SUPPLEMENT

Exome capture

Quality Control: DNA was extracted from peripheral blood leukocytes using Qiagen or Oragene Kits. The integrity and yield of native genomic DNA was verified by a PicoGreen assay for quantitation (Invitrogen) and run on a 0.8% Agarose gel for a qualitative QC. High-molecular weight DNA, gender determination, and fingerprint genotyping was also performed (Illumina iScan or BeadXpress) which ensures the tracking samples integrity throughout sample preparation and sequencing process.

Library Construction and Library Preparation: Approximately 3-4 µg of genomic DNA was used to generate a series of shotgun libraries construction steps including fragmentation through acoustic sonication (Covaris, INC. Woburn, MA), end-polishing and A-tailing, ligation of sequencing adaptors and PCR amplification with barcodes for multiplexing, and Solid Phase Reversible Immobilization (SPRI) bead cleanup was used for enzymatic purification throughout the library process, as well as final library size selection targeting 300-500bp fragments. Sample shotgun libraries were captured for exome enrichment using three in-solution capture targets in accordance with the manufacturer's instructions: SeqCap EZ Human Exome Library v1.0 (~32Mb, Roche/Nimblegen Madison, WI, USA), SeqCap EZ Human Exome Library v2.0 (~36.5Mb, Roche/Nimblegen Madison, WI, USA), and SureSelect Human All Exon kit v2 (~44Mb, Agilent Santa Clara, CA, USA) (8, 205, and 2 samples, respectively). Briefly, 1 µg of shotgun library is hybridized to biotinylated capture probes for 72 hours. Enriched fragments are recovered via streptavidin beads and PCR amplified.

DNA clustering, sequencing, and quality control: The concentration of each captured library was accurately determined through quantitative PCR (qPCR) according to the manufacturer's protocol (Kapa - Biosystems, Inc, Woburn, MA or Agilent Bioanalyzer, Agilent Santa Clara, CA, USA) to produce cluster

counts appropriate for the Illumina HiSeq 2000 or the Genome Analyzer II. Barcoded exome libraries were pooled using liquid handling robotics prior to clustering (Illumina cBot) and loading. Cluster amplification of denatured templates was performed according to the manufacturer's protocol (Illumina Inc, San Diego, CA). Massively parallel sequencing-by-synthesis with fluorescently labeled, reversibly terminating nucleotides was carried out on the HiSeq 2000 using paired-end 50-100-base runs or the Genome Analyzer II using paired/single-end-76 base runs. For all samples, the sequencing data was evaluated and assessed against quality metrics including (1) library complexity; (2) capture efficiency; (3) coverage distribution; (4) capture uniformity; (6) Transition (Ti)/Transversion (Tv) ratio; (7) distribution of known and novel variants relative to dbSNP (8) fingerprint concordance; (9) sample homozygosity and heterozygosity and; (10) sample contamination validation.

Read Mapping and variant calling: All samples were processed in real-time base-calls (RTA 1.7 software, converted to qseq.txt files, and aligned to the human reference (hg19) using the Burrows-Wheeler Aligner (BWA) (0.6.9) after sequence reads were trimmed to 50bp.(1) Duplicates were flagged and removed using the Picard suite of tools. Post processing of the aligned data was done using the (GATK v1.6-19) including local realignment and base quality recalibration.(2) Variant detection was done using the UnifiedGenotyper from GATK and called collectively and formatted to the variant call format (VCF) generating a multisample VCF file. Sites that specified filters were flagged using the VariantFiltrationWalker to mark sites of lower quality in agreement with BestPractices v.4 and Qual < 50, QD < 5, and AB > 0.75.(2) Genomic positions, the reference, and alternate allele were in all instances determined on the forward strand. conservation for single base variants and prediction of functional effects was assessed using PhastCons, GERP, Grantham scores, SIFT, and PolyPhen2 using the SeattleSeq Genomic Variation Server http://snp.gs.washington.edu/SeattleSeqAnnotation137/).

