

# Arrhythmogenic Cardiomyopathy in a Patient With a Rare Loss-of-Function *KCNQ1* Mutation

Qinmei Xiong, MD;\* Qing Cao, MD;\* Qiongqiong Zhou, MD; Jinyan Xie, MD; Yang Shen, MD; Rong Wan, PhD; Jianhua Yu, MD; Sujuan Yan, MD; Ali J. Marian, MD; Kui Hong, MD, PhD

**Background**—Ventricular tachycardia (VT) is a common manifestation of advanced cardiomyopathies. In a subset of patients with dilated cardiomyopathy, VT is the initial and the cardinal manifestation of the disease. The molecular genetic basis of this subset of dilated cardiomyopathy is largely unknown.

**Methods and Results**—We identified 10 patients with dilated cardiomyopathy who presented with VT and sequenced 14 common causal genes for cardiomyopathies and arrhythmias. Functional studies included cellular patch clamp, confocal microscopy, and immunoblotting. We identified nonsynonymous variants in 4 patients, including a rare missense p.R397Q mutation in the *KCNQ1* gene in a 60-year-old man who presented with incessant VT and had mild cardiac dysfunction. The p.R397Q mutation was absent in an ethnically matched control group, affected a conserved amino acid, and was predicted by multiple algorithms to be pathogenic. Co-expression of the mutant *KCNQ1* with its partner unit *KCNE1* was associated with reduced tail current density of slowly activating delayed rectifier  $K^+$  current (IKs). The mutation reduced membrane localization of the protein.

**Conclusions**—Dilated cardiomyopathy with an initial presentation of VT may be a forme fruste of arrhythmogenic cardiomyopathy caused by mutations in genes encoding the ion channels. The findings implicate *KCNQ1* as a possible causal gene for arrhythmogenic cardiomyopathy. (*J Am Heart Assoc.* 2015;4:e001526 doi: 10.1161/JAHA.114.001526)

**Key Words:** arrhythmias • cardiomyopathy • genetics • *KCNQ1* • mutation • ventricular tachycardia

Hereditary cardiomyopathies are primary myocardial diseases that typically manifest with ventricular dilatation, hypertrophy, and dysfunction.<sup>1</sup> Hereditary cardiomyopathies exhibit considerable phenotypic variability and diverse clinical manifestations.<sup>1</sup> In a subset of patients with hereditary cardiomyopathies, the cardinal features are early manifestations of ventricular arrhythmia and sudden cardiac death, typically in the context of normal cardiac structure

and function or disproportionate to structural and functional abnormalities. In this subset of dilated cardiomyopathy (DCM), ventricular dilation and dysfunction become apparent as the disease progresses, and clinical heart failure often manifests late in the course of the disease. This subset of DCM may be a forme fruste of arrhythmogenic cardiomyopathy (AC) as the phenotype contrasts with that of classic DCM, in which heart failure is the primary manifestation and arrhythmia occurs in the setting of advanced ventricular dysfunction. This subset of AC also differs from the classic arrhythmogenic right ventricular cardiomyopathy, which is characterized by fibrofatty infiltration of the myocardium with a predilection toward involvement of the right ventricle.<sup>2</sup> Considering the above, AC might be used to define a broader spectrum of hereditary cardiomyopathies, including the classic arrhythmogenic right ventricular cardiomyopathy, whereby a key characteristic feature is a propensity to ventricular arrhythmia out of proportion to the extent of ventricular dysfunction.

The molecular genetic basis of this subset of AC remains partly unknown. We report identification and functional characterization a rare nonsynonymous loss-of-function variant in the *KCNQ1* gene in a patient with this subset of AC, which points to the presence of a phenotypic and genetic

From the Cardiovascular Department (Q.X., Q.Z., Y.S., J.Y., S.Y., K.H.) and The Key Laboratory of Molecular Medicine (Q.C., J.X., R.W., K.H.), the Second Affiliated Hospital of Nanchang University, Nanchang, China; Center for Cardiovascular Genetics at The University of Texas Health Science Center—Houston and Texas Heart Institute, Houston, TX (A.J.M.).

\*Dr Xiong and Dr Cao contributed equally to this work.

**Correspondence to:** Ali J. Marian, MD, Center for Cardiovascular Genetics, 6700 Bertner Street, DAC900, Houston, TX 77030. E-mail: Ali.J.Marian@uth.tmc.edu

Kui Hong, MD, PhD, Cardiovascular Department, The Second Affiliated Hospital of Nanchang University, Nanchang 330006, China. E-mail: Hongkui88@163.com

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overlaps between the hereditary arrhythmia syndromes and cardiomyopathies.

## Methods

The institutional review board of the Second Affiliated Hospital of Nanchang University approved the study. All subjects gave a written informed consent to participate in the study.

## Study Population

We identified 10 patients with DCM, whose first clinical manifestation was ventricular tachycardia (VT) occurring prior to or disproportionate to left ventricular dysfunction. Two hundred healthy individuals with no apparent cardiovascular disease that had the same ethnic background as the cases were included as controls.

