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A Mutation in the S3 Segment of KCNQ1 Results in Familial Lone Atrial Fibrillation

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Abstract

Background—Mutations in several ion channel genes have been reported to cause rare cases of familial atrial fibrillation (AF).

Objective—We sought to determine the genetic basis for AF in a family with autosomal dominant AF.

Methods and Results—Family members were evaluated by 12-lead ECG, echocardiogram, signal averaged P wave analysis, and laboratory studies. Fourteen family members in AF-324 were studied. Six individuals had AF with a mean age at onset of 32 years (range 16–59). Compared to unaffected family members, those with AF had a longer mean QRS duration (100 vs. 86 ms ($p=0.015$), but no difference in the corrected QT interval (423 ± 15 ms vs. 421 ± 21 ms). The known loci for AF and other cardiovascular diseases were evaluated; evidence of linkage was obtained with marker D11S4088 located within KCNQ1, and a highly conserved serine in the third transmembrane region was found to be mutated to a proline (S209P). Compared to the wild type channel, the S209P mutant activates more rapidly, deactivates more slowly, and has a hyperpolarizing shift in the voltage activation curve. A fraction of the mutant channels are constitutively open at all voltages resulting in a net increase in the I_{Ks} current.

Conclusion—We have identified a family with lone AF due to a mutation in the highly conserved S3 domain of KCNQ1, a region of the channel not previously implicated in the pathogenesis of AF.

Keywords

Atrial fibrillation; genetics; mutation

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The authors declare that they have no competing interests.

Background

Atrial fibrillation (AF) is the most common sustained arrhythmia affecting over 2 million Americans¹ and is characterized by chaotic electrical activity in the atria. It is associated with an increased risk of heart failure, stroke, and death². Known risk factors for the arrhythmia are extensive and include age, sex, hypertension, valve disease, and heart failure². A family history of AF has been associated with an increased risk of AF in the general population³, but is more likely in younger individuals with AF in the absence of other known cardiac or medical conditions, so called lone AF^{3, 4}.

Multiple genetic loci have been described in families with Mendelian forms of AF though all the responsible genes have not been identified^{5–8}. A recent genome wide association study identified a locus on Chromosome 4q25 strongly associated with the risk of AF⁹. In addition, mutations in a number of ion channels have been described including potassium channels, gap junction proteins and the cardiac sodium channel¹⁰.

The I_{Ks} current is a major contributor to cardiac action potential repolarization and is composed of a tetramer of alpha or pore forming subunits, KCNQ1, with associated beta subunits of the KCNE family that modify channel function. Given its important role in repolarization, loss of function of this channel would be expected to prolong the action potential duration and QT interval. Indeed, loss of function mutations in these proteins cause long QT syndromes types 1 and 5 respectively. Conversely, a gain-of-function mutation in I_{Ks} that may be hypothesized to shorten action potential duration would be expected to result in shortening of the QT interval in the ventricle and possibly AF in the atria. Interestingly, a familial form of AF has been attributed to a serine to glycine substitution at amino acid 140 (S140G) in KCNQ1 that results in a gain of function in the I_{Ks} current. However, a number of affected family members paradoxically exhibited a prolonged long QT interval¹¹. Subsequently, other cases of AF also have been attributed to possible gain of function mutations in KCNQ1^{12–14}, but such mutations appear to be a rare cause of the arrhythmia.

In the current study, we describe the identification and characterization of a family with lone AF due to a novel mutation in a region of the KCNQ1 potassium channel not previously implicated in AF.

Methods

Clinical evaluation

All studies were performed with Institutional Review Board approval at Massachusetts General Hospital. Prior to any study procedures, written informed consent was obtained from the study patient. Each patient underwent a physical examination, standardized interview, 12-lead electrocardiogram, echocardiogram, and laboratory studies including a TSH. Patients in sinus rhythm had a signal-averaged electrocardiogram of the P wave (PHiRes, GE, Inc.). Three individuals with a noise level exceeding 1.0 μ V on the signal averaged electrocardiogram were excluded from further analysis (Subjects III-5, III-7 and III-8).

We defined affected individuals as those with electrocardiographically documented AF. We defined as unaffected only those individuals greater than 40 years of age, with no personal history of AF, and no offspring with a history of AF. All other family members were classified as unknown for the purpose of the genetic analyses.

