Supplemental Material

Details of 2 Genotype Positive Family Members that had Definite Arrhythmic Events

Supplemental Figure 1: Arrhythmic Events Among Males and Females Possessing a Rare *KCNE1* Variant**.** Outcomes of (**A**) Syncope, Appropriate ICD Shock, ACA, or SCD and (**B**) Appropriate ICD Shock, ACA, or SCD.

ICD = implantable cardioverter-defibrillator, ACA = aborted cardiac arrest, SCD = sudden cardiac death, ref = reference, HR = hazard ratio, CI = confidence intervals.

Supplemental Figure 2: Arrhythmic Events Among Individuals Possessing Rare *KCNE1* Variants Stratified by Protein Location. Outcomes of (**A**) Syncope, Appropriate ICD Shock, ACA, or SCD and (**B**) Appropriate ICD Shock, ACA, or SCD.

ICD = implantable cardioverter-defibrillator, ACA = aborted cardiac arrest, SCD = sudden cardiac death, HR = hazard ratio, CI = confidence intervals, ref = reference

Supplemental Figure 3: Arrhythmic Events Among Individuals Possessing the KCNE1-p.Asp76Asn Variant and Non-KCNE1-p.Asp76Asn Variants. Outcomes of (**A**) Syncope, Appropriate ICD Shock, ACA, or SCD and (**B**) Appropriate ICD Shock, ACA, or SCD.

ICD = implantable cardioverter-defibrillator, ACA = aborted cardiac arrest, SCD = sudden cardiac death, HR = hazard ratio, CI = confidence intervals, ref = reference

Supplemental Table 1: Evaluation for Evidence of Familial Genotype-Phenotype Segregation Among Putative Loss-of-Function *KCNE1* Variants

*****Number of families exhibiting genotype-phenotype segregation defined as at least 2 individuals from a single family.

Supplemental Table 2: Association of Clinical and Genetic Variables with Cardiac Events Among Probands Heterozygous for Rare *KCNE1* Variants

* β-blocker treated as a time dependent covariate. ICD = implantable cardioverter defibrillator, ACA = aborted cardiac arrest, SCD = sudden cardiac death, HR = hazard ratio, CI = confidence interval, ms = milliseconds.

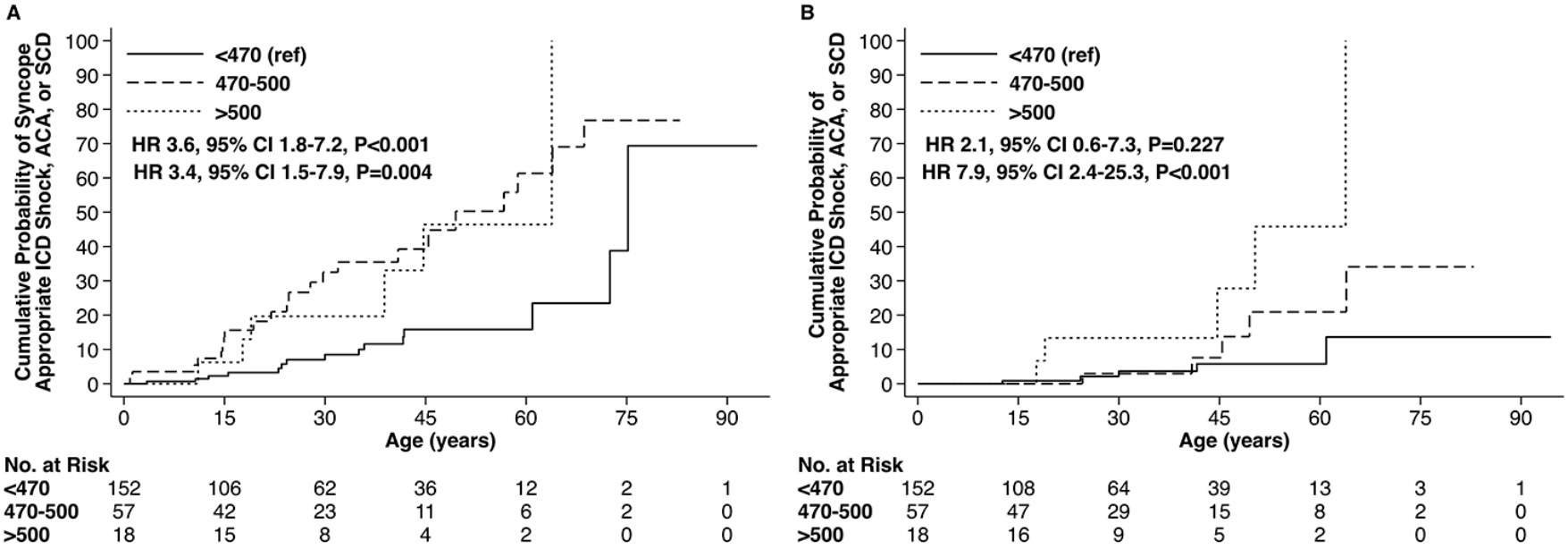
Supplemental Table 3: Evaluation of Rare *KCNE1* Variants Implicated in Type 5 Long QT Syndrome and Re-Classification of Variant Status According to ACMG Criteria