## DNA Sequencing

DNA was extracted from the peripheral blood samples and all exons and exon–intron boundaries of candidate genes responsible for hereditary cardiac arrhythmias (namely, *SCN5A*, *KCNQ1*, *KCNE1*, *KCNE2*) and *KCNH2* and hereditary cardiomyopathies (namely, *PKP2*, *DSP*, *DSG2*, *DSC2*, *LMNA*, *MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*) were amplified by polymerase chain reaction and sequenced by the Sanger method in forward and reverse directions using the Big Dye Terminator version 3.1 (Applied Biosystems, Carlsbad, CA).

## Site-Directed Mutagenesis

Site-directed mutagenesis was used to introduce a G>A substitution at coding position 1190 in the *KCNQ1* cDNA, corresponding to p.R397Q amino acid change. The clone was sequenced to verify introduction of the intended variant and exclude potential erroneous mutagenesis.

## Cellular Electrophysiology

Full-length wild-type (WT) *KCNQ1* cDNA (a gift from Dr Yihan Chen at Tongji University, Shanghai, China) and the *KCNQ1* cDNA carrying the p.R397Q mutation were subcloned into a pDouble-EGFP expression vector. Likewise, full-length *KCNE1* cDNA encoding human KCNE1 protein subcloned into the pDSRed-Monomer-N1 expression vector. *KCNQ1* and *KCNE1* plasmids were transiently co-transfected (2:1 molar ratio) into HEK293T cells using Lipofectamine 2000 transfection reagent (Invitrogen Life Technologies, Carlsbad, CA). Patch-clamp experiments were performed in the Green Fluorescence Protein (GFP)-positive transfected cells 48 hours after the transfection.

Whole-cell patch clamps were recorded with an EPC-10 patch clamp amplifier (HEKA Elektronik, Lambrecht, Germany). The pipette solution contained (in mmol/L) 100 K-aspartate, 45 KCl, 1 CaCl<sub>2</sub>, 5 EGTA, 5 HEPES, 5 ATP-Mg, and 5 phosphocreatine-disodium (pH adjusted to 7.2 with KOH). The extracellular solution contained (in mmol/L) 140 NaCl, 5.4 KCl, 1.8 CaCl<sub>2</sub>, 0.5 MgCl<sub>2</sub>, 0.33 NaH<sub>2</sub>PO<sub>4</sub>, 5.5 glucose, and 5.0 HEPES (pH adjusted to 7.4 with NaOH). Pipette resistance ranged from 3 to 5 MΩ. Slow Potassium (IKs) currents were obtained by depolarizing voltage steps from a holding potential of −80 mV to various test potentials. The activating current was elicited from −60 mV to +50 mV at 10-mV increments for 5 second, and the tail current was recorded on return to −30 mV for 5 second. Pulses were delivered every 15 second. The current density at +60 mV and the peak deactivation tail current at −30 mV were measured.

Fitmaster was used to collect data. The current–voltage (I–V) relation was fit by the Boltzmann equation:  $I = (I_{\text{MIN}} - I_{\text{MAX}}) / (1 + e^{(V - V_{1/2})/k}) + I_{\text{MAX}}$ , where  $I_{\text{MIN}}$ =minimally activated current,  $I_{\text{MAX}}$ =maximally activated current,  $V_{1/2}$ =the membrane potential at which 50% of the channels are activated, and  $k$ =slope factor. Origin (8.0; Microcal, Northhampton, MA) was used for performing Boltzmann curve fitting and for generating graphs.

## Immunofluorescence

HEK-293 cells were transiently transfected with either WT or mutant *KCNQ1* clones using Lipofectamine 2000. Forty-eight hours after the transfection, cells were fixed in 4% formaldehyde in phosphate-buffered saline and incubated overnight with a rabbit anti-KCNQ1 antibody (1:50 dilution; Merck Millipore). The secondary antibody was TRITC-conjugated donkey anti-rabbit secondary antibody (1:1000 dilution; Molecular Probes, Invitrogen). Images were collected with a Leica TCS confocal microscope (Leica Microsystems).

## Cell Protein Fractionation and Western Blotting

Triton X-114 temperature-induced phase separation method was used to isolate membrane fraction per a published protocol.<sup>3</sup> Aliquots of 100-μg protein extracts were electrophoresed, transferred to a polyvinylidene difluoride membrane and probed with antibodies against *KCNQ1* (1:1000 dilution; Merck Millipore), Na<sup>+</sup>/K<sup>+</sup> ATPase (1:800 dilution; Proteintech), and GAPDH (1:1000 dilution; Santa Cruz).

## Statistics

Values are expressed as means±standard errors of the mean. Equality of variances was tested by Levene's test. Variables with equal variances between 2 groups were compared by

*t* test and by the nonparametric Mann–Whitney test. Interactions between the experimental groups (HEK293 cells expressing WT and mutant KCNQ1) and responses of the currents to changes in voltage were analyzed by MANOVA (Stata64 for Mac, 10.1).

## Results

### Characteristics of the Study Population

Clinical characteristics of the study population are shown in Table.