Genetic Analysis

A blood sample (16 ml.) was obtained in acid citrate dextrose from every patient and DNA was isolated using the Puregene DNA Purification Kit (Gentra Systems, Inc., Minneapolis, Minnesota). Genetic analyses were performed on all available individuals, regardless of affection status. Polymorphic genomic short tandem repeat markers were used for mapping and amplified by PCR using standard conditions. Genotypes were ascertained without knowledge of clinical status. Oligonucleotide primers for the coding region of KCNQ1 were designed using the known cDNA and genomic sequence. PCR was performed using standard conditions, amplicons were purified, and DNA was sequenced using the ABI PRISM dye terminator method (Model 3730XL, Applied Biosystems, Foster City, California).

Statistical analyses

Two point and multipoint logarithm of the odds (LOD) scores were calculated assuming a disease penetrance of 0.95. Allele frequencies were estimated from the population. Two point LOD scores were calculated with the MLINK program. Continuous variables were tested for normality of distribution and two-sided t-tests were used for comparisons of means. P values of 0.05 or less were considered significant. All statistical analyses were performed using STATA version 10.0 (StataCorp LP, College Station, Texas).

Mutagenesis, Cloning, and Cell culture

Mammalian expression vectors pCI-KCNQ1 and pCI-KCNQ1-EGFP were obtained courtesy of Y.H. Chen¹¹ and M. Horie¹⁵, respectively (KCNQ1 reference sequence AF000571). Mutations in KCNQ1 were introduced into the wildtype KCNQ1 constructs using site directed mutagenesis (QuikChange kit, Stratagene, La Jolla, California) and the following primers: S209P Forward: CATCGTGGTCGTGGCCCCCATGGTGGTCCTCTG, S209P Reverse: CAGAGGACCACCATGGGGGCCACGACCACGATG, S209F Forward: CGTGGTCGTGGCCTTCATGGTGGTCCTCTGC, S209F Reverse: GCAGAGGACCACCATGAAGGCCACGACCACG. After introduction of the mutation, the coding region was sequenced to exclude the introduction of additional variants.

The coding region of KCNE1 (NM 000219) was amplified from human right ventricle cDNA (BD Clontech, Mountain View, California) by PCR reaction with primers: 5' hKCNE1: TGAGCCGAGGATCCATTGGAGGAAGG, 3' hKCNE1: GATCGCGGCCGCGGATGTGTCCAGTTTATGCCAGTGGTGG. The 5' BamHI and 3' Not I fragment was ligated into pXOOM and pcDNA3 mammalian expression vectors¹⁶ for expression under a CMV promoter.

Electrophysiology

COS-7 cells were transfected with 4 µg of KCNQ1-WT, S209P or S209F and 1 µg of pXOOM-KCNE1 using SuperFect transfection reagent (Qiagen Inc. Valencia, California). GFP positive cells were identified for electrophysiologic recording 2–3 days after transfections. Signals were amplified using an Axon 200B amplifier (Molecular Devices, Inc., Sunnyvale, CA), digitized with a Digidata 1322A A/D converter (Molecular Devices, Inc., Sunnyvale, CA) and analyzed with Clampex 9.2, Clampfit 9.2 (Molecular Devices, Inc., Sunnyvale, CA) or SigmaPlot 9.0 (Systat Software Inc., Point Richmond, CA). Specific recording protocols are provided as an inset in each figure. All experiments were performed at room temperature. Solutions used were as follows: extracellular solution 145 mM sodium gluconate, 4 mM potassium gluconate, 7 mM calcium gluconate, 4 mM magnesium gluconate, 5 mM HEPES, 5 mM glucose, 20 mM mannitol pH 7.4; intracellular solution was

145 mM potassium gluconate, 5 mM HEPES, 2 mM EGTA, 2 mM magnesium gluconate, pH 7.2.

The proportion of current due to constitutive, voltage independent current was calculated by taking the ratio of the instantaneously appearing current after a depolarization from a holding potential of -80mV to $+80\text{mV}$ to the maximal current achieved at the end of the depolarization.

Immunocytochemistry

COS-7 cells grown on 18 mm coverslips were transfected with 2 μg of KCNQ1–GFP or S209P–GFP with or without pcDNA3–KCNE1. Thirty six hours after transfection, the cells were rinsed with PBS, fixed in 4% cold paraformaldehyde and counterstained with DAPI. Coverslips were mounted onto glass slides and visualized using confocal microscopy using the Zeiss LSM system (Carl Zeiss MicroImaging, Inc. Thornwood, New York). Images were acquired digitally at the same gain and magnification for each condition. Cells were scored for membrane staining versus intracellular staining in 3 separate views for each transfected construct in a blinded fashion.

