published standardized guidelines for variant interpretation in 2015.[3] Despite that effort, the burden of VUS remains particularly high in GHDs. Studies have demonstrated that integrating detailed phenotypic information can significantly improve variant classification in disorders such as hypertrophic cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia (CPVT), and type 1 long QT syndrome (LQT1), through the development of phenotype-enhanced (PE) ACMG variant adjudication frameworks.[4-6]

For type 2 long QT syndrome (LQT2), the second most frequent long QT syndrome (LQTS) subtype, caused by loss-of-function variants in the *KCNH2*-encoded Kv11.1 potassium channel, the burden of VUS remains high at approximately 30%. This is particularly concerning, because untreated LQT2 can lead to serious outcomes, including arrhythmia-mediated syncope, seizures, sudden cardiac arrest, and sudden cardiac death.[7]

In the present study, we applied a PE adjudication approach to reduce the VUS burden in LQT2, building on principles established in previous studies.[5,6] Specifically, we incorporated the well known Schwartz score[8]—used for LQTS diagnosis—along with 2 well established LQT2-defining features (L2DFs)—1) biphasic or notched T waves on resting 12-lead electrocardiography (ECG),[9] and 2) LQTS-triggered events during emotional stress or auditory stimuli[8,10-12]—into the ACMG framework to enhance variant interpretation in LQT2.

METHODS

This study was approved by the Mayo Clinic (Mayo) Institutional Review Board (1216-97, 10-008295, and 16-008436) and Istituto Auxologico Italiano (Auxo; 2021_05_18_06). The research reported herein adhered to the Helsinki Declaration as revised in 2013. Detailed methods are provided in the Supplemental Methods.

RESULTS

COHORT DEMOGRAPHICS AND VARIANT ADJUDICATION. The cohort selection process and study cohort on both patient and variant-specific levels after application of inclusion and exclusion criteria are illustrated in **Figure 1**. Among patients with an ultra-rare missense variant in *KCNH2*, there were 318 individuals from Mayo and 255 from Auxo, encompassing 117 unique variants at Mayo and 92 at Auxo. At Mayo Clinic, initial variant classification included 68 (58%) as pathogenic (P), 11 (9%) as likely pathogenic (LP), and 38 (33%) as VUS. At Auxo, 20 (22%) were classified as P, 41 (44%) as LP, and 31 (34%) as VUS (**Figure 2**). Neither cohort included variants classified as likely benign (LB) or benign (B).

Overall, at a patient level, 255 of 318 (80%) at Mayo and 178 of 255 (70%) at Auxo had a P/LP variant according to their genetic test reports, and 63 patients (20%) at Mayo and 77 patients (30%) at Auxo harbored a VUS. In total, 140 of 573 patients (24%) had a VUS in *KCNH2* (Mayo: n = 63; Auxo: n = 77). Demographics and Schwartz score distributions (categorized as high, intermediate, or low likelihood

ABBREVIATIONS AND ACRONYMS

B = benign
CPVT = catecholaminergic polymorphic ventricular tachycardia
ECG = electrocardiography
GHD = genetic heart disease
LP = likely pathogenic
LB = likely benign
L2DF = LQT2-defining feature
LQT1 = type 1 long QT syndrome
LQT2 = type 2 long QT syndrome
LQTS = long QT syndrome
P = pathogenic
PE = phenotype-enhanced
QTc = heart rate-corrected QT interval
SUD = sudden unexplained death
VUS = variant of uncertain significance