### Genetic Variants

Synonymous variants, variants in the introns, common variants (minor allele frequency >0.01), listed in the NHLBI GO Exome Sequencing Project database (<http://evs.gs.washington.edu/EVS/>) and the “1000 Genomes—A Deep Catalog of Human Genetic Variation” (<http://browser.1000genomes.org/>) were excluded from detailed analysis. Three rare or novel nonsynonymous variants (namely, p.R397Q in *KCNQ1*, p.R824G in *DSG2*, and p.V1604M in *SCN5A* [c.4810G>A, rs199473280]), and 1 common variant p.R773K in *DSG2* (rs2278792, MAF≈0.27) were identified in 4 patients with AC (Table). The novel and rare variants were analyzed by PolyPhen 2 (<http://genetics.bwh.harvard.edu/pph2/>), SNPs&GO (<http://snps-and-go.biocomp.unibo.it>), and MutPred (<http://mutpred.mutdb.org>) to predict their

pathogenicity.<sup>4</sup> The p.R824G variant in *DSG2* was predicted to be benign by all 3 programs, and the p.V1604M in *SCN5A* was either annotated as possibly damaging or with a modest pathogenicity index. Therefore, these variants were not analyzed further.<sup>4</sup> In contrast, the p.R397Q, which results from a c.1190 G>A transversion in the *KCNQ1* gene (Figure 1A), was predicted to be probably damaging or disease-related and therefore, was selected for further analysis. The p.R397Q variant resides at the C-terminal domain of KCNQ1 protein (Figure 1B) and affects a conserved amino acid across species (<http://www.ebi.ac.uk/Tools/msa/clustalo/>) (Figure 1C). The p.R397Q variant was absent in 200 unrelated control individuals with the same ethnic background as well as in the “1000 Genomes,” “EVS,” and “ExAC” databases. No other potentially pathogenic variant in any of the genes screened including those encoding the desmosome and sarcomere/cytoskeletal proteins were identified in the index patient with the p.R397Q variant. No family member was available for genetic analysis.

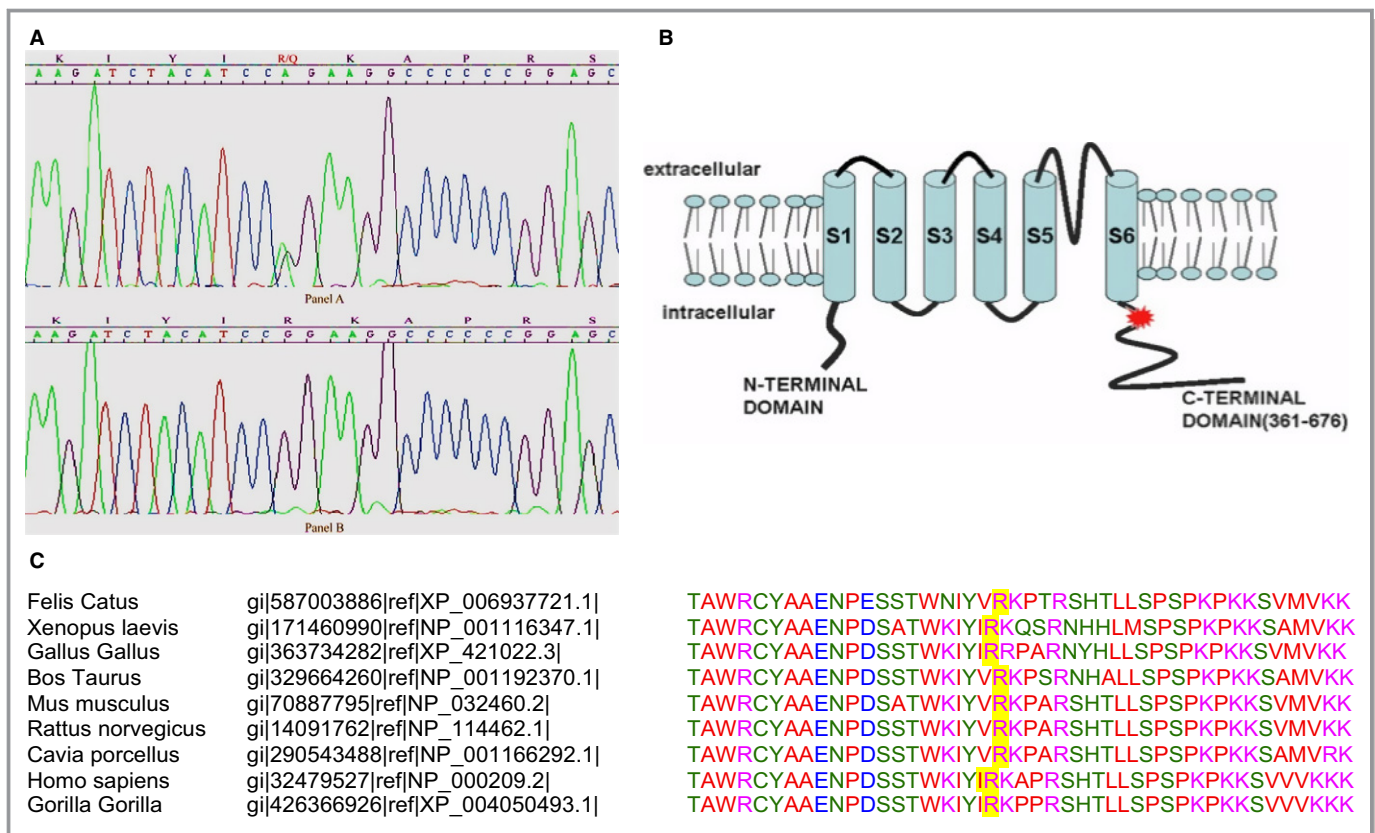
### Clinical Phenotype of the p.R397Q Carrier