*GRCh37 Chr:position, AF = allele frequency, OA = overall, EA = European ancestry, JLNS2 = Type 2 Jervell and Lange-Nielsen Syndrome, ACMG = American College of Medical Genetics, PP2 = PolyPhen-2, Ref = reference, N/A = not applicable, VUS = variant of unknown significance, Y = yes, PrD = probably damaging, D = damaging, B = benign, T = tolerated, PoD = possibly damaging.

Details of 2 Genotype Positive Family Members that had Definite Arrhythmic Events

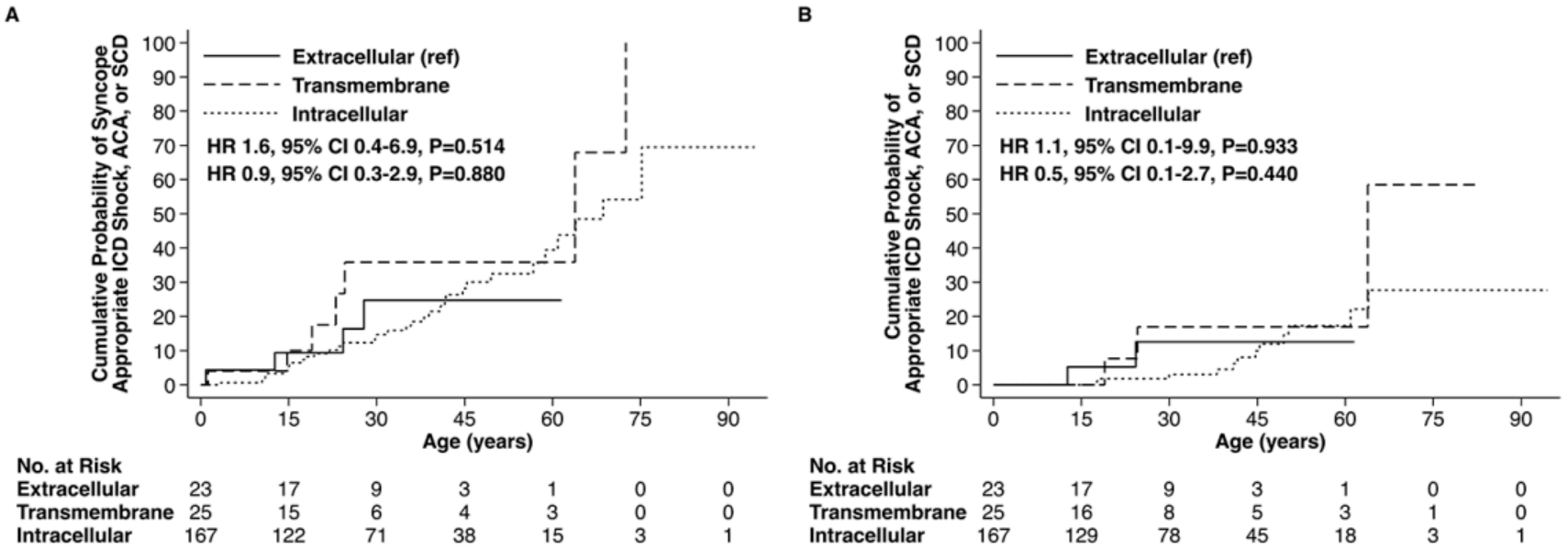
The first genotype positive family member that suffered a definite arrhythmic event was an asymptomatic male diagnosed with LQTS at 15 years of age following cascade screening for the KCNE1-p.Gly55Ser variant (gnomAD allele frequency in Europeans = 0.003582%). His presenting QTc was 488ms and he subsequently underwent ICD implantation due to family preference following the ACA of his sister. He was initiated on atenolol and had an appropriate ICD shock for torsades de pointes while at rest at 19 years of age in the absence of a QT-prolonging stressor. His QTc at the time of the event was 505ms and his QTc values following his initial presentation have ranged from 476ms to 512ms.