Whole Exome Sequencing

DNA was extracted from peripheral blood leukocytes using Qiagen or Oragene Kits. Sequencing was performed on HiSeq2000 or Genome Analyzer II (Illumina, San Diego, CA, USA) platform after in-solution enrichment of exonic and adjacent intronic sequences using SeqCap EZ Human Exome Library v1.0 (~32Mb, Roche/NimbleGen Madison, WI, USA), SeqCap EZ Human Exome Library v2.0 (~36.5Mb, Roche/NimbleGen Madison, WI, USA), or SureSelect Human All Exon kit v2 (~44Mb, Agilent Santa Clara, CA, USA). The ESP controls had been sequenced previously at University of Washington using the SeqCap EZ Human Exome Library v2.0 (~36.5 Mb, Roche/NimbleGen Madison, WI, USA). To eliminate potential issues relating to batch effects, all samples were realigned, recalibrated, and recalled together to one shared target after initial sequencing. In addition, we implemented the following set of filters to further ensure the validity of any variant: we only included variants that were covered at 20x, had a genotype quality >3, and required that a given variant only had missing information for <15 individuals (i.e. the variant was called in >95% of individuals). Overall, all samples had an on target transition/transversion ratio ≥3.0 and 89% of all samples had >90% of the target covered at ≥10x. Quality metrics for 728 exomes (diLQTS cases, drug exposed controls, and ESP controls) are listed in Supplemental Table 1. SNP and SKAT based power calculations as a function of MAF are depicted in Supplemental Figure 3.A and B, respectively.

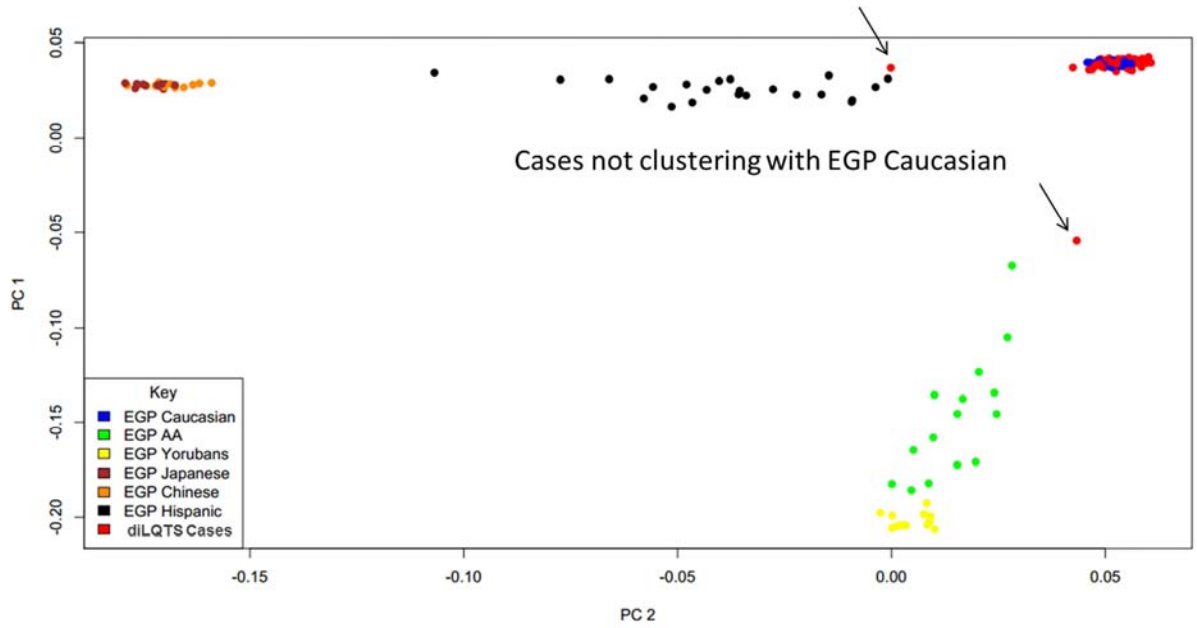
Ancestry confirmation

Among the diLQTS cases we performed PCA to ensure a homogenous study population and limit population stratification. Overall, we confirmed that 65/67 of the self-reported Caucasians were of European American ancestry, using the Environmental Genome Project (EGP) as reference (i.e. we included the principal components of the ethnically well characterized EGP samples (n=95) in our PCA analyses to ensure that diLQTS patients also clustered together with the EGP samples of European American ancestry) (Supplemental Figure 1) (3). Similarly, we confirmed that the drug exposed controls were all of European American ancestry and clustered in an unbiased way with the diLQTS cases (Supplemental Figure 2)