The index case was a 60-year-old man, who initially presented with episodes of palpitation and was found to have recurrent VT with left bundle-branch block morphology on a 12-lead ECG (Figure 2A). He had frequent ventricular ectopies and runs of nonsustained VT on 24-hour Holter monitoring during the initial evaluation. He had no family history of sudden cardiac death, cardiac arrhythmias, or heart failure. None of his living family

**Table.** Clinical Characteristics of the Study Population and Nonsynonymous Genetic Variants in the Candidate Genes

ID	Age, y	Sex	ECG Abnormality	24-Holter: PVC/%	Echocardiographic Findings									Genetic Variants	
					ST (mm)	PWT (mm)	LVEDD (mm)	LVESD (mm)	RVEDD (mm)	LAD (mm)	RAD (mm)	LVEF (%)	Gene	Nonsyn SNVs	
1	60	M	RBBB	3219/4.2	11	9	66	49	24	41	40	45	<i>KCNQ1</i>	p.R397Q	
2	59	F	LBBB		9	9	68	58	18	37	34	31	<i>DSG2</i>	p.R773K	
3	65	M			10	8							<i>DSG2</i>	p.R824G	
4	53	F	LVH	170/02	10	9	57	48	20	28		33			
5	52	M			11	6	58	46	28	39		42			
6	77	M		391/0/0.4	11	8	75	67	22	39	44	22			
7	16	M	T-wave inversion		9	8	60	46	19	33	32	43			
8	29	F	Sinus Bradycardia	4264/5.3	7	8	53	40	25	29		41			
9	57	M	AF, RBBB	13838/10.9	11	9	73	62	20	53	49	33	<i>SCN5A</i>	p.V1604M	
10	19	M	Sinus tachycardia	671/0.5	7	11	72	63	23	51	34	26			

AF indicates atrial fibrillation; ECG, electrocardiogram; LAD, left atrial dimension; LBBB, left bundle-branch block; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVH, left ventricular hypertrophy; Nonsyn SNVs, nonsynonymous single nucleotide variants; PVC, premature ventricular complex; PWT, posterior wall thickness; RAD, right atrial dimension; RBBB, right bundle-branch block; RVD, right ventricular dimension; ST, septal thickness.



**Figure 1.** Detection of the p.R397Q variant in *KCNQ1* gene. A, Electrophoregram showing a heterozygous G>A transversion corresponding to change from amino acid arginine to glutamine at position 397. B, Schematic illustration of position of the p.R397Q variant in the *KCNQ1* protein. The red asterisk marks the position of the variant amino acid at the C-terminal domain. C, Sequence alignment of the mutation location across multiple species (using Clustal Omega). The p.R397Q (highlighted) affects a highly conserved amino acid.

members were available for clinical or genetic studies. His 12-lead ECG at the baseline showed sinus rhythm with severe intraventricular conduction defect with right bundle-branch block morphology, a QTc of 480 ms, and repolarization abnormalities (Figure 2B). An echocardiogram showed an enlarged left ventricle and a mildly depressed left ventricular ejection fraction of 45% (Table). He had no obstructive coronary lesion on coronary angiography. He underwent radiofrequency catheter ablation of VT and ICD implantation and was treated with a  $\beta$ -blocker. He has remained free of cardiac symptoms and has had no recurrence of VT for 3 years since his initial treatment and no clinical evidence of heart failure. Follow-up echocardiograms showed persistent left ventricular dilatation and systolic dysfunction with a left ventricular end-diastolic diameter of 62 mm and an left ventricular ejection fraction of 42% 3 years after radiofrequency ablation of VT (last follow-up).