Results

Clinical characteristics

A total of fourteen family members from three generations were evaluated (Figure 1A, Table 1). The matriarch of the family (I-2) developed AF as a young adult and died of an embolic stroke at age 79. Six of her descendants developed AF at a mean age of 29.5 ± 16.6 years (range 16 to 59 years, Table 1). After obtaining blood samples from all willing family members, we evaluated the known genetic loci for AF as well as other heritable cardiovascular conditions in which AF has been reported including; dilated cardiomyopathy, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and long QT syndrome were evaluated. Evidence of linkage was obtained with marker D11S4088 located within the KCNQ1 gene (LOD 2.92, $\theta=0$).

Sequencing of KCNQ1 in affected family members revealed a cytosine to threonine substitution at position 625 that resulted in a change from a serine to a proline at position 209 in the final protein (S209P, Figure 1B). This variant was not present in over 1000 control chromosomes and has not previously been reported in the literature. The penetrance of this mutation was incomplete as individual II-7 is an obligate carrier, carries the S209P mutation, has an affected child (III-13), yet is unaffected with AF both by history and by longitudinal electrocardiographic monitoring. Serine 209 is located in S3b or the C-terminal half of the third transmembrane region of the channel protein (Figure 1D) and is highly conserved across phyla as far as *Drosophila* (Figure 1C).

Carriers of the S209P mutation had a longer QRS duration (100 ± 10.2 ms vs. 86 ± 7.3 ms, $p=0.015$, Figure 2) compared to non-carriers, although there was no difference in the PR interval (179 ± 15 ms vs. 164 ± 25 ms) or corrected QT interval (423 ± 15 ms vs. 421 ± 21 ms). Signal averaged electrocardiography revealed no difference in the P wave duration (143 ± 20 ms vs. 144 ± 58 ms) or the integral of the P wave (551 ± 144 ms vs. 578 ± 111 ms) between carriers and non-carriers. Echocardiograms were notable for a larger left ventricular end diastolic internal diameter (50 ± 4.8 mm vs. 45 ± 3.3 mm, $p = 0.04$) and a trend towards a large left atrial dimension (38 ± 3.7 mm vs. 33 ± 4.7 mm, $p = 0.06$) in carriers of the S209P genotype.

Electrophysiology

Whole cell voltage clamp recordings of COS-7 cells transiently transfected with wild-type and mutant channels are illustrated in Figure 3. As has been previously reported, KCNQ1 exhibits both voltage-dependent activation and inactivation at positive membrane potentials (Figure 3B). The co-expression of KCNQ1 with KCNE1 results in a channel with slower activation kinetics with a sigmoidal appearance, as well as slower deactivation kinetics (Figure 3B versus 3D and Table 2).^{17, 18} Comparison of voltage activation curves shows a significant shift in the voltage dependence of activation of KCNQ1 toward depolarized potentials upon the association with KCNE1, consistent with previous reports ($V_{1/2} = 1.61 \pm 1.9$ mV for WT KCNQ1, $V_{1/2} = 34.5 \pm 3.1$ mV for KCNQ1–KCNE1, Figure 4A and B).

Comparison of Figures 3A and 3B demonstrate the effect of the S209P mutation on KCNQ1 function. The mutation significantly slows KCNQ1 deactivation ($\tau_{\text{deact}} 148 \pm 27.3$ ms for KCNQ1 vs 401 ± 70.0 ms for S209P–KCNQ1 at -120 mV, $p=0.00018$), but does not have an appreciable effect on channel selectivity, activation kinetics or the voltage of half-maximal activation (see Table 2). Co-expression of S209P–KCNQ1 with KCNE1 yields a channel with distinctive characteristics. Whereas the wild-type channel activates with slow sigmoidal activation kinetics (Figure 3D), S209P–KCNQ1+KCNE1 shows a more rapid activation (Figure 3C). The kinetics of deactivation were also altered by the mutation with S209P–KCNQ1+KCNE1 channels closing more slowly (Table 2 and figure 5 D).