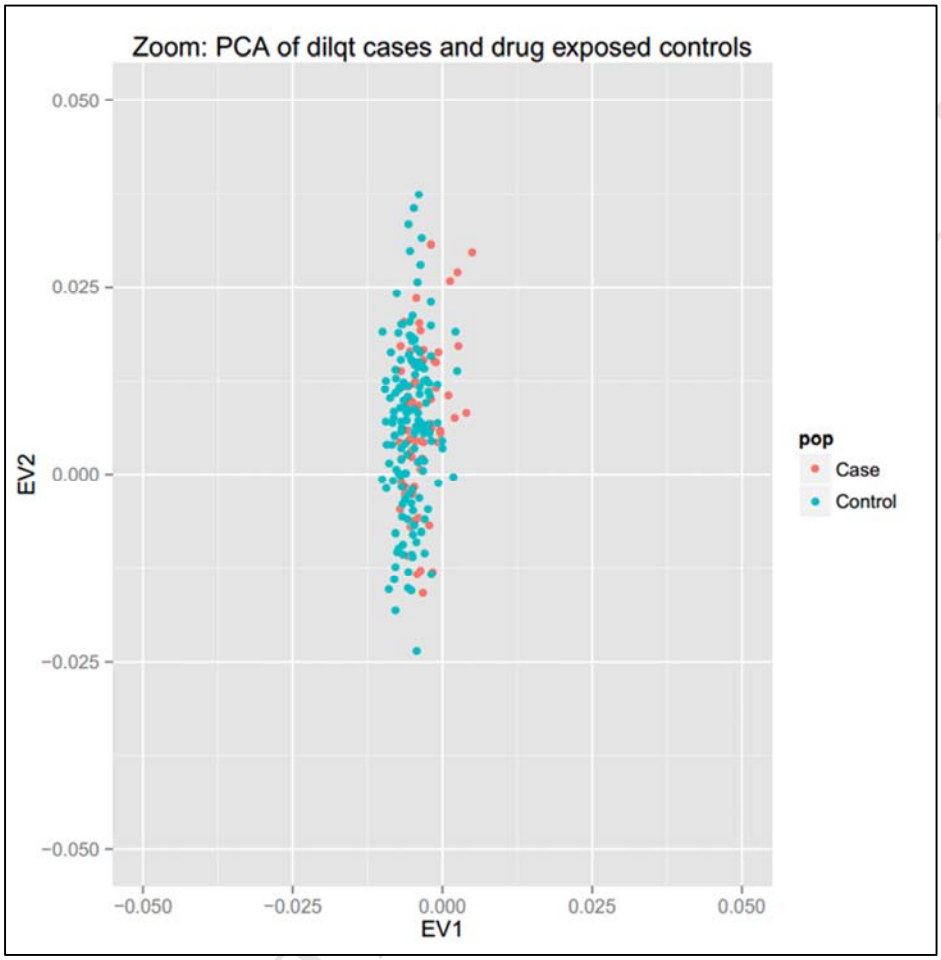
Association testing

In brief, the Variable Threshold (VT) test (one-sided) (4) and the sequence kernel association test (SKAT) (two-sided)(5) aggregate rare variants while excluding (VT) or strongly down-weighing (SKAT) variants with an observed minor allele frequency (MAF) greater than a prespecified threshold, as the effect size of common variants is generally small (6). In order to improve the signal-to-noise ratio and our ability to detect functional variation, we focused our analyses on AAC variants (missense, non-synonymous, and frame-shift) only. We also performed sub-group analyses on subjects exposed to sotalol or dofetilide and in cases who developed TdP.

Supplemental Figure 1: First and second principal components for diLQTS cases (n=67) with Environmental Genome Project (EGP) anchors. The arrows indicate the 2 out of 67 original cases eliminated from analysis.



Supplemental Figure 2: First and second principal components for cases (n=65) and drug-exposed controls (n=148)