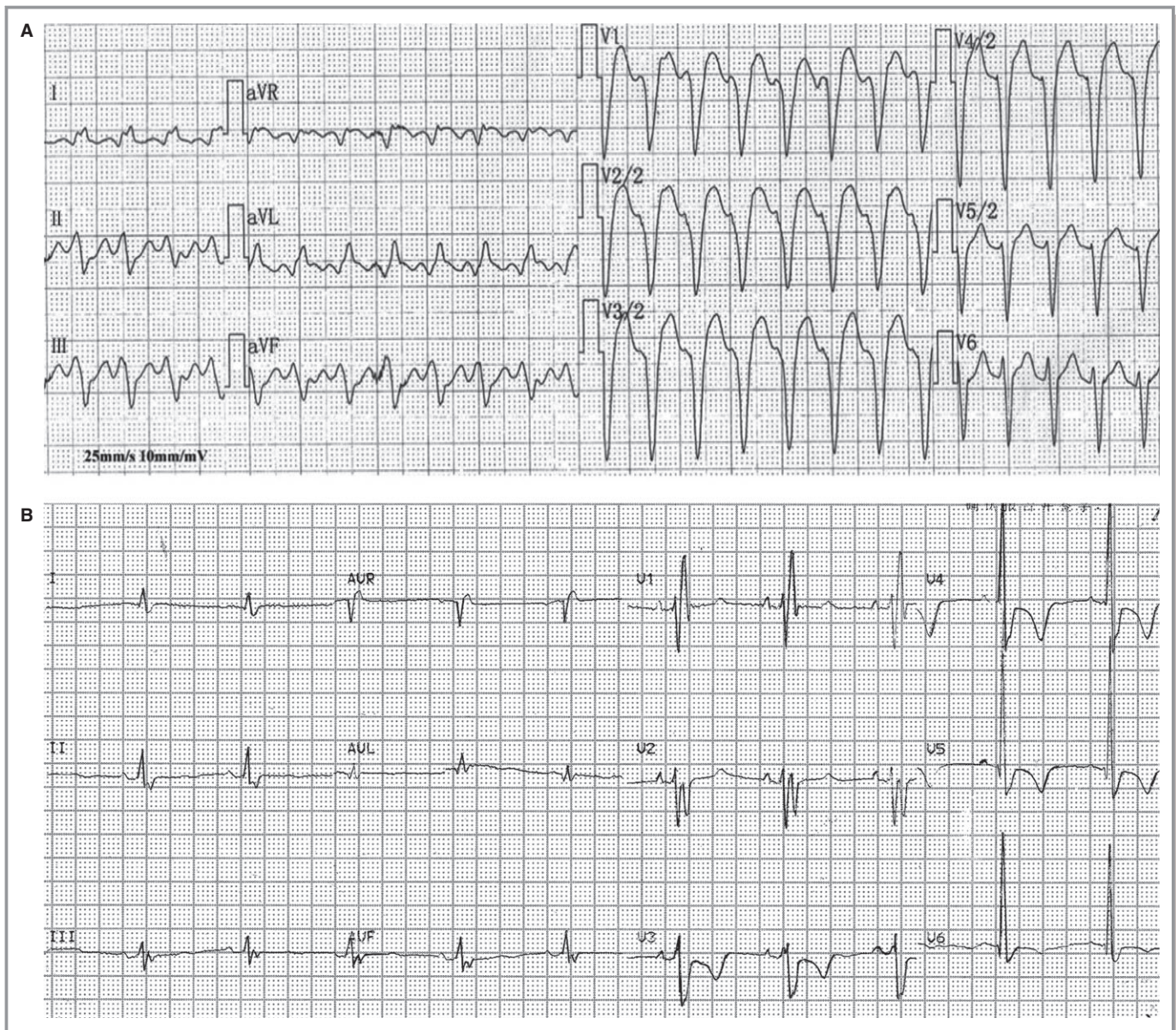
### Cellular Electrophysiology

*KCNQ1* is an essential component of a voltage-gated potassium channel involved in the slow repolarization phase of the action potentials (IKs) in cardiac myocytes. To

functionally characterize the p.R397Q variant, HEK293 cells were cotransfected with full-length WT or variant (p.R397Q) *KCNQ1* construct along with the full-length *KCNE1* clone. The transfected cells were identified by GFP expression, and currents were recorded by the patch-clamping technique. Expression of the mutant *KCNQ1* did not significantly change current density of activation and the current density at +70 mV (Figure 3). However, tail current density and peak tail current density at +70 mV were significantly reduced in GFP+ cells expressing the mutant protein (Figure 3).

### Membrane Trafficking

To examine whether the p.R397Q mutation affected trafficking and localization of *KCNQ1* to the cell membrane, HEK-293 cells transfected with either the WT or the mutant *KCNQ1* constructs. The transfected cells were analyzed by confocal fluorescence microscopy. As shown in Figure 4A, localization of the mutant *KCNQ1*-R397Q protein to cell membrane was reduced as compared with the *KCNQ1*-WT protein. Western blot analysis of cell protein fractions also showed reduced