The second family member that had a definite arrhythmic event was a previously asymptomatic male that possessed the KCNE1-p.Asp76Asn variant (gnomAD allele frequency in Europeans = 0.01106%) and was diagnosed with LQT5 as part of cascade screening at 50 years of age. His QTc on ECG at the time of diagnosis was 431ms and no subsequent ECGs were available for review. A β-blocker was not initiated and he died suddenly during long distance running at 61 years of age, had a normal cardiac autopsy (including normal coronary arteries), and history from family indicated he had not been exposed to a QT-prolonging drug. His fatal event at an older age may serve to illustrate the persistent arrhythmic risk that LQTS confers throughout a lifetime, though it is also acknowledged that a normal autopsy does not completely exclude other potential cardiac etiologies that may manifest clinically as SCD.



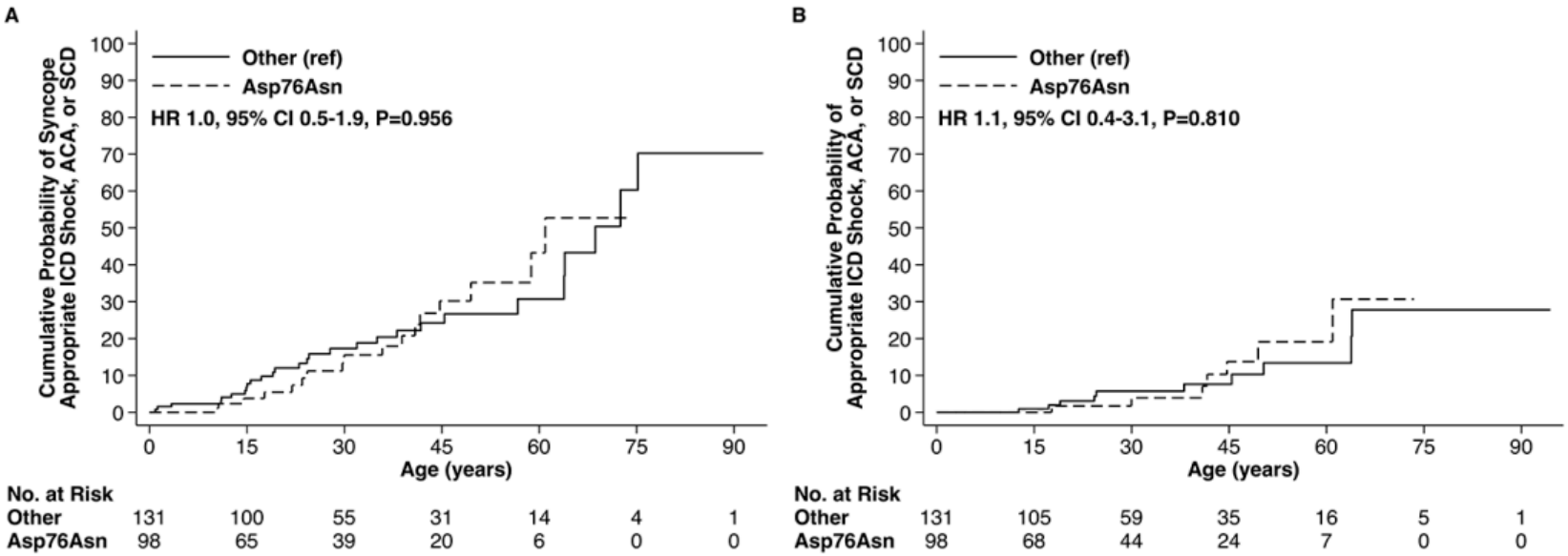
Supplemental Figure 1: Arrhythmic Events Among Individuals Possessing a Rare *KCNE1* Variant Stratified by QTc Tertiles

ICD = implantable cardioverter-defibrillator, ACA = aborted cardiac arrest, SCD = sudden cardiac death, ref = reference, HR = hazard ratio, CI = confidence intervals.