Supplemental Figure 3: Power Calculations

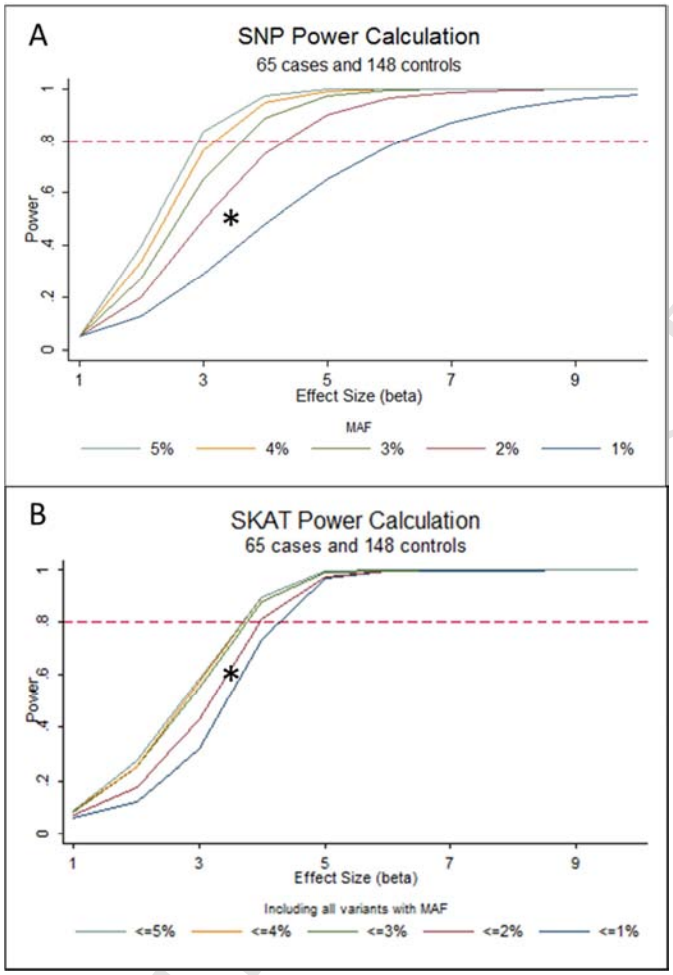
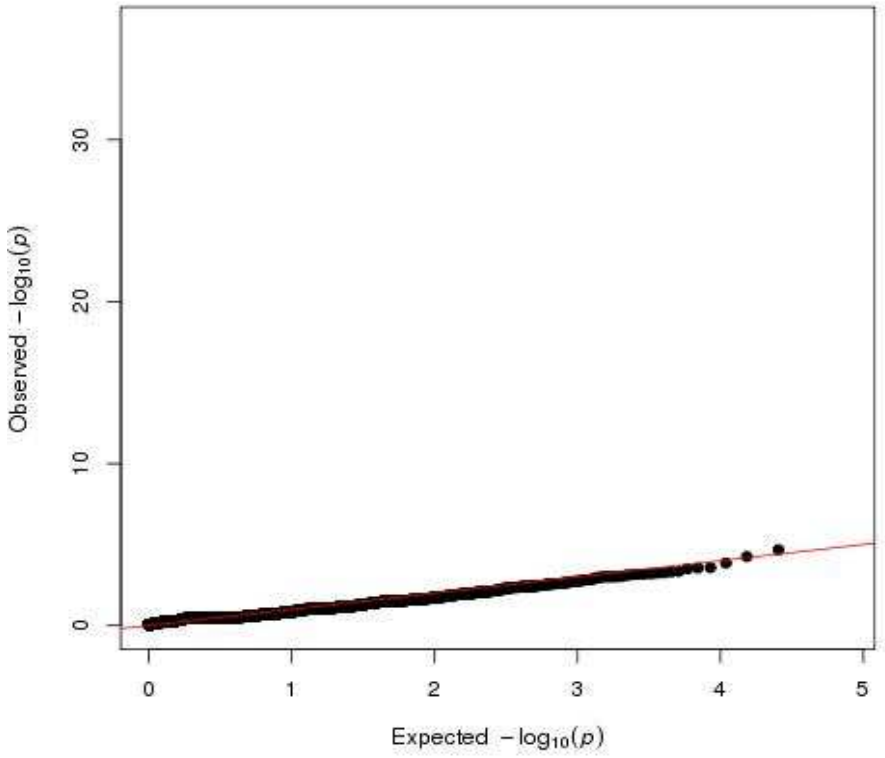


Figure Legend: Dashed line represents a power of 80%; nominal alpha=0.05; A: Power calculation is based on a single nucleotide polymorphism (SNP) in a log additive model, Bonferroni corrected $P<6.39x10^{-7}$. Based on the reported minor allele frequency [MAF] among cases and controls and the effect size derived from the unadjusted single nucleotide polymorphism analysis of [SNP] D85N in *KCNE1* (beta=3.4) we have indicated approximately how much power we have in the present study (*); B: Sequence Kernel Association Test (SKAT) power analysis using simulated data (500 simulations) assuming a causal variant prevalence of 30% and a protective variant prevalence of 20%, Bonferroni corrected $p<3.39x10^{-6}$. Assuming all SNPs have similar effect sizes as the D85N SNP in *KCNE1* (in unadjusted models) we have indicated the approximate power of the present study (*).