The voltage activation curve for the mutant channel is shifted leftward, resulting in a $V_{1/2}$ that is more negative for S209P–KCNQ1+KCNE1 than that for the wild-type channels ($V_{1/2} -7.9 \pm 4.4$ mV for S209P–KCNQ1+KCNE1 and 34.5 ± 3.1 mV for WT KCNQ1+KCNE1), suggesting that at any given membrane potential there will be more mutant channels open, resulting in more I_{Ks} current. However, the selectivity of the channels is not significantly altered ($E_{\text{rev}} -63.5 \pm 11.8$ mV for WT KCNQ1+KCNE1 and -73.5 ± 17.5 mV for S209P–KCNQ1+KCNE1, $p=0.41$).

Examination of the S209P mutant channel recordings also showed that a proportion of these channels appear to be constitutively open at all voltages. As seen in Figure 3A and Figure 3C, after the initial depolarization, the current is seen to activate instantaneously after patching onto a cell, and there is a residual current even after repolarization to -120 mV. These data suggest a voltage-independent constitutively open population of channels. This is in addition to the aforementioned increase in the voltage sensitivity of the mutant channels due to the leftward shift in the voltage-activation curve. However, on closer examination of these currents, we noted that the kinetics of deactivation of the mutated channels was significantly slowed ($t_{1/2}$ for deactivation 2,280 ms vs. 403 ms at -120 mV for wild type KCNQ1–KCNE1 channels). When we subjected these channels to a series of prolonged depolarizations at -80 mV, we found that a substantial fraction of the channels would eventually deactivate if given a sufficiently long time (Figure 5A). Figure 5B is a plot of the instantaneously appearing current upon depolarization to 80 mV, after prolonged inter-pulse holding potentials at -80 mV. The time course of decay of the instantaneously appearing current appears to follow similar kinetics to the channel's deactivation (τ for the loss of instantaneously appearing current 3.01 s). Thus, the effect of the S209P mutation appears to cause the channel to deactivate with markedly slowed kinetics (see also Figure 5D). It is important to note that during our recording conditions, in the majority of cells we noted a significant fraction of open channels immediately upon breaking into the cells.

The kinetics of activation and deactivation of the wild-type KCNQ1+KCNE1 channels are relatively slow compared to the frequency of membrane depolarization and repolarization in the human heart. The slow deactivation of these channels would be anticipated to result in a significant proportion of channels remaining open in diastole. This effect is amplified at

higher pacing rates, as more channels remain open, thereby resulting in more diastolic current¹⁹. Figure 5C compares the current seen with wild-type and S209P KCNQ1–KCNE1 channels as a function of pacing frequency. The wild-type channels have a significant increase in conducted current as the pacing rate increases, reflecting their deactivation kinetics. In contrast, due to the extremely slow deactivation kinetics and the more rapid activation of the mutant channel, a large number of these channels appear to be constitutively open even at lower pacing rates, thereby resulting in nearly maximal current even at these lower pacing rates.

In view of the autosomal dominant transmission in the family, we also examined the characteristics of channels consisting of heteromers of S209P and wild-type channels. Whole cell currents from COS-7 cells transfected with an equimolar ratio of KCNQ1 and S209P–KCNQ1 along with KCNE1 are shown in Figure 3F. The tracing qualitatively resembles the wild-type KCNQ1–KCNE1 complex. We did consistently observe a small but measurable instantaneous step up in the current with depolarization (see 3I, the magnification of the area of 3F in the dotted box) under the same recording conditions that produced no such current from wild-type channels and a significant instantaneously appearing current with S209–P KCNE1 channels. We also observed that tail currents at –120 mV do not return to zero current (see currents below the dotted line in 3F), reflecting a population of channels that remain open even at these voltages. This effect may be due to the fact that even at an equimolar expression, approximately one in sixteen potassium channel tetramers would be expected to be S209P tetramers. The fraction of constitutive current that we observed with this channel (0.10 ± 0.04) is greater than one sixteenth (0.0625) but is within experimental error. The voltage sensitivity of these channels is significantly shifted towards negative potentials (3.34 ± 6.6 mV vs 34.5 ± 3.1 mV). Activation kinetics of the channel are slightly faster than wild type, while selectivity is unchanged. (Table 2). These results suggest that relatively subtle changes in channel properties may be sufficient to predispose S209P mutation carriers to atrial fibrillation.

Trafficking of wild type and mutant KCNQ1

Several investigators have identified mutations in patients with Long QT syndrome that are associated with abnormal trafficking of the KCNQ1 protein. We therefore used a GFP-tagged S209P–KCNQ1 construct and observed that the mutant protein still traffics normally to the plasma-membrane (Figure 6A, 6B), in the presence or absence of KCNE1 (Figure 6C, 6D and 6E).