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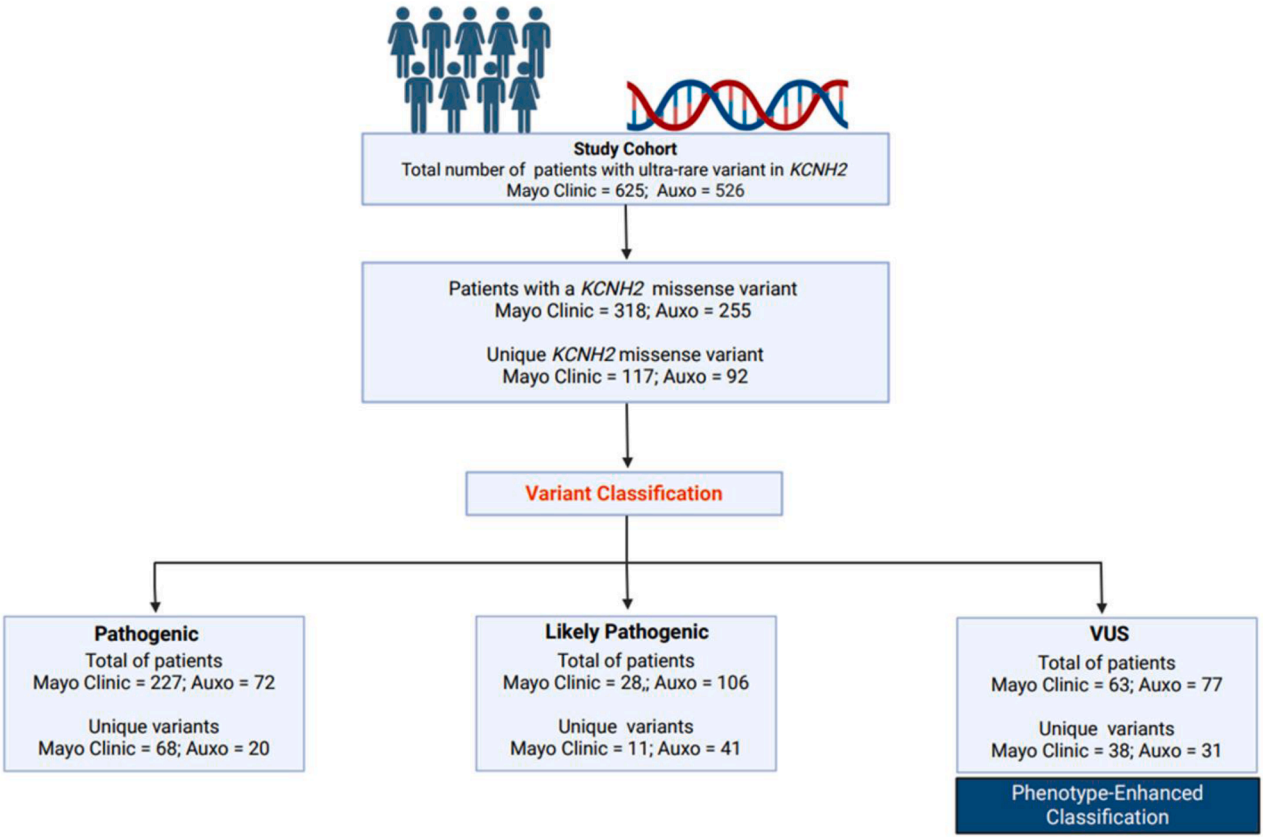
FIGURE 1 Patient and Variant Selection Process



The final cohort size of 63 Mayo Clinic and 77 Istituto Auxologico Italiano (Auxo) patients with a *KCNH2* missense variant of uncertain significance (VUS) was selected from an overall study cohort of 1,151 patients with LQT2. Created with BioRender.com.

for LQTS) are summarized in Table 1. More than one-half of the patients were female (62% at Mayo, 52% at Auxo). The mean ages at LQTS diagnosis were 20 ± 16 years (Mayo) and 28 ± 21 years (Auxo) and the mean baseline QTc was 470 ± 32 milliseconds at Mayo and 444 ± 36 milliseconds at Auxo.

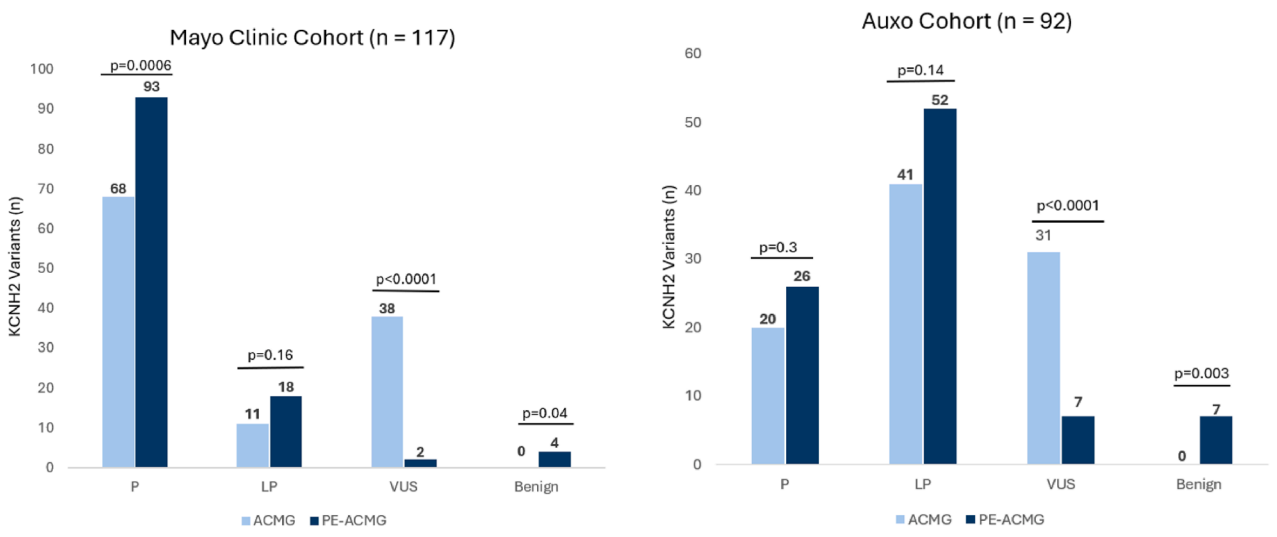
Evaluation of L2DF demonstrated a history of cardiac events, such as syncope, seizures, and sudden cardiac arrest triggered by auditory stimuli or emotional stress, present in 11 patients at Mayo (17%) and 2 patients at Auxo (3%). The classic LQT2-associated T-wave morphology (biphasic or notched) (Figure 3) was observed in 46 patients (73%) at Mayo and 20 patients (26%) at Auxo.