Supplemental Figure 4: QQ plot of the single nucleotide polymorphisms based association analyses of AAC variants



Supplemental Figure 5: Regulatory activity according to ENCODE in vicinity of two rare ACN9 variants

Figure Legend: The Encyclopedia of DNA Elements (ENCODE); source: http://genome.ucsc.edu/, http://regulomedb.org

Supplemental Table 1: Quality metrics for 728 exomes

	diLQTS Cases n=65	Drug Exposed Controls n=148	ESP controls n=515
Total reads	238,235,320 (± 102,658,621)	136,556,659 (±20,072,371)	157,379,197 (±57,927,330)
Reads mapped to hg19	212,270,857 (±87,890,868)	116,504,083 (±16,372,339)	129,688,214 (±49,119,489)
Reads mapped to the target	123,990,370 (±42,284,959)	72,354,298 (±10,463,282)	103,437,992 (±47,597,382)
On target transition/transversion	3.26 (±0.05)	3.23 (±0.03)	3.13 (±0.06)
% sites covered ≥1x	96.5 (±2.7)	97.9 (±0.3)	97.8 (±0.9)
% sites covered ≥5x	93.0 (±5.6)	95 (±3.4)	94.9 (±1.4)
% sites covered ≥10x	90.0 (±7.4)	93.7 (±1.2)	92.0 (±2.1)
% sites covered ≥20x	84 (±9.7)	88 (±2.5)	86.2 (±3.4)

Means and ±standard deviation (±SD) are presented; diLQTS, drug induced long QT; ESP, exome sequencing project

