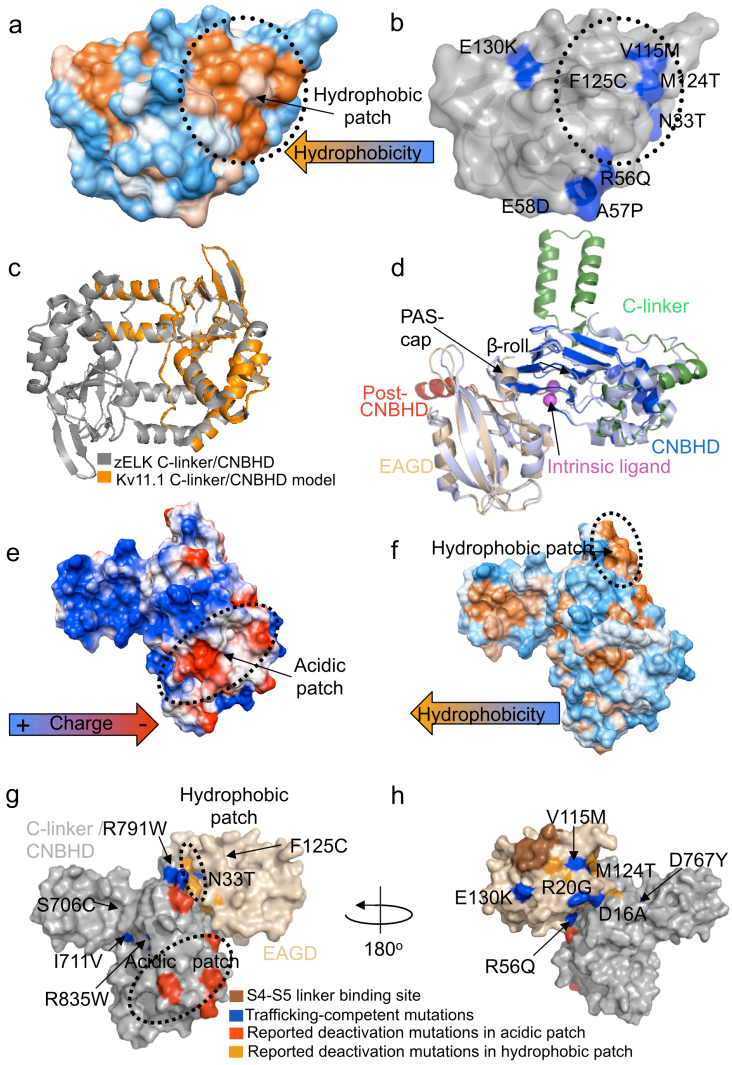
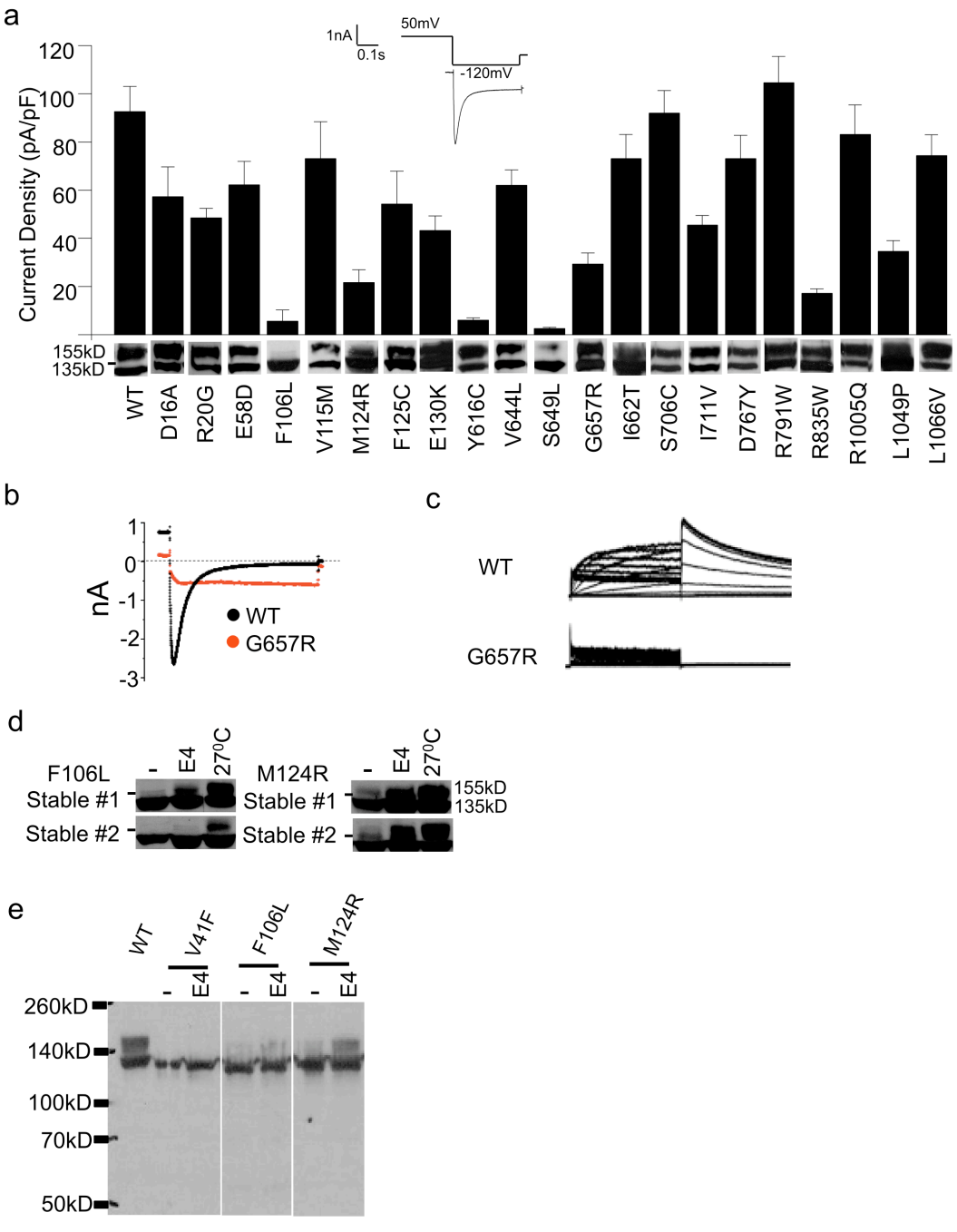
Supplementary Figures and Tables



Supplementary Figure 1. Properties of C-linker/CNBHD mutations. (a) Hydrophobic surface representation of the Kv11.1 PASD (PDB: 1BYW) rendered in UCSF Chimera. Residue colors range from blue (low hydrophobicity) to orange (high hydrophobicity). The hydrophobic patch important for deactivation is circled. (b) PASD (PDB: 1BYW) shown in the same orientation as (a) with trafficking-competent mutations highlighted in blue except for F125C, which is buried. (c) Our Kv11.1 C-linker/CNBHD model monomer (orange) aligned with the zELK crystal structure dimer (PDB: 3UKN) (gray). (d) Representation of the Kv11.1 EAGD (PDB: 4HP9) complexed with our Kv11.1 C-linker/ CNBHD model aligned to the EAGD-CNBHD complex from mouse (PDB: 4LLO). The Kv11.1 model is colored wheat (EAGD), green (C-linker), and blue (CNBHD), compared to mouse complex (PDB: 4LLO) in light blue. The intrinsic ligand is in magenta and a short post-CNBHD region is in red. (e) Electrostatic and (f) hydrophobic surface representations of the Kv11.1 C-linker/CNBHD model in same orientation as (c) rendered in UCSF Chimera. Residue colors for (e) range from blue (positive) to red (negative). The acidic and hydrophobic patches important for deactivation are circled. (g) Surface representation of our C-linker/CNBHD model in same orientation as (c) with EAGD showing the location of previously reported deactivation lysine mutants in acidic patch (D843, E847, D850, E857, D864) and near the hydrophobic patches (V794, V795, V796, V797, I798, L825)[33]. Trafficking-competent mutations from this study are colored blue. (h) Same as (g) but rotated 180° and showing residues 88-94 (brown) reported to interact with the S4-S5 linker[29].