ASSESSMENT OF A PE VARIANT RE-ADJUDICATION APPROACH. With our hypothesis that integrating both the Schwartz score and L2DFs could enhance *KCNH2* VUS resolution, we created our proposed PE-ACMG classification framework (Table 2), with which we re-adjudicated each ultra-rare *KCNH2* missense variant previously classified as a VUS.

Following integration of Schwartz-score and presence of L2DFs into the ACMG classification, among 69 VUS evaluated, 31 (45%) were upgraded to P (Mayo: n = 25 (66%); Auxo: n = 6 (19%)), 18 (25%) to LP (Mayo: n = 7 [18%]; Auxo: n = 11 [35%]), and 11 (16%) were downgraded to B (Mayo: n = 4 [11%]; Auxo: n = 7 [23%]). Only 9 variants (13%) remained classified as VUS (Mayo: n = 2 [6%]; Auxo: n = 7 [23%]) (Figure 4).

The overall VUS burden decreased substantially from 69 of 209 variants (33%) to 9 of 209 (4%). At Mayo Clinic, the number of VUS decreased from 38 (33%) to 2 (2%), and at Auxo from 31 (34%) to 7 (7%). These reductions were statistically significant across both cohorts ($P < 0.0001$) (Figure 2). Detailed variant-level data and final PE-ACMG classifications are presented in Supplemental Tables 1 and 2. New distribution of variant pathogenicity at all levels

FIGURE 2 **LQT2 Variant Classification Based on the Genetic Test Report and PE Frameworks**



Comparison of *KCNH2* rare variant classification between the genetic test report (ACMG; light blue) and our newly developed PE-ACMG variant classification framework (dark blue) that was applied for the VUS. Statistical analysis was performed using GraphPad Prism (v9.0.2 for Windows; GraphPad Software). LP = likely pathogenic; P = pathogenic; PE = phenotype-enhanced; VUS = variants of uncertain significance.

(P, LP, VUS, B) after PE-ACMG reclassification are shown in Figure 2. The phenotypes of re-classified VUS patients within each reclassification category are described below.

PHENOTYPE OF PATIENTS WITH A VUS UPGRADED TO P. A total of 69 patients had one of 31 variants that were upgraded to P. Their mean QTc was 468 ± 35 milliseconds, and the average Schwartz score was 4 ± 2. Classic LQT2 T-wave morphology (biphasic/notched) was present in 49 patients (71%), and 11 patients (16%) experienced cardiac events triggered by auditory stimuli or emotional stress.

PHENOTYPE OF PATIENTS WITH A VUS UPGRADED TO LP. Thirty-six patients had one of the 18 variants reclassified as LP. These patients had a mean QTc of 445 ± 40 milliseconds and a mean Schwartz score of 2 ± 1. Fifteen patients (42%) exhibited the LQT2-characteristic T-wave morphology, and 2 patients (6%) had a history of LQT2-triggered cardiac events.

PHENOTYPE OF PATIENTS WITH A VUS DOWNGRADED TO B. Among the 21 patients with one of the 11 variants downgraded to B, the mean QTc was 429 ± 18 milliseconds and the average Schwartz score 0.7 ± 0.4. None of these patients met any of the L2DFs, supporting a B classification. Notably, although referred with a diagnosis of possible LQTS, the diagnosis of LQTS was removed clinically, independently from the genetic testing, in all 21 patients.

PHENOTYPE OF PATIENTS WITH A VUS THAT REMAINED DESIGNATED AS VUS. Nine variants, present in 14 patients, remained classified as VUS. These individuals had a mean QTc of 447 ± 48 milliseconds and a mean Schwartz score of 2 ± 1. Biphasic or notched T waves were present in 3 patients (33%), and none experienced cardiac events. Among these 14 patients, none were dismissed as normal after their specialty center evaluation, and the clinical diagnosis of LQTS was maintained in all patients.