Supplemental Table 2: 20 High priority genes

GENE	Channel/Protein	CLQTS	SQTS	Brs	CPVT	Ref
CAV3	caveolin 3	1				Balijepalli RC, Kamp TJ. Caveolae, ion channels and cardiac arrhythmias. *Prog Biophys Mol Biol*. 2008;98:149-160 Beetz N, Hein L, Meszaros J, Gilsbach R, Barreto F, Meissner M, Hoppe UC, Schwartz A, Herzig S, Matthes J. Transgenic simulation of human heart failure-like L-type Ca2+-channels: implications for fibrosis and heart rate in mice. *Cardiovasc Res*. 2009;84:396-406
CACNB2	calcium channel, voltage-dependent, beta 2 subunit			1		Hedley PL, Jorgensen P, Schlamowitz S, Moolman-Smook J, Kanters JK, Corfield VA, Christiansen M. The genetic basis of Brugada syndrome: a mutation update. *Hum Mutat*. 2009;30:1256-1266
KCNE3	potassium voltage-gated channel, Isk-related family, member 3; MiRP2			1		Foell JD, Balijepalli RC, Delisle BP, Yunker AM, Robia SL, Walker JW, McEnery MW, January CT, Kamp TJ. Molecular heterogeneity of calcium channel beta-subunits in canine and human heart: evidence for differential subcellular localization. *Physiol Genomics*. 2004;17:183-200 Hedley PL, Jorgensen P, Schlamowitz S, Moolman-Smook J, Kanters JK, Corfield VA, Christiansen M. The genetic basis of Brugada syndrome: a mutation update. *Hum Mutat*. 2009;30:1256-1266 Ohno S, Toyoda F, Zankov DP, Yoshida H, Makiyama T, Tsuji K, Honda T, Obayashi K, Ueyama H, Shimizu W, Miyamoto Y, Kamakura S, Matsuura H, Kita T, Horie M. Novel KCNE3 mutation reduces repolarizing potassium current and associated with long QT syndrome. *Hum Mutat*. 2009;30:557-563
KCNJ5	potassium inwardly-rectifying channel, subfamily J, member 5	1				Holmegard HN, Theilade J, Benn M, Duno M, Haunso S, Svendsen JH. Genetic variation in the inwardly rectifying K channel subunits KCNJ3 (GIRK1) and KCNJ5 (GIRK4) in patients with sinus node dysfunction. *Cardiology*. 2010;115:176-181
CACNA1C	calcium channel, voltage-dependent, L type, alpha 1C subunit (CaV1.2)	1		1		Hedley PL, Jorgensen P, Schlamowitz S, Moolman-Smook J, Kanters JK, Corfield VA, Christiansen M. The genetic basis of Brugada syndrome: a mutation update. *Hum Mutat*. 2009;30:1256-1266
GPD1L	Glyerol-3-phosphate dehydrogenase 1-like protein			1		Hedley PL, Jorgensen P, Schlamowitz S, Moolman-Smook J, Kanters JK, Corfield VA, Christiansen M. The genetic basis of Brugada syndrome: a mutation update. *Hum Mutat*. 2009;30:1256-1266
KCNE2	potassium voltage-gated channel, Isk-related family, member 2; MiRP1	1				Jiang M, Xu X, Wang Y, Toyoda F, Liu XS, Zhang M, Robinson RB, Tseng GN. Dynamic partnership between KCNQ1 and KCNE1 and influence on cardiac IKs current amplitude by KCNE2. *J Biol Chem*. 2009;284:16452-16462
SCN1B	sodium channel, voltage-gated, type 1, beta			1		Watanabe H, Koopmann TT, Le Scouarnec S, Yang T, Ingram CR, Schott JJ, Demolombe S, Probst V, Anselme F, Escande D, Wiesfeld AC, Pfeufer A, Kaab S, Wichmann HE, Hasdemir C, Aizawa Y, Wilde AA, Roden DM, Bezzina CR. Sodium channel beta1 subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans. *J Clin Invest*. 2008;118:2260-2268
CASQ2	calsequestrin 2 (cardiac muscle)				1	Knollmann BC. New roles of calsequestrin and triadin in cardiac muscle. *J Physiol*. 2009;587:3081-3087
SCN4B	sodium channel, voltage-gated, type IV, beta	1				Medeiros-Domingo A, Kaku T, Tester DJ, Iturralde-Torres P, Itty A, Ye B, Valdivia C, Ueda K, Canizales-Quinteros S, Tusie-Luna MT, Makielski JC, Ackerman MJ. SCN4B-encoded sodium channel beta4 subunit in congenital long-QT syndrome. *Circulation*. 2007;116:134-142.
RYR2	ryanodine receptor 2 (cardiac)				1	Yano M, Yamamoto T, Ikeda Y, Matsuzaki M. Mechanisms of Disease: ryanodine receptor defects in heart failure and fatal arrhythmia. *Nat Clin Pract Cardiovasc Med*. 2006;3:43-52
ANK2	Ankyrin 2	1				Mohler PJ, Schott JJ, Gramolini AO, Dilly KW, Guatimosim S, duBell WH, Song LS, Haurogne K, Kyndt F, Ali ME, Rogers TB, Lederer WJ, Escande D, Le Marec H, Bennett V. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. *Nature*. 2003;421:634-639
KCNH2	potassium voltage-gated channel, subfamily H (eag-related), member 2; hERG; Kv11.1	1	1			Newton-Cheh C, Eijgelsheim M, Rice KM, de Bakker PI, Yin X, Estrada K, Bis JC, Marciante K, Rivadeneira F, Noseworthy PA, Sotoodehnia N, Smith NL, Rotter JI, Kors JA, Witteman JC, Hofman A, Heckbert SR, O'Donnell CJ, Uitterlinden AG, Psaty BM, Lumley T, Larson MG, Stricker BH. Common variants at ten loci influence QT interval duration in the QTGEN Study. *Nat Genet*. 2009;41:399-406);