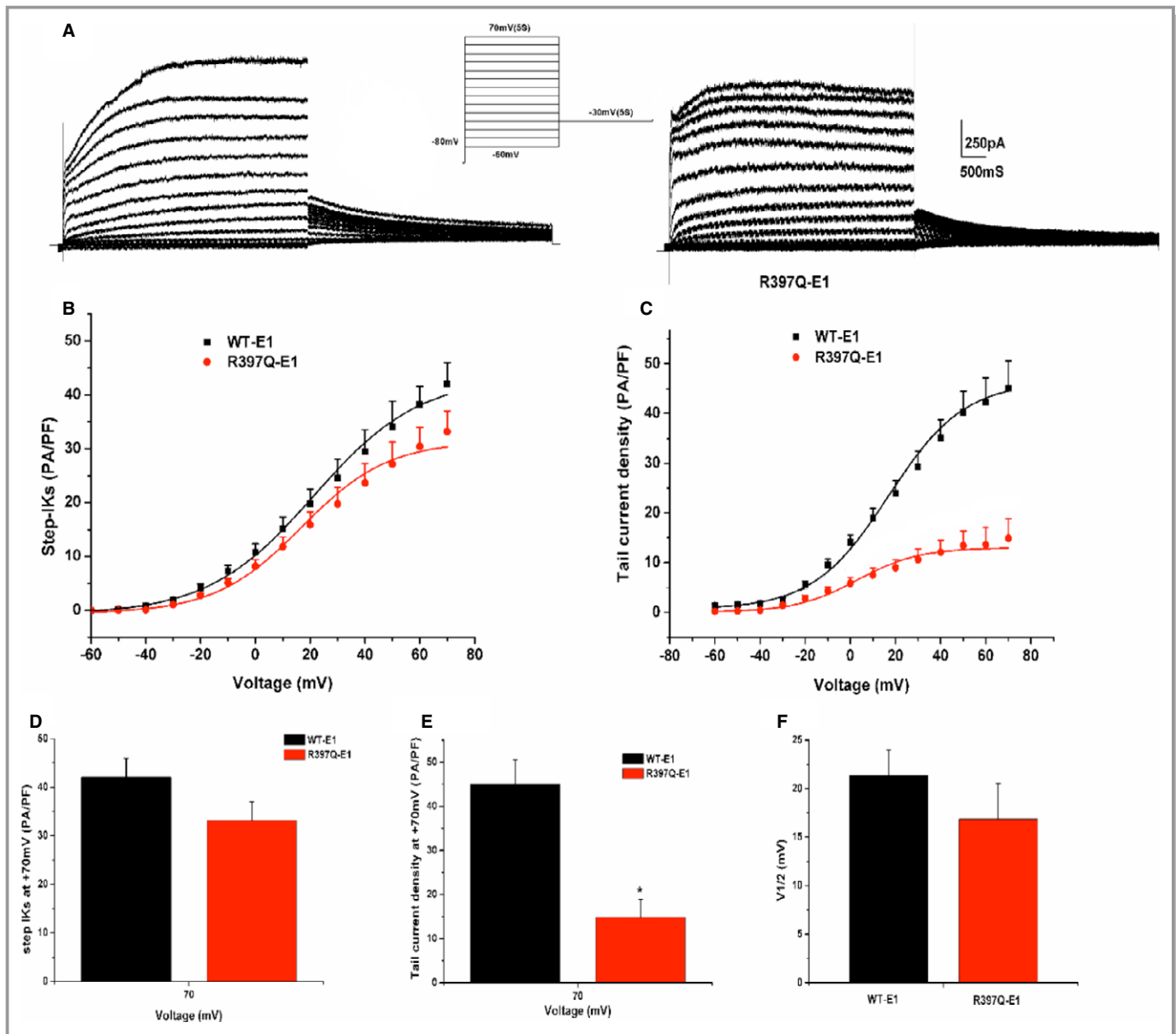
**Figure 2.** Twelve-lead electrocardiograms (ECG) of the index case with the p.R397Q mutation. A, Twelve-lead ECG of the index case during an episode of ventricular tachycardia at a heart rate of 167 bpm with left bundle-branch block morphology. Precordial leads V2, V3, V4, and V5 are shown in half voltage. B, Twelve-lead ECG of the index case at the baseline showing normal sinus rhythm at the rate of 65 bpm, indeterminate frontal QRS axis, intraventricular conduction delay with right bundle-branch block morphology and repolarization abnormalities.

levels of the mutant KCNQ1 protein in the membrane protein subfraction (Figure 4B and 4C).

## Discussion

Hereditary cardiomyopathies and arrhythmic syndromes are conventionally considered distinct groups of genetic disorders, commonly caused by mutations in genes encoding the structural/contractile proteins and ion channels, respectively.<sup>1,5</sup> There is, however, a considerable phenotypic overlap

between these 2 apparently distinct phenotypes. In accord with this notion, mutations in the *SCN5A* gene, which are classically responsible for the Brugada syndrome and conduction defects, are also associated with DCM, often in conjunction with atrioventricular block.<sup>6,7</sup> Likewise, mutations in *ABCC9*, which encode the SUR2A regulatory subunit of the cardiac K(ATP) channel, have been associated with DCM, Cantu syndrome, and cardiac arrhythmias.<sup>8–10</sup> The phenotype in the index patient with the p.R397Q mutation in the *KCNQ1* gene is consistent with a forme fruste of AC, as the primary