FUNCTIONAL ANALYSIS OF VARIANTS. Of the 69 VUS, only 18 had been characterized functionally by patch clamp analysis or Western blot including 14 of the VUS phenotypically upgraded from VUS to LP or P variants.[13-18] Among those upgraded variants that had been characterized, the concordance between a PE upgrade and demonstration of a significant in vitro loss-of-function or decreased protein expression was 86% (12/14) (Supplemental Tables 1 and 2). Among the 53 variants lacking traditional functional data, 48 were evaluated with the use of a high-throughput automated patch-clamp platform known as MAVE (multiplexed assays of variant effect).[19] The concordance rate between the phenotype-based classification and MAVE functional assessment was 60% (29/48).

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TABLE 1 Clinical Characteristics of Patients Evaluated at Either Mayo Clinic or Istituto Auxologico Italiano (Auxo) With a *KCNH2* Missense Variant Classified as a Variant of Uncertain Significance

	Mayo Clinic (n = 63)	Auxo (n = 77)
Female	39 (62)	40 (52)
Age at diagnosis, y	20 ± 16	28 ± 21
Proband	20 (32)	32 (42)
Family history of SCD <45 years of age	33 (52)	19 (25)
BB therapy at the time of stress test	21 (33)	12 (16)
LQT2-defining features		
Biphasic T-wave or notched T waves	46 (73)	20 (26)
Cardiac event with auditory stimuli or under emotional stress	11 (17)	2 (3)
Schwartz score		
Baseline QTc, ms	470 ± 32	444 ± 39
Maladaptive stress test	13 (21)	6 (8)
Torsades des pointes	4 (6)	2 (3)
T-wave alternans	2 (3)	0
Notched T-wave in 3 leads	41 (65)	20 (26)
Low heart rate for age	0	0
Syncope with stress	8 (13)	2 (3)
Syncope without stress	5 (8)	3 (4)
Congenital deafness	0	0
Family members with definite LQTS	47 (75)	63 (82)
First-degree family members with SUD <30 years of age	29 (46)	17 (22)
Schwartz score values for cohort		
High Schwartz score (≥3.5)	39 (62)	16 (21)
Intermediate Schwartz score (1.5-3)	16 (25)	24 (31)
Low Schwartz score (≤1)	8 (13)	37 (48)

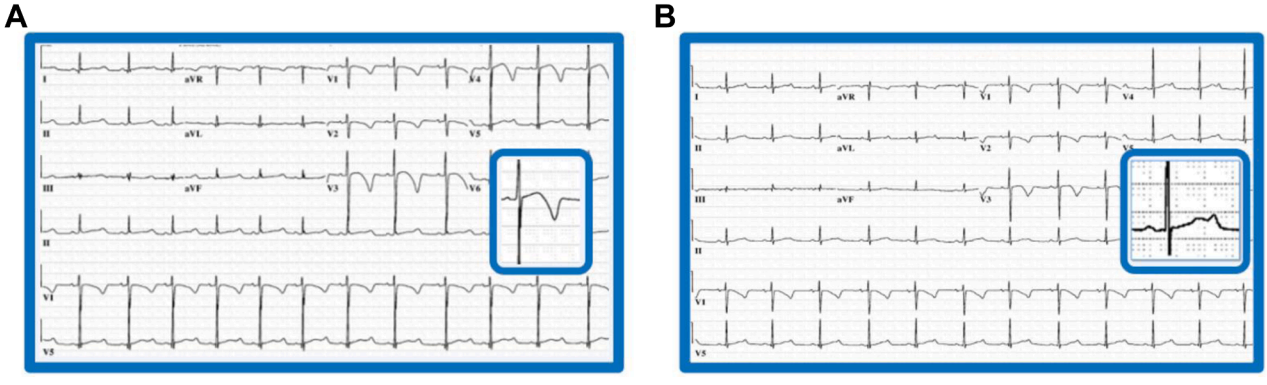
Values are n (%) or mean ± SD.

LQT2 = type 2 long QT syndrome; LQTS - long QT syndrome; SCD = sudden cardiac death; SUD = sudden unexpected death.

We conducted additional patch clamp characterization for 2 variants that were upgraded to P (L622F) and LP (R734C) based on PE-ACMG. Typical I_{Kr} tracings of voltage-dependent activation from KCNH2-WT+KCNE2, KCNH2-L622F+KCNE2, and KCNH2-R734C+KCNE2 are shown in Figures 5A to 5D with holding potential at −80 mV to various depolarization potentials. Analysis of the current-voltage relationship revealed that KCNH2-L622F (n = 10) resulted in a significant decrease ($P < 0.05$) in peak current density across the voltage from +10 mV to +40 mV (Figure 5B) and in tail current density across the voltage from +10 mV to +60 mV (Figure 5C) compared with KCNH2-WT (n = 10), indicating its loss of I_{Kr} current function. Specifically, at +20 mV, KCNH2-L622F (14.3 ± 3.3 pA/pF; n = 10) revealed a significant decrease (70.7%) in peak current density compared with KCNH2-WT (48.8 ± 8.3 pA/pF; n = 10; $P < 0.05$), and at +60 mV, KCNH2-L622F (9.6 ± 2.8 pA/pF; n = 10) revealed a significant decrease (94.5%) in tail current density compared with KCNH2-WT (175.8 ± 29.7 pA/pF; n = 10; $P < 0.05$).