Supplemental Figure 2. Properties of HEK cells lines stably expressing Kv11.1. (a) $I_{Kv11.1}$ peak densities and representative immunoblots (140kD molecular weight marker shown) for each of the mutations functionally characterized. From a holding potential of -80mV, cells were depolarized to 50mV and inward current was measured after a step to -120mV. (b) Representative $I_{Kv11.1}$ trace comparing WT with G657R. (c) Representative $I_{Kv11.1}$ traces using the activation protocol (see Fig. 3) comparing WT with G657R. (d) Immunoblots (140kD molecular weight marker shown) showing the trafficking phenotypes for two different F106L and M124 stable cell lines cultured under control conditions or at 27^0C or in 10mM E4031. (e) An example of an uncropped Immunoblot showing the trafficking phenotype of transiently transfected WT, V41F, F106L and M124R cultured under control conditions (-) or in 10mM E4031 (E4).

Supplementary Table 1. Kv11.1 missense mutations

Variant	Location	Type	SIFT	SNP&Go	KvSNP	Reference
D16A	EAGD	LQT2	Not Tolerated	Disease (8)	Disease (0.546)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R20G	EAGD	LQT2	Not Tolerated	Disease (8)	Disease (0.602)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
S26I	PASD	LQT2	Not Tolerated	Disease (6)	Benign (0.488)	Inherited Arrhythmias Database
K28E	PASD	LQT2	Not Tolerated	Disease (8)	Disease (0.749)	Inherited Arrhythmias Database
F29L	PASD	LQT2	Not Tolerated	Disease (8)	Disease (0.932)	Inherited Arrhythmias Database
I30T	PASD	LQT2	Not Tolerated	Disease (7)	Benign (0.265)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
I31S	PASD	LQT2	Not Tolerated	Disease (9)	Disease (0.914)	Inherited Arrhythmias Database
A32T	PASD	LQT2	Not Tolerated	Disease (8)	Disease (0.757)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
N33T	PASD	LQT2	Not Tolerated	Disease (9)	Disease (0.956)	Inherited Arrhythmias Database
V41F	PASD	LQT2	Not Tolerated	Disease (9)	Disease (0.819)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
I42N	PASD	LQT2	Not Tolerated	Disease (9)	Disease (1)	Chung SK et al. Heart Rhythm 2007;4(10):1306-1314
Y43C	PASD	LQT2	Not Tolerated	Disease (9)	Disease (1)	Inherited Arrhythmias Database
C44F	PASD	LQT2	Not Tolerated	Disease (10)	Disease (1)	Inherited Arrhythmias Database
N45Y	PASD	LQT2	Not Tolerated	Disease (9)	Disease (0.902)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
G47V	PASD	LQT2	Not Tolerated	Disease (10)	Disease (0.899)	Inherited Arrhythmias Database
C49Y	PASD	LQT2	Not Tolerated	Disease (10)	Disease (0.944)	Inherited Arrhythmias Database
G53D	PASD	LQT2	Not Tolerated	Disease (10)	Disease (1)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
G53R	PASD	LQT2	Not Tolerated	Disease (10)	Disease (1)	Inherited Arrhythmias Database
Y54H	PASD	LQT2	Not Tolerated	Disease (8)	Benign (0.427)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
S55L	PASD	LQT2	Not Tolerated	Disease (6)	Disease (0.888)	Inherited Arrhythmias Database
R56Q	PASD	LQT2	Not Tolerated	Disease (9)	Disease (0.784)	Inherited Arrhythmias Database
A57P	PASD	LQT2	Tolerated	Disease (8)	Benign (0.305)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
E58A	PASD	LQT2	Not Tolerated	Disease (8)	Disease (1)	Inherited Arrhythmias Database
E58D	PASD	LQT2	Tolerated	Disease (7)	Benign (0.306)	Inherited Arrhythmias Database
E58G	PASD	LQT2	Not Tolerated	Disease (8)	Disease (1)	Inherited Arrhythmias Database
E58K	PASD	LQT2	Not Tolerated	Disease (9)	Disease (0.63)	Inherited Arrhythmias Database
C64W	PASD	LQT2	Not Tolerated	Disease (9)	Benign (0.496)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
C64Y	PASD	LQT2	Not Tolerated	Disease (9)	Disease (0.512)	Inherited Arrhythmias Database
T65P	PASD	LQT2	Tolerated	Disease (7)	Disease (1)	Inherited Arrhythmias Database
C66G	PASD	LQT2	Not Tolerated	Disease (9)	Disease (0.924)	Inherited Arrhythmias Database
F68L	PASD	LQT2	Not Tolerated	Disease (8)	Disease (0.944)	Inherited Arrhythmias Database
H70N	PASD	LQT2	Tolerated	Disease (4)	Disease (0.862)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
H70R	PASD	LQT2	Tolerated	Disease (5)	Disease (0.704)	Inherited Arrhythmias Database
G71R	PASD	LQT2	Not Tolerated	Disease (8)	Disease (1)	Inherited Arrhythmias Database
P72L	PASD	LQT2	Not Tolerated	Disease (4)	Disease (0.954)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
P72Q	PASD	LQT2	Tolerated	Disease (2)	Disease (0.839)	Inherited Arrhythmias Database
T74M	PASD	LQT2	Not Tolerated	Disease (7)	Disease (1)	Inherited Arrhythmias Database
T74P	PASD	LQT2	Not Tolerated	Disease (8)	Disease (1)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
T74R	PASD	LQT2	Not Tolerated	Disease (9)	Disease (1)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
A78P	PASD	LQT2	Not Tolerated	Disease (6)	Disease (0.826)	Inherited Arrhythmias Database
A80P	PASD	LQT2	Tolerated	Disease (6)	Disease (0.838)	Grilo LS et al. Ann Noninvasive Electrocardiol 2001;16(2):213-218
A85V	PASD	LQT2	Tolerated	Disease (6)	Disease (0.742)	Inherited Arrhythmias Database
L86P	PASD	LQT2	Not Tolerated	Disease (9)	Disease (0.831)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
L86R	PASD	LQT2	Not Tolerated	Disease (8)	Disease (1)	Inherited Arrhythmias Database
L87P	PASD	LQT2	Tolerated	Disease (8)	Disease (0.903)	Inherited Arrhythmias Database
V94G	PASD	LQT2	Not Tolerated	Disease (7)	Disease (0.918)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
I96T	PASD	LQT2	Not Tolerated	Disease (8)	Disease (0.797)	Inherited Arrhythmias Database
I96V	PASD	LQT2	Tolerated	Disease (0)	Benign (0.35)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
F98S	PASD	LQT2	Not Tolerated	Disease (9)	Benign (0.307)	Tan HL et al. Circulation 2006;114(20):2096-2103
Y99S	PASD	LQT2	Not Tolerated	Disease (10)	Disease (0.867)	Inherited Arrhythmias Database
R100G	PASD	LQT2	Tolerated	Disease (9)	Disease (0.737)	Inherited Arrhythmias Database
R100Q	PASD	LQT2	Tolerated	Disease (8)	Disease (0.849)	Inherited Arrhythmias Database
R100W	PASD	LQT2	Not Tolerated	Disease (9)	Disease (0.768)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
K101E	PASD	SIDS	Not Tolerated	Disease (10)	Disease (0.889)	Inherited Arrhythmias Database
D102A	PASD	LQT2	Tolerated	Disease (8)	Disease (0.827)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
F106L	PASD	LQT2	Tolerated	Disease (7)	Disease (0.784)	Tan HL et al. Circulation 2006;114(20):2096-2103
F106Y	PASD	LQT2	Not Tolerated	Disease (9)	Benign (0.132)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
C108R	PASD	LQT2	Not Tolerated	Disease (10)	Benign (0.439)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
P114S	PASD	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
M124R	PASD	LQT2	Tolerated	Disease (9)	Benign (0.425)	Inherited Arrhythmias Database
M124T	PASD	LQT2	Not Tolerated	Disease (9)	Disease (0.652)	Inherited Arrhythmias Database
F125C	PASD	LQT2	Tolerated	Disease (9)	Benign (0.444)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
E130K	PASD	LQT2	Tolerated	Disease (4)	Benign (0.329)	Thu-Thuy LT et al. Jpn Heart J 2004;45(2):243-250
P141L	N-linker	LQT2	Tolerated	Disease (5)	Benign (0.409)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R148W	N-linker	SNP	Not Tolerated	Disease (4)	Disease (0.796)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R164H	N-linker	LQT2	Tolerated	Disease (5)	Disease (0.608)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R176W	N-linker	SNP	Not Tolerated	Disease (7)	Disease (0.799)	Inherited Arrhythmias Database
R181Q	N-linker	SNP	Tolerated	Disease (2)	Benign (0.11)	Inherited Arrhythmias Database