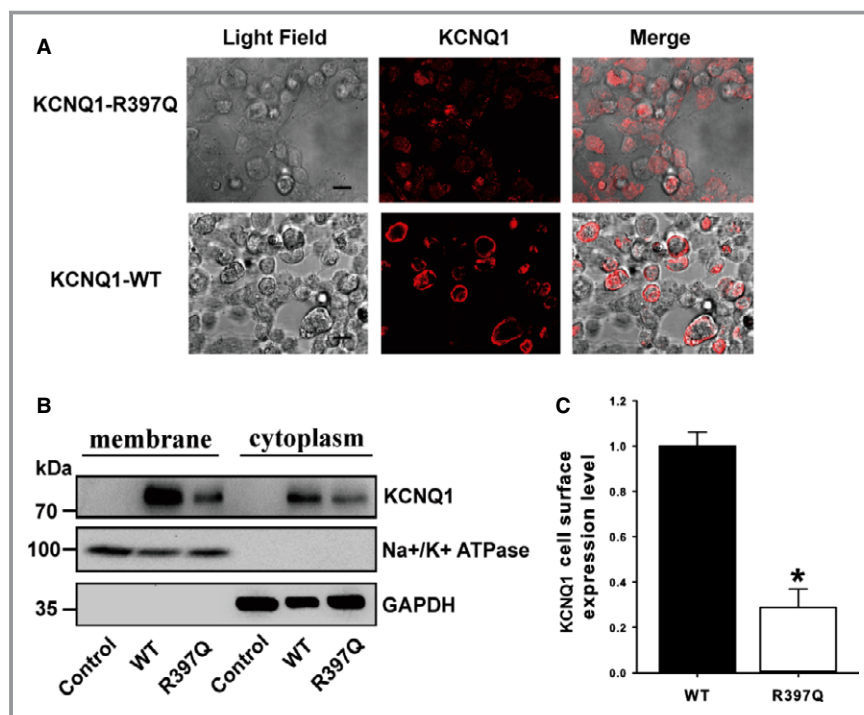


**Figure 3.** Cellular electrophysiological properties of variant channel. A, Representative traces of whole-cell I<sub>Ks</sub> (slowly activating delayed rectifier K<sup>+</sup> current) measured from HEK-293 Green Fluorescence Protein+ (GFP) (transfected) cells expressing either a wild-type (WT) or mutant KCNQ1 protein along with the WT KCNE1 protein (labeled as WT-E1 and R397Q-E1, respectively). B, The mean peak step I<sub>Ks</sub>-V relations are plotted for cells expressing either WT-E1 (n=26 cells) or the R397Q-E1 variant (n=20 cells), df=2, F=168, P<0.0001. C, Tail current densities are plotted as a function of test potentials and tail current–voltage relationships are shown for WT-E1 (N=26 cells) and R397Q-E1 (N=20 cells). D, Peak step current density (I<sub>Ks</sub>) recorded at the voltage of +70 mV (N=26 cells for WT-E1 and 20 cells for R397Q-E1). E, Peak tail current density recorded at the voltage of −30 mV (N=26 cells for WT-E1 and 20 cells for R397Q-E1). F, Half-maximum activation voltage (V<sub>1/2</sub>) of I<sub>Ks</sub> activation (N=26 cells for WT-E1 and 20 cells for R397Q-E1). \*P<0.01 vs WT-E1.

and initial manifestation was ventricular arrhythmias in the presence of mild cardiac systolic dysfunction and no clinical heart failure. Identification of a rare loss-of-function variant in the *KCNQ1* gene in the index case suggests broadening the spectrum of AC to encompass not only the classic arrhythmogenic right ventricular cardiomyopathy and left ventricular–dominant arrhythmogenic cardiomyopathy, but also a subset of cardiomyopathies, whose primary manifestation is ventric-

ular tachyarrhythmias occurring initially in the absence of a discernible left ventricular dysfunction or disproportionate to it.

While cellular electrophysiological findings in the index case are in accord with the known function of the I<sub>Ks</sub> channels and support the pathogenic role of the p.R397Q in arrhythmogenesis, the underlying mechanism of ventricular dilatation and dysfunction remains unclear. Alterations in



**Figure 4.** Membrane localization of variant KCNQ1. A, Confocal fluorescence microscopic picture of HEK-293 cells transfected with either *KCNQ1*-WT or *KCNQ1*-p.R397Q. Scale bar=20  $\mu$ m. B, Membrane and cytoplasm protein fractions isolated from HEK-293 cells transiently transfected with empty vectors (control), wild-type *KCNQ1* (WT), or mutant *KCNQ1* (R397Q).  $\text{Na}^+/\text{K}^+$  ATPase and GAPDH are used as positive controls for cell membrane and cytoplasmic protein fractions, respectively. C, Densitometric analysis of the relative levels of the WT and mutant KCNQ1 proteins in the cell membrane, as compared to  $\text{Na}^+/\text{K}^+$  ATPase protein levels. N=3 independent Western blots, \* $P$ <0.001 by  $t$  test and  $P$ <0.01 by nonparametric Mann–Whitney test.