					Pfeufer A, Sanna S, Arking DE, Muller M, Gateva V, Fuchsberger C, Ehret GB, Orru M, Pattaro C, Kottgen A, Perz S, Usala G, Barbalic M, Li M, Putz B, Scuteri A, Prineas RJ, Sinner MF, Gieger C, Najjar SS, Kao WH, Muhleisen TW, Dei M, Happle C, Mohlenkamp S, Crisponi L, Erbel R, Jockel KH, Naitza S, Steinbeck G, Marroni F, Hicks AA, Lakatta E, Muller-Myhsok B, Pramstaller PP, Wichmann HE, Schlessinger D, Boerwinkle E, Meitinger T, Uda M, Coresh J, Kaab S, Abecasis GR, Chakravarti A. Common variants at ten loci modulate the QT interval duration in the QTSCD Study. *Nat Genet*. 2009;41:407-414 Newton-Cheh C, Eijgelsheim M, Rice KM, de Bakker PI, Yin X, Estrada K, Bis JC, Marciante K, Rivadeneira F, Noseworthy PA, Sotoodehnia N, Smith NL, Rotter JI, Kors JA, Witteman JC, Hofman A, Heckbert SR, O'Donnell CJ, Uitterlinden AG, Psaty BM, Lumley T, Larson MG, Stricker BH. Common variants at ten loci influence QT interval duration in the QTGEN Study. *Nat Genet*. 2009;41:399-406.
KCNQ1	potassium voltage-gated channel, KQT-like subfamily, member 1	1	1		Pfeufer A, Sanna S, Arking DE, Muller M, Gateva V, Fuchsberger C, Ehret GB, Orru M, Pattaro C, Kottgen A, Perz S, Usala G, Barbalic M, Li M, Putz B, Scuteri A, Prineas RJ, Sinner MF, Gieger C, Najjar SS, Kao WH, Muhleisen TW, Dei M, Happle C, Mohlenkamp S, Crisponi L, Erbel R, Jockel KH, Naitza S, Steinbeck G, Marroni F, Hicks AA, Lakatta E, Muller-Myhsok B, Pramstaller PP, Wichmann HE, Schlessinger D, Boerwinkle E, Meitinger T, Uda M, Coresh J, Kaab S, Abecasis GR, Chakravarti A. Common variants at ten loci modulate the QT interval duration in the QTSCD Study. *Nat Genet*. 2009;41:407-414
SCN5A	Na(V)1.5, sodium channel, voltage-gated, type V, alpha subunit	1		1	Newton-Cheh C, Eijgelsheim M, Rice KM, de Bakker PI, Yin X, Estrada K, Bis JC, Marciante K, Rivadeneira F, Noseworthy PA, Sotoodehnia N, Smith NL, Rotter JI, Kors JA, Witteman JC, Hofman A, Heckbert SR, O'Donnell CJ, Uitterlinden AG, Psaty BM, Lumley T, Larson MG, Stricker BH. Common variants at ten loci influence QT interval duration in the QTGEN Study. *Nat Genet*. 2009;41:399-406 Pfeufer A, Sanna S, Arking DE, Muller M, Gateva V, Fuchsberger C, Ehret GB, Orru M, Pattaro C, Kottgen A, Perz S, Usala G, Barbalic M, Li M, Putz B, Scuteri A, Prineas RJ, Sinner MF, Gieger C, Najjar SS, Kao WH, Muhleisen TW, Dei M, Happle C, Mohlenkamp S, Crisponi L, Erbel R, Jockel KH, Naitza S, Steinbeck G, Marroni F, Hicks AA, Lakatta E, Muller-Myhsok B, Pramstaller PP, Wichmann HE, Schlessinger D, Boerwinkle E, Meitinger T, Uda M, Coresh J, Kaab S, Abecasis GR, Chakravarti A. Common variants at ten loci modulate the QT interval duration in the QTSCD Study. *Nat Genet*. 2009;41:407-414
KCNE1	Potassium voltage-gated channel, Isk-related family, member 1; minK peptide	1			Newton-Cheh C, Eijgelsheim M, Rice KM, de Bakker PI, Yin X, Estrada K, Bis JC, Marciante K, Rivadeneira F, Noseworthy PA, Sotoodehnia N, Smith NL, Rotter JI, Kors JA, Witteman JC, Hofman A, Heckbert SR, O'Donnell CJ, Uitterlinden AG, Psaty BM, Lumley T, Larson MG, Stricker BH. Common variants at ten loci influence QT interval duration in the QTGEN Study. *Nat Genet*. 2009;41:399-406 Holm H, Gudbjartsson DF, Arnar DO, Thorleifsson G, Thorgeirsson G, Stefansdottir H, Gudjonsson SA, Jonasdottir A, Mathiesen EB, Njolstad I, Nyrnes A, Wilsgaard T, Hald EM, Hveem K, Stoltenberg C, Lochen ML, Kong A, Thorsteinsdottir U, Stefansson K. Several common variants modulate heart rate, PR interval and QRS duration. *Nat Genet*. 2010;42:117-122
KCNJ2	potassium inwardly-rectifying channel, subfamily J, member 2	1	1		Pfeufer A, Sanna S, Arking DE, Muller M, Gateva V, Fuchsberger C, Ehret GB, Orru M, Pattaro C, Kottgen A, Perz S, Usala G, Barbalic M, Li M, Putz B, Scuteri A, Prineas RJ, Sinner MF, Gieger C, Najjar SS, Kao WH, Muhleisen TW, Dei M, Happle C, Mohlenkamp S, Crisponi L, Erbel R, Jockel KH, Naitza S, Steinbeck G, Marroni F, Hicks AA, Lakatta E, Muller-Myhsok B, Pramstaller PP, Wichmann HE, Schlessinger D, Boerwinkle E, Meitinger T, Uda M, Coresh J, Kaab S, Abecasis GR, Chakravarti A. Common variants at ten loci modulate the QT interval duration in the QTSCD Study. *Nat Genet*. 2009;41:407-414 Hattori T, Makiyama T, Akao M, Ehara E, Ohno S, Iguchi M, Nishio Y, Sasaki K, Itoh H, Yokode M, Kita T,