Supplementary Table 1. Kv11.1 missense mutations

G187S	N-linker	SNP	Tolerated	Disease (4)	Benign (0.085)	Inherited Arrhythmias Database
A190T	N-linker	SNP	Tolerated	Disease (2)	Benign (0.019)	Inherited Arrhythmias Database
A203T	N-linker	SNP	Tolerated	Disease (1)	Benign (0.098)	Inherited Arrhythmias Database
V215G	N-linker	SNP	Not Tolerated	Disease (6)	Benign (0.219)	Inherited Arrhythmias Database
M218V	N-linker	LQT2	Tolerated	Disease (3)	Disease (0.625)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
G238S	N-linker	LQT2	Tolerated	Disease (0)	Benign (0.464)	Inherited Arrhythmias Database
R242G	N-linker	LQT2	Tolerated	Neutral (1)	Disease (0.631)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
P251A	N-linker	SNP	Tolerated	Neutral (2)	Benign (0.45)	Inherited Arrhythmias Database
P251S	N-linker	LQT2	Tolerated	Neutral (1)	Disease (0.8)	Inherited Arrhythmias Database
R252G	N-linker	LQT2	Tolerated	Disease (2)	Disease (0.607)	Tan HL et al. Circulation 2006;114(20):2096-2103
H254Q	N-linker	SNP	Tolerated	Neutral (2)	Benign (0.296)	Inherited Arrhythmias Database
N257H	N-linker	SNP	Tolerated	Neutral (1)	Benign (0.268)	Inherited Arrhythmias Database
D259N	N-linker	LQT2	Tolerated	Neutral (1)	Disease (0.613)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R273Q	N-linker	SIDS	Tolerated	Disease (5)	Disease (0.874)	Inherited Arrhythmias Database
A277D	N-linker	LQT2	Tolerated	Disease (5)	Disease (0.68)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
V279M	N-linker	SIDS	Tolerated	Neutral (3)	Disease (0.839)	Inherited Arrhythmias Database
M291T	N-linker	LQT2	Tolerated	Disease (4)	Disease (0.877)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
G294V	N-linker	SIDS	Tolerated	Disease (4)	Disease (0.708)	Tester DJ et al. Cardiovasc Res 2005;67:388-396.
P297S	N-linker	LQT2	Tolerated	Disease (4)	Disease (0.721)	Kapa S et al. Circulation 2009;120:1752-1760
R301L	N-linker	LQT2	Tolerated	Disease (6)	Disease (0.794)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
G306W	N-linker	LQT2	Not Tolerated	Disease (4)	Disease (0.631)	Inherited Arrhythmias Database
R312C	N-linker	LQT2	Not Tolerated	Disease (5)	Disease (0.893)	Inherited Arrhythmias Database
G314S	N-linker	LQT2	Tolerated	Neutral (8)	Benign (0.362)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
S320L	N-linker	LQT2	Not Tolerated	Disease (7)	Disease (1)	Inherited Arrhythmias Database
D323N	N-linker	LQT2	Tolerated	Disease (2)	Benign (0.379)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R328C	N-linker	LQT2	Not Tolerated	Disease (8)	Benign (0.445)	Inherited Arrhythmias Database
P334L	N-linker	LQT2	Tolerated	Disease (9)	Disease (0.51)	Inherited Arrhythmias Database
D342V	N-linker	LQT2	Tolerated	Disease (8)	Disease (0.734)	Itoh H et al. Circ Arrhythm Electrophysiol 2009;2:511-523
P347S	N-linker	SNP	Tolerated	Disease (2)	Benign (0.258)	Inherited Arrhythmias Database
T367S	N-linker	SNP	Tolerated	Disease (1)	Benign (0.336)	Inherited Arrhythmias Database
I400N	N-linker	LQT2	Not Tolerated	Disease (10)	Disease (1)	Inherited Arrhythmias Database
H402R	N-linker	LQT2	Not Tolerated	Disease (10)	Disease (0.956)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
W410S	S1	LQT2	Not Tolerated	Disease (10)	Disease (0.957)	Inherited Arrhythmias Database
L413P	S1	LQT2	Not Tolerated	Disease (10)	Benign (0.298)	Inherited Arrhythmias Database
Y420C	S1	LQT2	Not Tolerated	Disease (9)	Disease (1)	Inherited Arrhythmias Database
T421M	S1	LQT2	Not Tolerated	Disease (9)	Disease (0.78)	Inherited Arrhythmias Database
A422T	S1	LQT2	Not Tolerated	Disease (9)	Disease (0.99)	Inherited Arrhythmias Database
P426H	S1/S2	LQT2	Not Tolerated	Disease (9)	Disease (0.787)	Inherited Arrhythmias Database
Y427C	S1/S2	LQT2	Not Tolerated	Disease (9)	Disease (1)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
Y427H	S1/S2	LQT2	Not Tolerated	Disease (9)	Disease (1)	Inherited Arrhythmias Database
Y427S	S1/S2	LQT2	Not Tolerated	Disease (9)	Disease (0.924)	Inherited Arrhythmias Database
S428L	S1/S2	LQT2	Tolerated	Disease (9)	Disease (1)	Inherited Arrhythmias Database
F431L	S1/S2	LQT2	Not Tolerated	Disease (10)	Disease (0.929)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
T436M	S1/S2	LQT2	Tolerated	Disease (0)	Disease (0.674)	Inherited Arrhythmias Database
P440L	S1/S2	LQT2	Tolerated	Disease (3)	Benign (0.338)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
E444D	S1/S2	LQT2	Tolerated	Neutral (2)	Disease (0.539)	Inherited Arrhythmias Database
P451L	S1/S2	LQT2	Not Tolerated	Disease (9)	Disease (0.953)	Inherited Arrhythmias Database
D456Y	S2	LQT2	Not Tolerated	Disease (9)	Disease (1)	Inherited Arrhythmias Database
D460Y	S2	LQT2	Not Tolerated	Disease (10)	Disease (1)	Inherited Arrhythmias Database
F463L	S2	LQT2	Not Tolerated	Disease (9)	Disease (0.931)	Yang HT et al. Clin Exp Pharmacol Physiol 2009;36(8):822-827
D466Y	S2	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
N470D	S2	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Inherited Arrhythmias Database
T473N	S2/S3	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
T474I	S2/S3	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Inherited Arrhythmias Database
Y475C	S2/S3	LQT2	Not Tolerated	Disease (9)	Disease (1)	Inherited Arrhythmias Database
V476I	S2/S3	LQT2	Tolerated	Disease (3)	Disease (0.817)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
A490T	S2/S3	LQT2	Not Tolerated	Disease (9)	Benign (0.265)	Inherited Arrhythmias Database
H492Y	S2/S3	LQT2	Not Tolerated	Disease (10)	Disease (1)	Itoh H et al. Circ Arrhythm Electrophysiol 2009;2:511-523
Y493C	S3	LQT2	Not Tolerated	Disease (9)	Disease (1)	Inherited Arrhythmias Database
Y493S	S3	LQT2	Not Tolerated	Disease (10)	Disease (0.924)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
D501H	S3	LQT2	Not Tolerated	Disease (10)	Disease (0.775)	Inherited Arrhythmias Database
D501N	S3	LQT2	Not Tolerated	Disease (10)	Disease (0.835)	Inherited Arrhythmias Database
K525N	S4	LQT2	Not Tolerated	Disease (9)	Benign (0.4)	Inherited Arrhythmias Database
R528P	S4	LQT2	Not Tolerated	Disease (10)	Benign (0.225)	Inherited Arrhythmias Database
R531Q	S4	LQT2	Not Tolerated	Disease (9)	Disease (1)	Inherited Arrhythmias Database
R531W	S4	LQT2	Not Tolerated	Disease (10)	Diseae (0.909)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R534C	S4	LQT2	Not Tolerated	Disease (10)	Disease (0.856)	Inherited Arrhythmias Database
R534L	S4	LQT2	Not Tolerated	Disease (10)	Disease (0.906)	Inherited Arrhythmias Database
L552S	S5	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database