Similarly, KCNH2-R734C (n = 14) also resulted in a significant decrease ($P < 0.05$) in peak current density across the voltage from +10 mV to +40 mV (Figure 5E) and in tail current density across the voltage from −10 mV to +60 mV (Figure 5F) compared with KCNH2-WT (n = 14), indicating its loss of I_{Kr} current function as well. Specifically, at +30 mV, KCNH2-R734C (17.4 ± 2.4 pA/pF; n = 14) revealed a significant decrease (43.5%) in peak current density compared with KCNH2-WT (30.8 ± 2.1 pA/pF; n = 14;

FIGURE 3 Abnormal T-Wave Morphologies Observed in Type 2 Long QT Syndrome



(A) 12-lead ECG showing a biphasic T-wave characterized by an initial positive deflection followed by a negative deflection. (B) A 12-lead electrocardiogram showing a notched T wave characterized by a second positive deflection interrupted its descending phase. Created using Biorender.com.

TABLE 2 Proposed PE-ACMG Diagnostic Criteria for Variants in the LQT2-Susceptibility Gene, *KCNH2*

Proposed VUS Re-classification	Description
Re-classify to pathogenic (PS5)	Schwartz score ≥3.5 and ≥1 L2DFs in ≥1 individual
Re-classify to likely pathogenic (PM7)	Schwartz score ≥3.5 and 0 L2DFs; or Schwartz score 1.5-3 and ≥1 L2DFs in ≥1 individual
Support benign classification (BP8)	Schwartz score ≤1 in all individuals and 0 L2DFs in ≥1 individual
Remain as VUS	Schwartz score 1.5-3 and 0 L2DFs in ≥1 individual; Schwartz score ≤1 in all individuals and ≥1 L2DFs in ≥1 individual

BP8 = benign supporting; L2DFs = LQT2-defining features; PM7 = pathogenic moderate; PS5 = pathogenic strong; VUS = variant of uncertain significance.

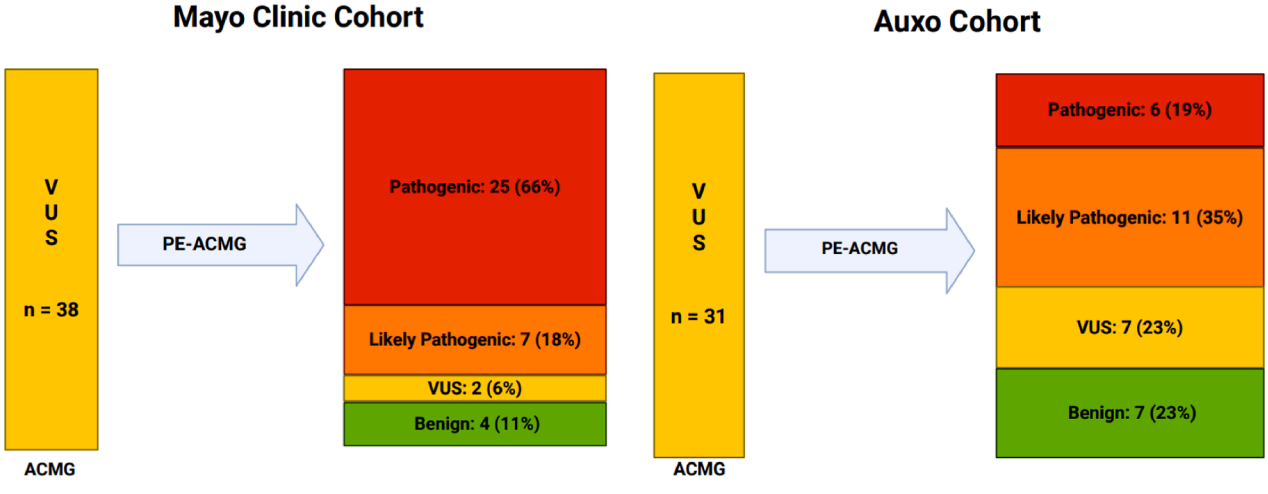
$P < 0.05$), and at +60 mV, KCNH2-R734C (19.7 ± 3.7 pA/pF; n = 14) revealed a significant decrease (85.3%) in tail current density compared with KCNH2-WT (133.9 ± 13.3 pA/pF; n = 14; $P < 0.05$).