Supplemental Figure 2: Arrhythmic Events Among Individuals Possessing Rare *KCNE1* Variants Stratified by Protein Location

ICD = implantable cardioverter-defibrillator, ACA = aborted cardiac arrest, SCD = sudden cardiac death, HR = hazard ratio, CI = confidence intervals, ref = reference



Supplemental Figure 3: Arrhythmic Events Among Individuals Possessing the KCNE1-p.Asp76Asn Variant and Non-KCNE1-p.Asp76Asn Variants

ICD = implantable cardioverter-defibrillator, ACA = aborted cardiac arrest, SCD = sudden cardiac death, HR = hazard ratio, CI = confidence interval, ref = reference

Supplemental Table 1: Evaluation for Evidence of Familial Genotype-Phenotype Segregation Among Putative Loss-of-Function *KCNE1* Variants

KCNE1 Variant Amino Acid Change	Familial Genotype-Phenotype Segregation* QTc > 460 ms
Whole gene deletion	-
Asn5Ter	0/2
Thr7Ile	0/1
Ala8Val	0/1
Thr10Met	0/1
Leu16LeufsTer46	-
Gln22Ter	1/1
Ser28Leu	1/3
Arg33Met	-
Lys41Asn	-
Tyr46Cys	1/1
Phe53Cys	-
Gly55Ser	1/2
Thr58_Leu59delinsProPro	0/1
Ile61Val	-
Arg67Cys	1/1
Arg67His	2/8
Arg67Leu	-
Lys70Met	-
Ser74Leu	0/1
Asp76Asn	5/21
Val80Ile	-
Ile82Val	-
Arg98Trp	0/7
Arg98Gln	-
Val99Leu	-
Val109Ile	1/1
Thr125Met	-

*Number of families exhibiting genotype-phenotype segregation, defined as at least 2 individuals within a family possessing QTc > 460ms on presenting ECG.

Supplemental Table 2: Association of Clinical and Genetic Variables with Cardiac Events Among Probands Heterozygous for Rare *KCNE1* Variants

Clinical and Genetic Variables	Composite of Syncope, Appropriate ICD Shock, ACA, SCD				Composite of Appropriate ICD Shock, ACA, SCD			
	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Female Sex	1.2 (0.5-2.5)	0.71	1.0 (0.5-2.2)	0.92	1.0 (0.2-4.6)	0.97	0.5 (0.1-2.5)	0.40
QTc tertiles (ms) <470	Reference	-	-	-	Reference	-	-	-
470-500	1.2 (0.5-2.8)	0.63	1.2 (0.5-2.7)	0.65	0.7 (0.2-3.0)	0.65	0.7 (0.2-2.8)	0.60
>500	1.4 (0.5-3.5)	0.50	1.3 (0.4-3.9)	0.68	3.1 (0.8-12.0)	0.11	3.6 (0.8-16.6)	0.11
Time on β-Blocker*	1.0 (0.9-1.2)	0.61	1.0 (0.9-1.2)	0.52	1.0 (0.8-1.1)	0.59	1.0 (0.9-1.1)	0.52
Variant Location								
Extracellular	Reference	-	-	-	Reference	-	-	-
Transmembrane	0.9 (0.2-3.7)	0.83	0.8 (0.2-3.8)	0.76	0.7 (0.1-4.7)	0.67	0.3 (0.0-2.21)	0.24
Intracellular	0.6 (0.2-2.0)	0.42	0.6 (0.2-1.9)	0.37	0.4 (0.1-2.3)	0.30	0.3 (0.1-1.7)	0.18

* β-blocker treated as a time dependent covariate. ICD = implantable cardioverter defibrillator, ACA = aborted cardiac arrest, SCD = sudden cardiac death, HR = hazard ratio, CI = confidence interval, ms = milliseconds.