Supplementary Table 1. Kv11.1 missense mutations

A558E	S5	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
A558P	S5	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
L559H	S5	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
A561P	S5	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Inherited Arrhythmias Database
A561T	S5	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
A561V	S5	LQT2	Not Tolerated	Disease (9)	Disease (0.954)	Inherited Arrhythmias Database
H562P	S5	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Inherited Arrhythmias Database
H562R	S5	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
L564P	S5	LQT2	Not Tolerated	Disease (10)	Disease (0.955)	Inherited Arrhythmias Database
A565T	S5	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
C566S	S5	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Inherited Arrhythmias Database
W568C	S5	LQT2	Not Tolerated	Disease (10)	Disease (1)	Inherited Arrhythmias Database
W568R	S5	LQT2	Not Tolerated	Disease (10)	Disease (1)	Inherited Arrhythmias Database
Y569H	S5	LQT2	Not Tolerated	Dsease (9)	Disease (0.94)	Inherited Arrhythmias Database
I571L	S5	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
I571V	S5	LQT2	Not Tolerated	Disease (7)	Disease (0.999)	Inherited Arrhythmias Database
G572C	S5/Pore	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Inherited Arrhythmias Database
G572D	S5/Pore	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Inherited Arrhythmias Database
G572R	S5/Pore	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Inherited Arrhythmias Database
G572S	S5/Pore	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
G572V	S5/Pore	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
M574V	S5/Pore	LQT2	Tolerated	Disease (1)	Benign (0.453)	Tan HL et al. Circulation 2006;114(20):2096-2103
E575G	S5/Pore	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Inherited Arrhythmias Database
R582C	S5/Pore	LQT2	Not Tolerated	Disease (8)	Disease (0.684)	Inherited Arrhythmias Database
R582L	S5/Pore	LQT2	Not Tolerated	Disease (6)	Disease (0.819)	Inherited Arrhythmias Database
G584R	S5/Pore	LQT2	Not Tolerated	Disease (10)	Disease (0.875)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
G584S	S5/Pore	LQT2	Tolerated	Disease (8)	Benign (0.453)	Inherited Arrhythmias Database
W585C	S5/Pore	LQT2	Not Tolerated	Disease (10)	Disease (1)	Inherited Arrhythmias Database
N588D	S5/Pore	LQT2	Tolerated	Disease (7)	Disease (0.686)	Inherited Arrhythmias Database
I593K	S5/Pore	LQT2	Not Tolerated	Disease (10)	Disease (1)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
I593R	S5/Pore	LQT2	Not Tolerated	Disease (9)	Disease (1)	Inherited Arrhythmias Database
I593G	S5/Pore	LQT2	Not Tolerated	Disease (9)	Disease (1)	Inherited Arrhythmias Database
G594D	S5/Pore	LQT2	Tolerated	Disease (9)	Disease (0.917)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
P596H	S5/Pore	LQT2	Tolerated	Disease (3)	Disease (0.529)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
P596L	S5/Pore	LQT2	Tolerated	Disease (3)	Disease (0.543)	Inherited Arrhythmias Database
P596R	S5/Pore	LQT2	Tolerated	Disease (0)	Disease (0.694)	Inherited Arrhythmias Database
Y597C	S5/Pore	LQT2	Not Tolerated	Disease (7)	Disease (0.999)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
S599R	S5/Pore	LQT2	Tolerated	Disease (3)	Benign (0.316)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
G601C	S5/Pore	LQT2	Not Tolerated	Disease (7)	Benign (0.401)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
G601S	S5/Pore	LQT2	Tolerated	Disease (3)	Benign (0.21)	Inherited Arrhythmias Database
G604S	S5/Pore	LQT2	Not Tolerated	Disease (4)	Disease (0.999)	Inherited Arrhythmias Database
P605L	S5/Pore	LQT2	Tolerated	Disease (4)	Disease (0.968)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
P605S	S5/Pore	LQT2	Not Tolerated	Disease (3)	Disease (0.999)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
D609G	pore-helix	LQT2	Tolerated	Disease (7)	Disease (0.999)	Inherited Arrhythmias Database
D609H	pore-helix	LQT2	Not Tolerated	Disease (7)	Disease (0.99)	Inherited Arrhythmias Database
D609N	pore-helix	LQT2	Tolerated	Disease 5)	Disease (0.692)	Inherited Arrhythmias Database
Y611H	pore-helix	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Inherited Arrhythmias Database
V612L	pore-helix	LQT2	Tolerated	Disease (6)	Disease (1)	Inherited Arrhythmias Database
T613M	pore-helix	LQT2	Not Tolerated	Disease (9)	Disease (0.853)	Inherited Arrhythmias Database
A614V	pore-helix	LQT2	Not Tolerated	Disease (9)	Disease (0.814)	Inherited Arrhythmias Database
L615F	pore-helix	LQT2	Not Tolerated	Disease (8)	Disease (0.999)	Inherited Arrhythmias Database
L615V	pore-helix	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
Y616C	pore-helix	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
S621N	pore-helix	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Inherited Arrhythmias Database
S621R	pore-helix	LQT2	Not Tolerated	Disease (10)	Disease (0.956)	Inherited Arrhythmias Database
L622F	pore-SF	LQT2	Not Tolerated	Disease (8)	Disease (0.999)	Inherited Arrhythmias Database
T623I	pore-SF	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
V625E	SF	LQT2	Not Tolerated	Disease (8)	Disease (0.999)	Inherited Arrhythmias Database
G626A	SF	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
G626D	SF	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
G626S	SF	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
G626V	SF	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Jahr S et al. Human Mutation 2000;15(6):584
F627L	SF	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
G628S	SF	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
G628V	SF	LQT2	Not Tolerated	Disease (9)	Disease (0.953)	Inherited Arrhythmias Database
N629D	S6/Pore	LQT2	Not Tolerated	Disease (6)	Diseaes (0.961)	Inherited Arrhythmias Database
N629I	S6/Pore	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
N629K	S6/Pore	LQT2	Not Tolerated	Disease (9)	Disease (0.91)	Inherited Arrhythmias Database
N629S	S6/Pore	LQT2	Not Tolerated	Disease (9)	Disease (0.954)	Inherited Arrhythmias Database