Discussion

We have identified a family with lone AF due to a mutation in KCNQ1. Affected family members exhibit early onset of AF, a normal corrected QT interval, and mild left ventricular dilatation. AF in this family was linked to the KCNQ1 gene and found to be due to a mutation of a highly conserved residue in the third transmembrane domain of the channel. Expression of the mutant channel in a heterologous system demonstrated rapidly activating channels and slowed deactivation as well a shift in the sensitivity to voltage activation to more hyperpolarized potentials. The net effect of these changes is to cause a gain of function in the I_{Ks} current, with an increased outward flux of potassium ions at all heart rates.

Several mutations in the KCNQ1 gene have been identified in familial AF, yet screening of large series of probands demonstrates that mutations in this gene and in other potassium channels are rare¹⁰. An important feature of KCNQ1 mutations seen in families with AF appears to be the unexpected effects on ventricular repolarization. Two kindreds with AF and KCNQ1 mutations have been reported to have prolonged QT intervals, while other families with AF and mutations in the gene exhibit short QT or normal QT intervals¹⁴. It

remains unclear why the mutations associated with AF result in such variable effects on ventricular repolarization, but interactions with different partner proteins in atrium and ventricle may be relevant, as may be the trophic effects of these mutations in each chamber. Of note, the affected family members in this report had a normal QT interval, but a prolonged ventricular depolarization as manifest by an increased QRS duration.

In an elegant recent study, Restier, Cheng, and Sanguinetti, have delineated the mechanism by which two previously described variants in KCNQ1, S140G and V141M lead to AF²⁰. Using a series of mutations at these residues, they demonstrated a marked slowing in channel deactivation, and identified a charge-pair interaction between the mutations associated with AF and residues in the S2 (E160) and S4 (E237) segments of the channel. The Serine 209 mutation we have described is similar in many respects to these S1 mutations, yet is located in the S3b domain which is thought to form part of a “voltage-sensor paddle”²¹. Whether the mutation we have identified alters function of the voltage sensor or interactions with KCNE1 remains unclear. Ultimately crystallization of the channel will greatly aid our understanding of the relation between these mutations and channel function.

In conclusion, we have identified a family with lone AF due to a mutation in the S3b or voltage sensor paddle region of KCNQ1. This work further extends our understanding of the relationship between KCNQ1 and atrial arrhythmogenesis.

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Abbreviations

AF atrial fibrillation

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Figure 1. Family AF-324

A) Pedigree of family AF-324. Unaffected individuals are depicted in white, affected individuals in black and obligate carriers in grey. B) Electrophoretograms from a control subject (WT) and an affected family member (III-2) illustrating the S209P mutation. C) Serine 209 is well conserved across many species. Variations from the human sequence are illustrated in bold. Alignments were performed with the following sequences: human (NP000209), mouse (AAP93874), dog (XP540790), chick (XP421022), zebrafish (XP685670) and fruit fly (AAN71343). D) Topology of the KCNQ1 channel. There are six transmembrane regions, the fourth of which is positively charged and acts as the voltage sensor. The pore lining region lies between the fifth and sixth transmembrane regions. The location of the S209P mutation is indicated within the S3b region.

Figure 2. Representative leads from an electrocardiogram of a family member (III-13) with paroxysmal, lone atrial fibrillation and an unaffected sibling (III-12). The electrocardiogram of subject III-13 was notable for intraventricular conduction delay (lead V1) and bifid P waves (lead I).

Figure 3. The effect of the S209P mutation of KCNQ1 whole cell currents

Whole cell currents recorded from COS cells transiently transfected with S209P-KCNQ1 (A) or wild-type KCNQ1 (B). Co-expression of S209P-KCNQ1 (C) or KCNQ1 (D) with KCNE1. Note the markedly different current characteristics in the mutant channels with the presence of a large voltage independent current, as reflected by a large instantaneous rise in whole cell current with depolarization. Whole cell currents recorded with a 1:1 mixture of KCNQ1:S140PKCNQ1 with KCNE1 (E). Panels F and G are the insets of panels D and E respectively. Note the small instantaneous current step with depolarization in the KCNQ1+S140P-KCNQ1+KCNE1 (G) compared to the wild type KCNQ1+KCNE1 (F). The X axis of each scale bar represents 1 second. The recording protocol is illustrated in the upper right of the figure. The holding potential was -80 mV with test potentials ranging from -90 mV to $+120$ mV, followed by hyperpolarization to -120 mV. For clarity, every other test potential is depicted.