DISCUSSION

LQTS AND GENETIC PURGATORY. Variant classification and interpretation of a VUS is critically important in diagnosis, management, and genotype-guided therapy in patients with GHDs such as LQTS. In 2015, the ACMG released guidelines for variant interpretation that are used by commercial and research genetic companies.[3] However, in this second paper about phenotype enhancement for variant adjudication in LQTS, we show that in LQT2, the number of VUS is still around 30%, as previously shown for LQT1.[6] We again demonstrated that the "one-size-fits-all" approach in GHDs deprioritizes the clinical phenotype and as a result increases the number of VUS as shown in this and previous studies of channelopathies and cardiomyopathies.[4-6,20] Those studies have shown that by incorporating a patient's phenotype through previously developed and validated diagnostic and phenotype scores, the burden of VUS can be significantly lowered with the use of PE-ACMG variant adjudication.[4-6]

Although variant-specific functional data can assist with classification and diagnosis, as we showed here that the functional data confirmed our final classification based on PE-ACMG for 2 of our variants, the feasibility of acquiring such data remains limited in routine clinical practice. Although recent studies have demonstrated that high-throughput automated patch clamp technology can functionally assess VUS in genes encoding cardiac ion channels, the clinical utility and scalability of applying these in vitro assays for novel variant assessment remains uncertain.[3,19,21,22] This challenge is particularly pronounced in LQTS, where hundreds of ultra-rare or private mutations have been identified, many of which are found in single families or individuals. This rarity often precludes the (rapid) generation of functional data to assist in variant classification and limits statistical power for elucidating critical observations through genotype-phenotype correlation. In

FIGURE 4 Re-Classification of VUS in the Mayo Clinic and Auxologico Cohorts Using Our Newly Developed PE-ACMG



Created using Biorender.com. PE = phenotype-enhanced; VUS = variant of uncertain significance.

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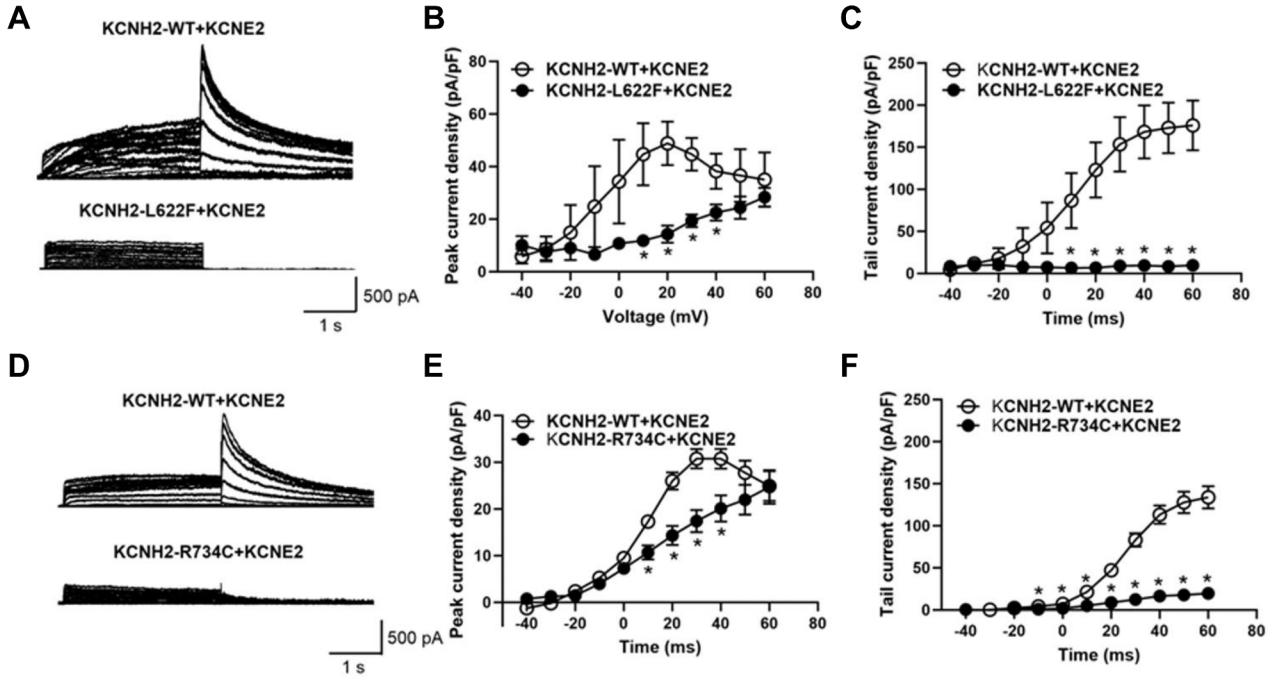
FIGURE 5 KCNH2-L622F and KCNH2-R734C Missense Variants Significantly Reduced I_{Kr} Current Density in Heterologous TSA 201 Cells