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N629T	S6/Pore	LQT2	Not Tolerated	Disease (8)	Disease (0.999)	Chung SK et al. Heart Rhythm 2007;4(10):1306-1314
V630A	S6/Pore	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
V630L	S6/Pore	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
P632S	S6/Pore	LQT2	Not Tolerated	Disease (7)	Disease (1)	Inherited Arrhythmias Database
N633D	S6/Pore	LQT2	Tolerated	Disease (6)	Disease (0.866)	Inherited Arrhythmias Database
N633S	S6/Pore	LQT2	Not Tolerated	Disease (4)	Disease (0.859)	Inherited Arrhythmias Database
T634I	S6/Pore	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
N635D	S6/Pore	LQT2	Tolerated	Neutral (1)	Benign (0.372)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
N635I	S6/Pore	LQT2	Not Tolerated	Disease (7)	Disease (0.907)	Inherited Arrhythmias Database
N635K	S6/Pore	LQT2	Not Tolerated	Disease (6)	Benign (0.374)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
E637D	S6/Pore	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
E637G	S6/Pore	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Amoros I et al. Heart Rhythm 2011;8(3):463-470
E637K	S6/Pore	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Inherited Arrhythmias Database
K638E	S6/Pore	LQT2	Not Tolerated	Disease (10)	Disease (0.933)	Inherited Arrhythmias Database
K638N	S6/Pore	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
F640L	S6	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
F640V	S6	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
S641F	S6	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Inherited Arrhythmias Database
V644F	S6	LQT2	Not Tolerated	Disease (9)	Disease (0.777)	Inherited Arrhythmias Database
V644L	S6	LQT2	Not Tolerated	Disease (6)	Disease (1)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
M645I	S6	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
M645L	S6	LQT2	Not Tolerated	Disease (9)	Disease (0.913)	Inherited Arrhythmias Database
M645V	S6	LQT2	Not Tolerated	Disease (9)	Disease (0.914)	Inherited Arrhythmias Database
G648S	S6	LQT2	Not Tolerated	Disease (9)	Disease (0.953)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
S649L	S6	LQT2	Not Tolerated	Disease (9)	Disease (1)	Inherited Arrhythmias Database
F656C	S6	LQT2	Not Tolerated	Disease (10)	Disease (1)	Inherited Arrhythmias Database
G657R	S6	LQT2	Not Tolerated	Disease (10)	Disease (0.92)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
G657S	S6	LQT2	Not Tolerated	Disease (9)	Disease (1)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
S660L	S6	LQT2	Not Tolerated	Disease (10)	Disease (1)	Inherited Arrhythmias Database
I662T	S6	LQT2	Not Tolerated	Disease (9)	Disease (1)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
L678P	C-linker	LQT2	Tolerated	Disease (9)	Disease (0.565)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
H687Y	C-linker	LQT2	Not Tolerated	Disease (9)	Disease (0.821)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
L693P	C-linker	LQT2	Not Tolerated	Disease (10)	Disease (0.955)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R696C	C-linker	LQT2	Not Tolerated	Disease (10)	Disease (1)	Inherited Arrhythmias Database
R696P	C-linker	LQT2	Not Tolerated	Disease (10)	Disease (0.861)	Inherited Arrhythmias Database
S706C	C-linker	LQT2	Not Tolerated	Disease (9)	Disease (1)	Inherited Arrhythmias Database
S706F	C-linker	LQT2	Not Tolerated	Disease (10)	Disease (1)	Itoh H et al. Circ Arrhythm Electrophysiol 2009;2:511-523
I711V	C-linker	LQT2	Not Tolerated	Disease (7)	Disease (0.953)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
P721L	C-linker	LQT2	Not Tolerated	Disease (10)	Disease (1)	Inherited Arrhythmias Database
I728F	C-linker	LQT2	Not Tolerated	Disease (9)	Disease (0.816)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
S735L	C-linker	LQT2	Tolerated	Disease (4)	Disease (0.998)	Inherited Arrhythmias Database
R744P	C-linker	LQT2	Not Toerated	Disease (1)	Disease (0.668)	Aidery P Biochem Biophys Res Commun 2012;418(4):830-835
G749V	CNBHD	LQT2	Not Tolerated	Disease (9)	Disease (0.999)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R752Q	CNBHD	SIDS	Not Tolerated	Disease (8)	Disease (1)	Inherited Arrhythmias Database
R752W	CNBHD	LQT2	Not Tolerated	Disease (9)	Disease (1)	Inherited Arrhythmias Database
M756V	CNBHD	SIDS	Tolerated	Neutral (1)	Disease (0.766)	Itoh H et al. Circ Arrhythm Electrophysiol 2009;2:511-523
K757N	CNBHD	LQT2	Not Tolerated	Disease (8)	Disease (0.705)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
D767Y	CNBHD	LQT2	Not Tolerated	Disease (10)	Disease (.954)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
V770A	CNBHD	LQT2	Not Tolerated	Disease (8)	Disease (0.914)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
D774Y	CNBHD	LQT2	Not Tolerated	Disease (10)	Disease (0.919)	Inherited Arrhythmias Database
R784W	CNBHD	LQT2	Not Tolerated	Disease (9)	Disease (0.954)	Inherited Arrhythmias Database
G785V	CNBHD	LQT2	Not Tolerated	Disease (6)	Disease (1)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
E788D	CNBHD	LQT2	Not Tolerated	Disease (9)	Disease (1)	Inherited Arrhythmias Database
E788K	CNBHD	LQT2	Not Tolerated	Disease (10)	Disease (0.853)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R791W	CNBHD	LQT2	Not Tolerated	Disease (8)	Disease (0.701	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
G800W	CNBHD	LQT2	Not Tolerated	Disease (9)	Disease (1)	Inherited Arrhythmias Database
F805C	CNBHD	LQT2	Not Tolerated	Disease (10)	Disease (1)	Inherited Arrhythmias Database
F805S	CNBHD	LQT2	Not Tolerated	Disease (10)	Disease (1)	Inherited Arrhythmias Database
G806E	CNBHD	LQT2	Not Tolerated	Disease (10)	Disease (0.999)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
G816V	CNBHD	LQT2	Tolerated	Disease (9)	Benign (0.096)	Krishnan Y et al. Pacing Clin Electrophysiol 2012;35(1):3-16
S818L	CNBHD	LQT2	Not Tolerated	Disease (9)	Disease (0.905)	Inherited Arrhythmias Database
S818P	CNBHD	LQT2	Not Tolerated	Disease (10)	Disease (1)	Inherited Arrhythmias Database
G820R	CNBHD	LQT2	Not Tolerated	Disease (8)	Disease (0.556)	Inherited Arrhythmias Database
V822M	CNBHD	LQT2	Not Tolerated	Disease (7)	Diseaes (0.917)	Inherited Arrhythmias Database
R823W	CNBHD	LQT2	Not Tolerated	Disease (10)	Disease (1)	Inherited Arrhythmias Database
R835W	CNBHD	LQT2	Not Tolerated	Disease (9)	Disease (0.959)	Inherited Arrhythmias Database
D837G	CNBHD	LQT2	Tolerated	Disease (9)	Disease (0.9)	Inherited Arrhythmias Database
D837Y	CNBHD	LQT2	Not Tolerated	Disease (9)	Disease (0.973)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
P846S	CNBHD	LQT2	Tolerated	Disease (9)	Disease (0.881)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303