expression and function of various cardiac myocytes ion channels in heart failure, including IKs, is well demonstrated.<sup>11</sup> However, the pathogenic role of such changes in regulating cardiac mechanical functions, beyond predisposition to cardiac arrhythmias and potentially left ventricular dysfunction resulting from incessant and recurrent arrhythmias, remains largely uncertain. Likewise, the molecular mechanism(s) by which mutations in *KCNQ1* might cause cardiac dysfunction remains to be determined but not implausible. KCNQ1 in conjunction with KCNE1 form the major repolarization channels in cardiac myocytes, which are responsible for the IKs in the heart. Functionally, IKs are regulated by a number of interacting proteins and post-translational modifications.<sup>12–16</sup> The IKs currents and the channel subunits KCNQ1 and KCNE1 proteins are regulated by the  $\beta$ -adrenergic-mediated protein kinase A–dependent phosphorylation, a process that might be pathogenic in heart failure.<sup>14,17–20</sup> Likewise, IKs are calcium-responsive currents, partly because of interaction of the KCNQ1 with calmodulin, which is a constitutive component of the  $\text{K}^+$  channels.<sup>16</sup> One might speculate that altered interactions of KCNQ1 and

calmodulin, in the presence of KCNQ1 mutations, could perturb intracellular calcium homeostasis and affect the contractile performance of cardiac myocytes. In conjunction with this notion, KCNQ1 is known to regulate muscle contractility, albeit in the vascular bed, but it is not known to regulate cardiac myocyte contractility.<sup>21</sup> Furthermore, intracellular ATP also regulates the IKs currents, and variants that are known to affect sensitivity of the IKs to ATP have been shown to be pathogenic.<sup>22</sup> Moreover, nonsynchronous regional ventricular contraction resulting from intraventricular conduction delay consequent to the KCNQ1 mutation might offer a mechanical explanation for cardiac dysfunction.<sup>23,24</sup> Finally, it is also possible that ventricular dilatation and dysfunction resulted from sustained and incessant ventricular arrhythmias (tachycardia-induced cardiomyopathy) and persisted for 3 years (the last follow-up) even after cessation of tachyarrhythmias upon ablation. Thus, despite a dearth of direct mechanistic data on the role of KCNQ1 in regulating myocardial structure and function, complex biological functions of the KCNQ1 in modulating the biology of myocytes offer plausible explanations for the putative mechanism(s).

The findings, while establishing the functionality of the p.R397Q variant, are not sufficient to establish a causal role in AC, particularly given the absence of the family data. In view of the presence of a large number of nonsynonymous variants in each genome, family data, by offering the opportunity to assess cosegregation of the candidate variant with inheritance of the phenotype, are essential in supporting the causality. None of the proband's family members had a history of sudden cardiac death, cardiac arrhythmias, or clinical heart failure. However, they were not available for phenotypic characterization and genetic analysis. We screened over a dozen known genes responsible for hereditary cardiomyopathies and arrhythmic syndromes, and no other potentially pathogenic variant was identified in the index case. Nevertheless, the known genes account for approximately two thirds of the cases of hereditary cardiomyopathies and arrhythmias. Therefore, the possibility of a concomitant presence of another pathogenic variant(s) that contributes to cardiac dilatation, dysfunction, and even arrhythmias in the index case cannot be excluded. Nevertheless, the complex genetic etiology of hereditary disorders and presence of multiple pathogenic variants is becoming increasingly recognized. Given the relative abundance of putatively functional variants in each genome, the clinical phenotype likely results from interactions of multiple variants, exerting a gradient of effect sizes.<sup>2,25–27</sup> The p.R397Q, which is a rare functional variant with a relatively large functional effect size, in conjunction with yet-to-be identified functional variant(s), might be responsible for the clinical phenotype of AC in the index case.

Loss-of-function mutations in the *KCNQ1* gene are known to cause long QT syndrome type 1, whereas gain-of-function mutation causes sinus bradycardia, familial atrial fibrillation, short QT syndrome, and sudden infant death syndrome.<sup>28–32</sup> A 12-lead ECG in the index case with the p.R397Q mutation in the *KCNQ1* gene showed a QTc interval of 480 ms in the presence of severe intraventricular conduction defect. The clinical phenotype, which is distinct from the classic long QT syndrome type 1, is consistent with the loss-of-function effect of the p.R397Q variant on trafficking of the KCNQ1 protein to the membrane and decreased IKs tail current density. The p.R397Q variant is located in the C-terminal domain of the  $\alpha$  subunit of functional KCNQ1 channel complex, which is considered an interacting domain necessary for the assembly of the channels at the membrane.<sup>33</sup>

Phenotypic spectrum of the *KCNQ1* mutations seems to expand beyond the conventional arrhythmic syndromes, such as the long QT1 syndrome, and atrial fibrillation.<sup>34</sup> Recent reports have also implicated *KCNQ1* variants in myocardial pathology, including left ventricular noncompaction syndrome, cardiac hypertrophy, and myocardial fibrosis.<sup>35–37</sup> Notably, the p.R378Q variant in the *KCNQ1* gene was identified in a

21-year-old female victim of sudden cardiac death who on cardiac autopsy exhibited myocytes hypertrophy, disarray, fibrosis, and fatty replacement, a phenotype reminiscent of AC.<sup>35</sup> Nevertheless, the data are scant and insufficient to consider *KCNQ1* as a causal gene for hereditary cardiomyopathies.

In conclusion, the findings of the present study advocate for the broader phenotypic spectrum of AC encompassing cardiomyopathies whose cardinal clinical manifestation is ventricular arrhythmia occurring disproportionate to the underlying ventricular dysfunction, and implicate *KCNQ1* as a possible genetic etiology.

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## Disclosures

None.

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