(A) Whole cell I_{Kr} current representative tracings from TSA201 cells expressing KCNH2-WT+KCNE2 or KCNH2-L622F+KCNE2 determined from a holding potential of −80 mV and testing potentials from −40 mV to +60 mV in 10-mV increments with 3 s duration. (B) Peak current-voltage relationship for KCNH2-WT+KCNE2 (n = 10) and KCNH2-L622F+KCNE2 (n = 10). (C) Tail current-voltage relationship for KCNH2-WT+KCNE2 (n = 10) and KCNH2-L622F+KCNE2 (n = 10). (D) Whole cell I_{Kr} current representative tracings from expressing KCNH2-WT+KCNE2 or KCNH2-R734C+KCNE2. (E) Peak current-voltage relationship for KCNH2-WT+KCNE2 (n = 14) and KCNH2- R734C+KCNE2 (n = 14). (F) Tail current-voltage relationship for KCNH2-WT+KCNE2 (n = 14) and KCNH2-R734C+KCNE2 (n = 14). All values represent mean ± SEM. *$P < 0.05$ vs KCNH2-WT+KCNE2.

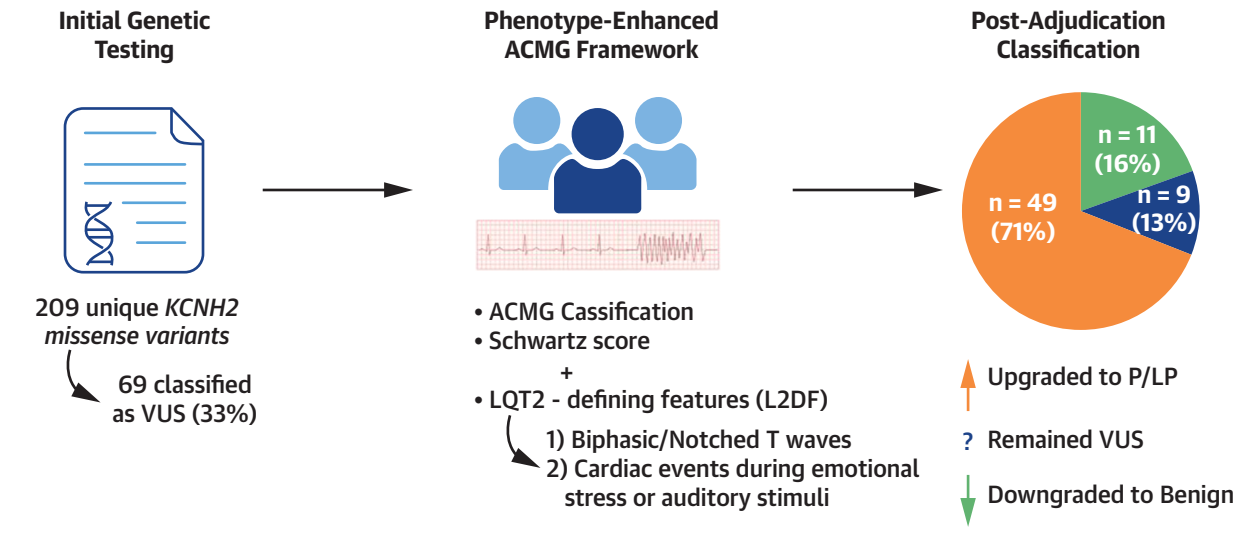
these contexts, relying solely on laboratory-based functional validation, which remains more heavily weighted in the current ACMG criteria than the strength of the clinical phenotype, is impractical.

In contrast, when applied judiciously, phenotype-informed adjudication can enable clinicians to reclassify a VUS to LP/P or downgrade it to LB/B based on compelling clinical evidence. This reclassification not only improves diagnostic clarity but also supports cascade screening of at-risk relatives and enables proactive interventions, such as avoidance of QT-prolonging drugs or initiation of appropriate therapies.

USING PHENOTYPE FOR RARE VARIANT ADJUDICATION OF VUS IN LQT2. Lately, we have seen the effort to add the phenotype in variant classification in monogenetic GHDs such as channelopathies and cardiomyopathies.[4-6,23] In those studies, phenotyping was stratified with the use of previously published and validated diagnostic and phenotype scores. For LQTS, the Schwartz score has long been a well established diagnostic tool for objectively quantifying the veracity of the clinical diagnosis of LQTS.[8] In addition, each of the 3 most common genotypes—types 1, 2, and 3—have well characterized clinical features that aid in both diagnosis and subtype differentiation in LQTS.[8,9,11] In LQT2 specifically, patients often present with notched or biphasic T waves on ECG, emotionally or auditorily triggered cardiac events, and QT prolongation.[10-12] In the present study, we showed that PE significantly reduced VUS burden in LQT2 using 2 independent cohorts (**Central Illustration**). These clear distinctions in phenotype across re-classification categories support the robustness of our PE-ACMG framework and its biological plausibility.