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N861H	CNBHD	LQT2	Not Tolerated	Disease (10)	Disease (1)	Inherited Arrhythmias Database
N861I	CNBHD	LQT2	Not Tolerated	Disease (10)	Disease (1)	Inherited Arrhythmias Database
G873S	C-Term	SNP	Tolerated	Neutral (4)	Benign (0)	Koo SH et al. Br J Clin Pharmacol 2006;61(3):301-308
T875M	C-Term	SNP	Tolerated	Neutral (6)	Benign (0.092)	Inherited Arrhythmias Database
R885C	C-Term	SIDS	Not Tolerated	Disease (1)	Disease (0.719)	Inherited Arrhythmias Database
R887H	C-Term	SNP	Tolerated	Disease (4)	Benign (0.354)	Inherited Arrhythmias Database
R894C	C-Term	LQT2	Not Tolerated	Disease (5)	Disease (0.681)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R894L	C-Term	LQT2	Tolerated	Disease (2)	Disease (0.575)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
T895M	C-Term	SIDS	Tolerated	Neutral (3)	Benign (0)	Otagiri T et al. Pediatr Res 2008;64(5):482-487
K897T	C-Term	SNP	Tolerated	Neutral (0)	Benign (0.426)	Inherited Arrhythmias Database
G903R	C-Term	LQT2	Tolerated	Disease (3)	Disease (0.63)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
S906L	C-Term	LQT2	Tolerated	Neutral (0)	Disease (0.636)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
P910L	C-Term	SNP	Tolerated	Neutral (3)	Benign (0.236)	Inherited Arrhythmias Database
A913V	C-Term	LQT2	Tolerated	Neutral (7)	Disease (0.895)	Inherited Arrhythmias Database
A915V	C-Term	SNP	Tolerated	Neutral (7)	Benign (0.079)	Inherited Arrhythmias Database
P917L	C-Term	SNP	Tolerated	Neutral (2)	Benign (0.317)	Inherited Arrhythmias Database
R920Q	C-Term	LQT2	Tolerated	Disease (2)	Disease (0.839)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R920W	C-Term	LQT2	Tolerated	Disease (7)	Diseaes (0.739)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R922Q	C-Term	LQT2	Tolerated	Neutral (2)	Disease (0.836)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R922W	C-Term	LQT2	Tolerated	Disease (0)	Disease (0.739)	Inherited Arrhythmias Database
G924A	C-Term	LQT2	Tolerated	Neutral (3)	Disease (0.508)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
G924E	C-Term	LQT2	Tolerated	Neutral (2)	Disease (1)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
S937N	C-Term	LQT2	Tolerated	Neutral (7)	Benign (0.366)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R948C	C-Term	LQT2	Tolerated	Neutral (0)	Disease (0.892)	Inherited Arrhythmias Database
R954C	C-Term	SIDS	Tolerated	Disease (3)	Disease (1)	Inherited Arrhythmias Database
L955V	C-Term	LQT2	Tolerated	Neutral (7)	Disease (0.892)	Biliczki P et al. Heart Rhythm 2008;5(8):1159-1167
S960N	C-Term	LQT2	Tolerated	Neutral (2)	Disease (0.929)	Inherited Arrhythmias Database
P963T	C-Term	LQT2	Tolerated	Neutral (3)	Benign (0.352)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
G965R	C-Term	SNP	Tolerated	Neutral (3)	Benign (0.044)	Koo SH et al. Br J Clin Pharmacol 2006;61(3):301-308
P967L	C-Term	SNP	Tolerated	Neutral (3)	Benign (0.101)	Inherited Arrhythmias Database
P968L	C-Term	LQT2	Tolerated	Neutral (3)	Benign (0.181)	Inherited Arrhythmias Database
N996I	C-Term	LQT2	Tolerated	Disease (8)	Disease (0.882)	Tan HL et al. Circulation 2006;114(20):2096-2103
R1005Q	(RXR)	LQT2	Tolerated	Disease (1)	Disease (0.715)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R1007H	(RXR)	LQT2	Tolerated	Disease (1)	Disease (0.777)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R1033W	C-Term	LQT2	Tolerated	Disease (1)	Disease (0.598)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R1035W	CCD	SNP	Tolerated	Neutral (2)	Benign (0.403)	Inherited Arrhythmias Database
G1036D	CCD	LQT2	Tolerated	Neutral (3)	Disease (0.605)	Biliczki P et al. Heart Rhythm 2008;5(8):1159-1167
V1038M	CCD	LQT2	Tolerated	Neutral (3)	Benign (0.114)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
S1040G	CCD	SIDS	Tolerated	Neutral (7)	Disease (0.583)	Inherited Arrhythmias Database
R1047L	CCD	SNP	Tolerated	Disease (1)	Disease (0.676)	Inherited Arrhythmias Database
L1049P	CCD	LQT2	Not Tolerated	Disease (6)	Benign (0.051)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
R1055Q	CCD	SNP	Tolerated	Neutral (1)	Benign (0.275)	Inherited Arrhythmias Database
A1058E	CCD	SNP	Tolerated	Disease (3)	Benign (0)	Inherited Arrhythmias Database
L1066V	CCD	LQT2	Not Tolerated	Disease (2)	Benign (0.463)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
Q1068R	CCD	SNP	Tolerated	Disease (1)	Benign (0.091)	Inherited Arrhythmias Database
P1075L	C-Term	LQT2	Tolerated	Disease (4)	Disease (0.82)	Chung SK et al. Heart Rhythm 2007;4(10):1306-1314
Y1078C	C-Term	LQT2	Tolerated	Disease (4)	Benign (0.168)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
P1093L	C-Term	LQT2	Tolerated	Neutral (2)	Benign (0.46)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
L1108V	C-Term	SNP	Tolerated	Neutral (6)	Benign (0.252)	Inherited Arrhythmias Database
M1115V	C-Term	LQT2	Tolerated	Neutral (6)	Disease (0.678)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
A1116V	C-Term	LQT2	Tolerated	Neutral (6)	Benign (0.259)	Kapplinger JD et al. Heart Rhythm 2009;5(9):1297-1303
H1153Y	C-Term	LQT2	Tolerated	Neutral (5)	Benign (0.215)	Inherited Arrhythmias Database
G1154S	C-Term	SNP	Tolerated	Neutral (4)	Benign (0.133)	Inherited Arrhythmias Database
P1157L	C-Term	SIDS	Not Tolerated	Neutral (4)	Disease (0.695)	Tester DJ and Ackerman MJ. Cardiovasc Res 2005;67:388-396

Numbers in parentheses (1-10 for SNP&Go and 0-1 for KvSNP) are a reliability index with larger numbers more reliable. References indicate the literature source identifying the missense variant. Abbreviationss: SNP (non synonymous single nucleotide polymorphism), SIDS (sudden infant death syndrome) LQT2 (type 2 Long QT Syndrome).

Supplementary Table 2. Properties of Kv11.1 EAGD mutations

LQT2	Class	27	E4	WT	Reference
D16A	3				This study
R20G	n/a				This study
S26I	2	+	+	+	This study
K28E	2	+	+	+	This study
F29L	2	+	+	+	This study
I30T	2	+	+	+	This Study
I31S	2	-	-	+	Anderson et al. Circulation 2006;113(3):365-373
A32T	2	+	+	+	This study
N33T	3				This study and Gianulis and Trudeau J Biol Chem 2011;286(25):22160-22169
V41F	2	-	-	+	This study
I42N	2	+	-	+	This study
Y43C	2	+	-	+	This study
C44F	2	-	-	+	This study
N45Y	2	-	-	+	This study
G47V	2	+	-	+	This study
C49Y	2	+	-	+	This study
G53D	2	+	-	+	This study
G53R	2	+	+	+	This study
Y54H	2	+	+	+	This study
S55L	2	+	-	+	This study
R56Q	3				This study and Gianulis and Trudeau J Biol Chem 2011;286(25):22160-22169
A57P	n/a				This study
E58A	2	+	+	+	This study
E58D	2				This study
E58G	2	+	-	+	This study
E58K	2	+	+	+	This study
C64W	2	+	-	+	This study
C64Y	2	+	+	+	This study
T65P	2	+	+	+	Paulussen A et al. J Biol Chem 2002;277(50):48610-48616
C66G	2	+	-	+	This study
F68L	2	+	-	+	This study
H70N	2	+	+	+	This study
H70R	2	+	+	+	This study
G71R	2	-	-	+	This study
P72L	2	+	+	+	This study
P72Q	2	+	+	+	This study
T74M	2	-	-	+	This study
T74P	2	-	-	+	This study
T74R	2	-	-	+	This study
A78P	2	+	+	+	This study
A80P	2	n/a	n/a	n/a	Grilo LS et al. Ann Noninvasive Electrocariol 2011;16(2):213-218
A85V	2	+	+	+	This study
L86P	2	+	-	+	This study
L86R	2	+	-	+	This study
L87P	2	+	-	+	This study
V94G	2	+	-	+	This study
I96T	2	+	+	+	This study
I96V	n/a				
F98S	2	+	-	+	This study
Y99S	2	+	+	+	This study
R100G	2	+	+	+	This study
R100Q	2	+	-	+	This study
R100W	2	+	-	+	This study
K101E	2	-	-	+	This study
D102A	n/a				
F106L	2	+	+	+	This study
F106Y	2	+	+	+	This study
C108R	2	-	-	+	This study
P114S	2	+	+	+	This study
V115M	n/a				This study
M124R	2	+	+	+	This study
M124T	n/a				This study & Hayashi et al. Clinical Science 2004;107:175-182
F125C	n/a				This study
E130K	n/a				This study