Supplemental Table 3: Evaluation of Rare *KCNE1* Variants Implicated in Type 5 Long QT Syndrome and Re-Classification of Variant Status According to ACMG Criteria

***KCNE1* Variant**		**Channel**	**gnomAD AF (%)**		***In Silico* Analysis**			**Functional**	**Documented**	**ACMG Classification**
Nucleotide	**Amino Acid**	**Location**	**OA**	**EA**	**PP2**	**SIFT**	**CADD**	**Work (Ref)**	**JLNS2 Culprit**	
21:35,821,283-35,884,669*	Whole gene deletion	N/A	-	-	-	-	-	-	-	VUS
c.12dup	Asn5Ter	N/A	-	-	-	-	-	-	Y	Pathogenic
c.20C>T	Thr7Ile	E	0.0004065	-	PrD	D	22.5	-	Y	VUS
c.23C>T	Ala8Val	E	0.01155	0.003952	B	T	4.126	-	-	Likely Benign
c.29C>T	Thr10Met	E	0.02094	0.02134	B	T	0.007	-	-	Likely Benign
c.48delG	Leu16LeufsTer46	N/A	-	-	-	-	-	-	Y	Pathogenic
c.50G>A	Trp17Ter	N/A	0.0004063	-	-	-	37	-	Y	Likely Pathogenic
c.51G>A	Trp17Ter	N/A	0.0004063	0.0008960	-	-	36	-	Y	Likely Pathogenic
c.64C>T	Gln22Ter	N/A	-	-	-	-	36	-	-	Pathogenic
c.83C>T	Ser28Leu	E	0.005414	0.007110	B	D	16.03	-	-	VUS
c.98G>T	Arg33Met	E	-	-	PoD	T	22.3	-	-	VUS
c.123G>C	Lys41Asn	E	0.0008123	-	B	T	14.01	-	-	Likely Benign
c.137A>G	Tyr46Cys	T	0.003232	-	PrD	D	26.0	-	-	VUS
c.139G>T	Val47Phe	T	-	-	PoD	D	23.3	1	Y	Likely Pathogenic
c.152_153delinsAT	Leu51His	T	-	-	-	-	-	-	Y	Likely Pathogenic
c.158T>G	Phe53Cys	T	-	-	PrD	D	25.3	-	-	VUS
c.163G>A	Gly55Ser	T	0.01218	0.003582	PoD	T	23.6	-	-	VUS
c.172_177	Thr58_Leu59	T	0.001443	0.002369	-	-	-	-	-	VUS

delACCCCTGinsCCCCCT	delinsProPro									
c.181A>G	Ile61Val	T	0.003232	0.006675	B	T	19.74	-	-	Likely Benign
c.199C>T	Arg67Cys	I	0.002844	0.001792	PrD	D	33	-	-	VUS
c.200G>A	Arg67His	I	0.005774	0.004738	PrD	D	31	-	-	VUS
c.200G>T	Arg67Leu	I	0.0004062	0.0008958	B	D	25.1	-	-	VUS
c.209A>T	Lys70Met	I	0.0004062	-	PrD	D	26.5	-	-	VUS
c.221C>T	Ser74Leu	I	0.001804	0.001580	PrD	D	25.4	2	-	VUS
c.226G>A	Asp76Asn	I	0.006856	0.01106	PoD	D	24.0	1,2	Y	Likely Pathogenic
c.238G>A	Val80Ile	I	0.005412	0.004737	B	T	13.95	-	-	Likely Benign
c.244A>G	Ile82Val	I	-	-	PrD	D	23.7	-	-	VUS
c.292C>T	Arg98Trp	I	0.002886	0.002368	PrD	D	25.2	-	-	VUS
c.293G>A	Arg98Gln	I	0.004468	0.001791	PoD	D	24.2	-	-	VUS
c.295G>C	Val99Leu	I	-	-	B	T	7.132	-	-	VUS
c.325G>A	Val109Ile	I	0.01408	0.005535	B	T	0.014	3	-	Likely Benign
c.374C>T	Thr125Met	I	0.01414	0.003976	B	T	0.004	-	-	Likely Benign

*GRCh37 Chr:position, AF = allele frequency, OA = overall, EA = European ancestry, JLNS2 = Type 2 Jervell and Lange-Nielsen Syndrome, ACMG = American College of Medical Genetics and Genomics, PP2 = PolyPhen-2, Ref = reference, N/A = not applicable, E = extracellular, T = transmembrane, I = intracellular, VUS = variant of unknown significance, Y = yes, PrD = probably damaging, D = damaging, B = benign, T = tolerated, PoD = possibly damaging.

References

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