Figure 4. Biophysical characteristics of mutant and wild-type channels

A) Normalized tail currents for KCNQ1+KCNE1, S209P-KCNQ1+KCNE1, and S209P-KCNQ1+KCNE1. Voltages of half maximal activation are indicated in Table 2.
 B) Tail currents for KCNQ1 and S209P-KCNQ1.

Figure 5.

A) Response of S209P-KCNQ1+KCNE1 channels to depolarizations at various intervals. COS cells transfected with S209P-KCNQ1+KCNE1 were subjected to 1 second depolarizations to 80 mV with holding potentials of -80mV at the indicated durations. Figure shows one representative trace.

B) The number of channels remaining open after holding potentials of different durations at -80mV. The height of the instantaneous step-up in current with depolarization at the end of the holding potential duration indicated on the X-axis was measured. Results were normalized to the maximal current obtained with a prolonged depolarization to 80mV for n=6 cells.

C) Cells transfected with KCNQ1+KCNE1 or S209P-KCNQ1+KCNE1 were subjected to a 100 depolarizing pulses to +60mV at the indicated frequency. The amplitude of the current during the final depolarizing pulse was normalized to the maximal value for each channel. The effect of the voltage independent current carried by S209P-KCNQ1 channels is most marked at low stimulation frequencies.

D) Deactivation kinetics of KCNQ1-KCNE1 and S209P KCNQ1-KCNE1 channels. The current traces shown are insets from the traces shown in figure 3, and show deactivation at -120mV. Kinetics for S209P KCNQ1-KCNE1 channels are significantly slower than wild-type channels.

Figure 6. Trafficking of S209P-KCNQ1 mutation for AF

Confocal images of the KCNQ1 (A) and S209P (B) constructs in COS-7 cells. Membrane staining is noted. When the KCNQ1 (C) or S209P (D) constructs are co-expressed with KCNE1, there is again no difference in membrane staining between the wild-type and mutant constructs. The degree of membrane staining for each transfection is quantified in a blinded fashion as described in the methods section (E).

Table 1

Clinical characteristics of Family AF-324.

ID	AF	Current age or age of death	Onset of AF (yrs)	Type of AF	PR (ms)	QRS (ms)	QT (ms)	EF (%)	LA (mm)	LVID (mm)	Total P wave duration (ms)	Integral of P wave	S209P mutation
II-2	Y	71	16	Permanent	-	-	-	-	-	-	-	-	NA
II-5	Y	68	59	Paroxysmal	180	98	417	77	33	45	149	596	+
II-7	N	63	-	-	184	112	407	67	40	44	126	630	+
III-2	Y	50	17	Permanent	-	84	440	60	40	54	-	-	+
III-3	N	48	-	-	184	82	448	63	34	48	230	690	-
III-4	Y	47	39	Permanent	-	94	426	75	43	54	-	-	+
III-5	N	50	-	-	168	82	412	70	29	44	-	-	-
III-6	N	49	-	-	132	82	409	-	-	-	108	432	-
III-7	N	48	-	-	160	92	437	79	35	47	-	-	-
III-8	N	46	-	-	146	76	403	76	30	41	-	-	-
III-10	N	44	-	-	206	92	395	60	41	48	126	630	-
III-11	Y	43	25	Paroxysmal	194	104	411	74	35	55	168	336	+
III-12	N	33	-	-	156	96	445	56	29	41	112	560	-
III-13	Y	31	21	Paroxysmal	158	108	442	61	38	50	128	640	+

Abbreviations: EF, ejection fraction; LVID, left ventricular internal dimension, NA; not available.

Table 2

Electrophysiological properties of wild-type or mutant S209P-KCNQ1 channels.

Construct	E_{rev} (mV)	$t_{1/2}$ (activation, ms)	τ (deactivation, ms)	$V_{1/2}$ (mV)
KCNQ1	-72.7 ± 4.92	0.048 ± 0.008	148 ± 27	1.61 ± 1.9
S209P-KCNQ1	-72.4 ± 2.32	0.077 ± 0.011	401 ± 70	-1.78 ± 5.2
KCNQ1 + KCNE1	-63.5 ± 11.8	1.51 ± 0.065	403 ± 32	34.5 ± 3.1
S209P-KCNQ1 + KCNE1	-73.5 ± 17.5	0.47 ± 0.029	2280 ± 338	-7.9 ± 4.4