Class column indicates loss-of-function category where type 2 and 3 mutations have abnormal trafficking and gating, respectively. Mutations labeled n/a (not available) were not studied (I96V, D102A), traffic normally but not functionally characterized (A57P), or traffic normally but do not exhibit loss-of-function characteristics (R20G,E58D, V115M, M124T, F125C, E130K). (+) and (-) indicates an increase or not in the 155kD band on immunoblot for type 2 homomeric channels when cultured at 27^0C, in E4031 or with WT. In addition to the results reported here (This study), results reported elsewhere are also listed and cited in the References column.

Supplementary Table 3. Properties of Kv11.1 C-linker/CNBHD mutations

LQT2	Class	27	E4	WT	Reference
L678P	n/a				
H687Y	2	+	+	+	This study
L693P	n/a				
R696C	2	+	-	+	This study
R696P	2	-	-	+	This study
S706C	n/a				This study
S706F	2	n/a	n/a	+	Itoh H et al. Circ Arrhythm Electrophysiol 2009;2:511-523
I711V	n/a				This study
P721L	2	-	-	+	This study
I728F	n/a				
S735L	2	-	-	+	This study
R744P	2	n/a	n/a	+	Aidery P et al. Biochem Biophys Res Commun 2012;418(4):830-835
G749V	2	+	-	+	This study
R752Q	2	+	+	+	This study
R752W	2	+	-	+	Anderson CL et al. Circulation 2006;13(3):365-373
M756V	2	n/a	n/a	+	Itoh H et al. Circ Arrhythm Electrophysiol 2009;2:511-523
K757N	2	+	+	+	This study
D767Y	3				This study
V770A	2	+	-	+	This study
D774Y	2	-	-	+	This study
R784W	2	+	+	+	This study
G785V	2	-	-	+	This study
E788D	2	+	-	+	This study
E788K	2	+	-	+	This study
R791W	3				This study
G800W	2	+	-	+	This study
F805C	2	+	-	+	Anderson CL et al. Circulation 2006;13(3):365-373
F805S	2	-	-	+	This study
G806E	2	-	-	+	This study
G816V	2	+	n/a	+	Krishnan Y et al. Pacing Clin Electrophysiol 2012;35(1):3-16
S818L	2	-	-	+	Anderson CL et al. Circulation 2006;13(3):365-373
S818P	2	-	-	+	This study
G820R	2	+	+	+	This study
V822M	2	-	-	+	Anderson CL et al. Circulation 2006;13(3):365-373
R823W	2	-	-	+	Anderson CL et al. Circulation 2006;13(3):365-373
R835W	3				This study
D837G	2	+	-	+	This study
D837Y	2	-	-	+	This study
P846S	2	+	-	+	This study
N861H	2	+	-	+	This study
N861I	2	+	-	+	This study

Class column indicates loss-of-function category where type 2 and 3 mutations have abnormal trafficking and gating, respectively. Mutations labeled n/a (not avaiable) were not studied (L678P, L693P, I728F) or traffic normally but do not exhibit loss-of-function characterisitcs (S706C). (+) and (-) indicates an increase or not in the 155kD band on immunoblot for type 2 homomeric channels when cultured at 27^0C, in E4031 or with WT. In addition to the results reported here (This study), results reported elsewhere are also listed and cited in the References column.

Supplementary Table 4. Properties of Kv11.1 pore mutations

LQT2	Class	27	E4	WT	Reference
L552S	2	+	+	+	This study
A558E	2	-	-	-	This study
A558P	2	-	-	-	This study
L559H	2	-	-	-	This study
A561P	2	-	-	-	This study
A561T	2	-	-	n/a	Anderson CL et al. Circulation 2006;13(3):365-373
A561V	2	-	-	+	Anderson CL et al. Circulation 2006;13(3):365-373
H562P	2	-	-	+	Anderson CL et al. Circulation 2006;13(3):365-373
H562R	2	-	-	+	This study
L564P	2	-	-	-	This study
A565T	2	-	-	-	This study
C566S	2	-	-	+	This study
W568C	2	-	-	-	This study
W568R	2	-	-	+	This study
Y569H	2	-	-	-	This study
I571L	2	+	+	+	Anderson CL et al. Circulation 2006;13(3):365-373
I571V	2	+	+	+	This study
G572C	2	-	-	-	This study
G572D	2	-	-	-	This study
G572R	2	-	-	-	This study
G572S	2	-	+	-	Zhao JT et al. J Cardiovasc Electrophysiol 2009;20(8):923-930 & Anderson CL et al 2006
G572V	2	-	-	+	This study
M574V	n/a				
E575G	2	+	+	+	This study
R582C	2	+	n/a	n/a	Fougere RR et al. Heart Rhythm 2011;8(8):1273-1280 & This study (not shown)
R582L	2	+	+	+	This study
G584R	n/a				
G584S	3				Zhao JT et al. J Cardiovasc Electrophysiol 2009;20(8):923-930
W585C	2	-	-	-	This study
N588D	2	+	+	+	This study
I593G	2	-	-	-	This study
I593K	2	-	-	-	This study
I593R	2	+	+	-	Anderson CL et al. Circulation 2006;13(3):365-373
G594D	2	-	+	-	This study
P596H	2	-	+	-	This study
P596L	2	+	+	-	This study
P596R	2	+	+	-	Anderson CL et al. Circulation 2006;13(3):365-373
Y597C	2	-	+	-	This study
S599R	2	+	+	+	This study
G601C	2	+	+	+	This study
G601S	2	+	+	+	Anderson CL et al. Circulation 2006;13(3):365-373
G604S	2	-	-	-	This study
P605L	2	-	-	-	This study
P605S	2	-	-	-	This study
D609G	2	-	-	-	This study
D609H	2	-	-	-	This study
D609N	2	-	-	-	This study
Y611H	2	-	-	-	Anderson CL et al. Circulation 2006;13(3):365-373
V612L	2	-	+	+	Anderson CL et al. Circulation 2006;13(3):365-373
T613M	2	-	-	-	This study
A614V	2	-	-	-	Anderson CL et al. Circulation 2006;13(3):365-373
L615F	2	-	+	+	This study
L615V	2	n/a	n/a	+	Fu-De H et al. Circulation 2001;104:1071-1075
Y616C	4				This study
S621N	2	-	-	-	This study
S621R	2	-	-	-	This study
L622F	n/a			-	
T623I	2	+	+	+	Anderson CL et al. Circulation 2006;13(3):365-373
V625E	2	-	-	-	This study