It was noticed that our 2 cohorts of individuals carrying a VUS show important differences concerning the presence of the arrhythmia triggers (17% vs 3%), of the typical T-wave morphology (73% vs 26%), and of QTc (470 ± 32 vs 444 ± 36 milliseconds). These

CENTRAL ILLUSTRATION **Phenotype-Enhanced Variant Adjudication of Variants Classified as VUS in LQT2**



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The impact of phenotype-enhanced ACMG variant adjudication on reclassifying *KCNH2* missense variants in suspected type 2 long QT syndrome (LQT2). The diagram highlights the flow from initial testing to reclassification outcomes. Created with the use of Biorender.com. LP = likely pathogenic; P = pathogenic; PE = phenotype-enhanced; VUS = variant of uncertain significance.

differences probably reflect the source of the referrals at Mayo and at Auxo. Patients would not travel to Rochester, Minnesota, without a very valid reason and not without a prior consultation: In other words, independently from the genetic results, the presence of a phenotype highly suggestive for LQTS is very likely. In contrast, also because of the ECG screening, which is mandatory in Italy to be allowed to practice competitive sports, among the many seriously affected patients referred to Auxo there are also those sent just because of an even modest prolongation of the QT interval. Therefore, it is not surprising that among the subjects carrying a VUS, those seen at Mayo tend to have a more severe phenotype. The importance of different patterns of referrals for possible LQTS patients, as well as different approaches to therapy, has recently received attention because lumping together different cohorts might lead to incorrect conclusions.[24,25] This concern does not apply to the present study.

STUDY LIMITATIONS. As shown with *RYR2*-mediated catecholaminergic polymorphic ventricular tachycardia (CPVT1), *MYH7*-mediated hypertrophic cardiomyopathy, and LQT1, the application of an objective measure of clinical strength to the existing generic ACMG variant classification and reporting guidelines significantly enhances the classification of rare *KCNH2* variants identified via LQTS-specific genetic testing. However, the clinical utility of a PE approach to rare *KCNH2* variant adjudication depends on accurate clinical phenotyping, including assessment of the L2DFs outlined in this work. Although the L2DFs were designed to be objective measures of LQT2, variability may still exist in their assessment.

In the present study, LQTS phenotyping was assessed by 2 LQTS specialists in the context of 2 highly specialized LQTS clinics within tertiary/quaternary medical centers. As such, widespread use of this scoring system among clinicians may be subject to variability. Although LQT2 is one of the GHDs with

a relatively specific clinical phenotype (ie, biphasic/notched T wave, cardiac event under auditory stimuli or emotional stress, etc), it likely represents one of the few GHDs, besides LQT1 and CPVT1, where the application of a PE approach may be useful clinically. In disorders where the clinical phenotype is less specific or the genetic source is oligo- or polygenic in nature, the effectiveness of a PE approach may be limited. Finally, the criteria used in this study were developed for the tight monogenic link between LQT2 and *KCNH2* and were not intended to address the association of some *KCNH2* variants with other diseases, such as short QT syndrome subtype 1.

CONCLUSIONS

This study demonstrates the value of incorporating patient phenotype data to aid in the interpretation of KCNH2 VUS revealed by genetic testing. Overall, the use of PE-ACMG significantly decreased the VUS burden of KCNH2 missense variants by more than one-third in 2 independent cohorts of patients being evaluated for LQTS. Given the well defined phenotype observed in LQT2, variant classification guidelines should include and emphasize phenotypic criteria. By incorporating structured clinical and electrocardiographic markers, this approach reduces diagnostic uncertainty and facilitates more informed patient care. Future efforts should focus on validating this strategy across additional GHDs and refining its implementation into routine clinical workflows.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Incorporating patient-specific clinical features into genetic variant interpretation can significantly enhance diagnostic clarity in LQT2. This study demonstrates that applying a phenotype-enhanced ACMG framework—using Schwartz scores and LQT2-defining features—can markedly reduce the proportion of *KCNH2* variants classified as uncertain. By upgrading or downgrading variants based on clinical context, this approach enables more definitive diagnoses, earlier initiation of LQT2-directed therapies, and more accurate identification of at-risk relatives for cascade testing.

TRANSLATIONAL OUTLOOK: This work highlights the importance of integrating clinical phenotyping into genetic adjudication protocols to overcome limitations of variant interpretation based solely on sequence data. The success of phenotype-enhanced ACMG classification in LQT2 suggests that it could be adapted for other monogenic cardiovascular diseases. Broader adoption of this strategy may lead to more precise, actionable genetic diagnoses, accelerating the application of precision medicine in cardiovascular care.

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

APPENDIX For a supplemental Methods section and supplemental tables, please see the online version of this paper.