Supplementary Table 4. Properties of Kv11.1 pore mutations

G626A	4*				This study
G626D	2	-	-	-	This study
G626S	2	-	+	n/a	This study
G626V	2	-	-	+	This study
F627L	2	+	+	n/a	This study
G628S	4				Zhou et al. J Biol Chem 1998;273(33):21061-21066
G628V	2	-	-	n/a	This study
N629D	2	+	+	-	Anderson CL et al. Circulation 2006;13(3):365-373
N629I	2	-	-	-	This study
N629K	2	-	-	-	This study
N629S	2	+	+	-	Anderson CL et al. Circulation 2006;13(3):365-373
N629T	n/a				
V630A	2	+	+	-	Anderson CL et al. Circulation 2006;13(3):365-373
V630L	2	+	+	+	Anderson CL et al. Circulation 2006;13(3):365-373
P632S	2	-	-	-	This study
N633D	2	n/a	n/a	+	Hsueh CH et al. Biochem Biophys Res Commun 2008;373(4):572-578
N633S	2	+	+	n/a	This study
T634I	2	-	-	-	This study
N635D	2	-	+	-	This study
N635I	2	+	+	+	This study
N635K	n/a				
E637D	2	-	-	-	This study
E637G	2	-	-	-	This study
E637K	2	-	-	n/a	This study
K638E	2	-	-	n/a	This study
K638N	2	-	-	-	This study
F640L	2	-	-	-	This study
F640V	2	-	+	-	Anderson CL et al. Circulation 2006;13(3):365-373
S641F	2	-	+	-	This study
V644F	2	-	-	-	This study
V644L	3				This study
M645I	n/a				This study
M645L	n/a				This study
M645V	n/a				This study
G648S	n/a				This study
S649L	4				This study
F656C	n/a	n/a	n/a	n/a	This study
G657R	4				This study
G657S	n/a				
S660L	n/a	+	+	+	This study
I662T	n/a				This study

Class column indicates loss-of-function category where type 2, 3 and 4 mutations have abnormal trafficking, gating, and loss of conduction, respectively. Mutations labeled not available (n/a) were not studied (M574V, G584R, L622F, N629T, N635K, G657S), traffic normally but were not functionally characterized (M645I, M645L, M645V, G648S, S660L, F656C), or traffic normally but do not exhibit a loss-of-function phenotype (I662T). (+) and (-) indicates an increase or not in the 155kD band on immunoblot for type 2 homomeric channels when cultured at 27^0C, in E4031 or with WT. In addition to the results reported here (This study), results reported elsewhere are also listed and cited in the References column.

Supplementary Table 5. Membrane insertion efficiency

LQT2	TMD	ΔG	ΔΔG
WT (403-427)	S1	0.591	
W410S	S1	1.204	0.613
L413P	S1	1.677	1.086
Y420C	S1	0.34	-0.251
T421M	S1	0.314	-0.277
A422T	S1	0.785	0.194
WT (452-474)	S1	1.539	
D456Y	S2	0.231	-1.308
D460Y	S2	0.37	-1.169
F463L	S2	1.348	-0.191
D466Y	S2	0.253	-1.286
N470D	S2	1.588	0.49
WT (493-514)	S3	0.819	
Y493C	S3	0.922	0.103
Y493S	S3	1.293	0.474
D501N	S3	0.206	-0.613
D501H	S3	0.345	-0.474
WT (522-536)	S4	4.73	
K525N	S4	4.732	0.002
R528P	S4	4.162	-0.568
R531Q	S4	4.802	0.072
R531W	S4	3.593	-1.137
R534C	S4	4.558	-0.172
R534L	S4	2.629	-2.101
WT (551-571)	S5	-1.539	
L552S	S5	-0.684	0.855
A558E	S5	-0.036	1.503
A558P	S5	-0.434	1.105
L559H	S5	0.345	1.884
A561P	S5	-0.567	0.972
A561T	S5	-1.146	0.393
A561V	S5	-1.887	-0.348
H562P	S5	-1.684	-0.145
H562R	S5	-1.043	0.496
L564P	S5	-0.436	1.103
A565T	S5	-1.245	0.294
C566S	S5	-0.796	0.743
W568R	S5	-0.976	0.563
W568C	S5	-1.176	0.363
Y569H	S5	-0.284	1.255
I571L	S5	-1.719	-0.18
I571V	S5	-1.462	0.077
WT(639-666)	S6	0.575	
F640V	S6	0.784	0.209
F640L	S6	0.493	-0.082
S641F	S6	0.004	-0.571
V644L	S6	0.293	-0.282
V644F	S6	0.388	-0.187
M645I	S6	0.288	-0.287
M645L	S6	0.183	-0.392
M645V	S6	0.56	-0.015
G648S	S6	0.732	0.157
S649L	S6	-0.557	-1.132
F656C	S6	0.843	0.268
G657R	S6	1.287	0.712
G657S	S6	0.811	0.236
S660L	S6	-0.539	-1.114
I662T	S6	0.847	0.272

Differences between ΔG values calculated for each TM segment (1-6) were compared to WT (ΔΔG). Positive ΔΔG values indicate decreased TMD insertion efficiency and negative ΔΔG values indicate increased TMD insertion efficiency.

Supplementary Table 6. Pathogenicity predictions for Kv11.1 mutations

Domain	SIFT	SNP&Go	KvSNP
PASD (LQT2)	46/63 (73%)	63/63 (100%)	50/63 (79%)
N-linker (LQT2)	6/25 (24%)	20/25 (80%)	20/25 (80%)
N-linker (SNP)	3/12 (25%)	9/12 (75%)	2/12 (17%)
VSD (LQT2)	31/36 (86%)	35/36 (97%)	31/36 (86%)
Pore (LQT2)	85/100 (85%)	99/100 (99%)	93/100 (93%)
C-linker/CNBD (LQT2)	33/39 (85%)	38/39 (97%)	38/39 (97%)
C-term (LQT2)	7/38 (18%)	18/38 (47%)	26/38 (68%)
C-term (SNP)	0/16 (0%)	4/16 (25%)	1/16 (6%)

Total	Total	Total	Total
LQT2 (structural)	110/138 (80%)	136/138 (99%)	119/138 (86%)
LQT2 (non structural)	13/63 (21%)	38/63 (60%)	46/63 (73%)
SNP	3/28 (11%)	13/28 (46%)	3/28 (11%)

Fraction of mutations and SNPs predicted to be damaging are tabulated by domain (top). Total numer of mutations predicted to be damaging in structural domains (PASD, VSD, pore, C-linker/CNBD) versus nonstructural domains (N-linker and C-term) and total SNPs (bottom). Abbreviations: (VSD) voltage sensor domain, (LQT2) Long QT Syndrome type 2, (SNP) non synonymous single nucleotide polymorphism.

Supplementary Table 7. Bioinformatic tools

Tool	Calculation	Website	Reference
Swiss-Model	CNBD model	http://swissmodel.expasy.org	Arnold K et al. Bioinformatics 2006;22:195-201
Molprobity	CNBD model evaluation	http://molprobity.biochem.duke.edu	Davis IW et al. Nucleic Acids Res 2007;35:375-383
UCSF Chimera	modeling	http://www.cgl.ucsf.edu/chimera	Pettersen EF et al. J Comput Chem 2004:25(13):1605-1612
YASARA	modeling	http://yasara.org	Van Durme J et al. Bioinformatics 2011;27(12):1711-1712
Pymol	modeling	http://www.pymol.org	PyMOL Molecular Graphics System, Version 1.2r3pre, Schrödinger, LLC
ΔG predictor	TM insertion efficieny	http://dgpred.cbr.su.se	Hessa T et al. Nature 2007;450(7172):1026-1030
Paircoil2	Coiled coil prediction	http://paircoil2.csail.mit.edu	McDonnell AV et al. Bioinformatics 2006;22(3):356-358
SIFT	mutant damage prediction	http://sift.jcvi.org	Ng PC and Henikoff S. Nucleic Acids Res 2003;31(13):3812-3814
SNP&GO	mutant damage prediction	http://snps-and-go.biocomp.unibo.it/snps-and-go	Calabrese R et al. Hum Mutat 2009;30:1237-1244
KvSNP	mutant damage prediction	http://www.bioinformatics.leeds.ac.uk/KvDB/KvSNP.html	Stead LF et al. Bioinformatics 2011;27(16):2181-2186

Tools used in this study with web and literature sources cited.