AKAP9	Yotiao	1		Horie M, Kimura T. A novel gain-of-function KCNJ2 mutation associated with short-QT syndrome impairs inward rectification of Kir2.1 currents. *Cardiovasc Res*. 2012;93:666-673 Chen L, Marquardt ML, Tester DJ, Sampson KJ, Ackerman MJ, Kass RS. Mutation of an A-kinase-anchoring protein causes long-QT syndrome. *Proc Natl Acad Sci U S A*. 2007;104:20990-20995
SCN3B	sodium channel, voltage-gated, type III, beta		1	Hakim P, Gurung IS, Pedersen TH, Thresher R, Brice N, Lawrence J, Grace AA, Huang CL. Scn3b knockout mice exhibit abnormal ventricular electrophysiological properties. *Prog Biophys Mol Biol*. 2008;98:251-266
SNTA1	syntrophin, alpha 1	1		Wu G, Ai T, Kim JJ, Mohapatra B, Xi Y, Li Z, Abbasi S, Purevjav E, Samani K, Ackerman MJ, Qi M, Moss AJ, Shimizu W, Towbin JA, Cheng J, Vatta M. alpha-1-syntrophin mutation and the long-QT syndrome: a disease of sodium channel disruption. *Circ Arrhythm Electrophysiol*. 2008;1:193-201

congenital long QT syndrome ,CLQTS; short QT syndrome, SQTS; Brugada syndrome, BrS; catecholaminergic polymorphic ventricular tachycardia, CPVT; arrhythmogenic right ventricular dysplasia/cardiomyopathy, ARVD/C

Supplemental Table 3: Unadjusted Single Marker Association Analysis of Amino Acid Coding Variants (top 40 associations shown)

VAR	REF	ALT	OR	P
chr16:28607196	G	A	3.51017	0.000106797
chrY:21154466	T	A	3.96503	0.000119661
chr19:44352666	G	A	2.15699	0.000876645
chr1:95330372	G	A	0.421592	0.000888664
chr19:56953963	G	A	2.08238	0.000926153
chr6:150239484	C	T	9.0566	0.00114638
chr17:2202323	T	C	5.95304	0.00126189
chr7:100695138	G	A	3	0.00137488
chr3:81698130	T	C	2.1591	0.00139457
chr22:32589090	C	T	2.54017	0.00140638
chr2:24387178	G	GC	0.166942	0.00143699
chr9:132374678	T	C	3.80582	0.00167525
chr17:18565350	G	C	2.04587	0.00173651
chr19:56953585	T	C	0.514924	0.0022612
chr19:39914748	G	A	1.94579	0.002301
chr12:50537815	A	G	0.5041	0.0024567
chr9:100388197	C	T	2.16879	0.00253366
chr7:2646796	G	A	2.62416	0.00253693
chr18:33557466	A	G	2.17352	0.0026022
chrX:2833605	C	T	0.383838	0.00273281
chr4:120241902	T	C	2.24297	0.00300863
chr1:152283862	G	C	0.349664	0.00315216
chr5:156479509	A	G	0.433252	0.00316589
chr1:182496829	A	G	0.477997	0.00336919
chr7:96747192	T	C	5.94141	0.00340747
chr6:74497009	A	G	1.91018	0.00343721
chr6:74497152	G	A	1.91018	0.00343721
chr21:42817930	G	A	0.520083	0.00347427
chr17:3324810	A	G	2.19381	0.00348741
chr3:19574945	A	G	0.290497	0.00360426
chr1:152192631	C	T	2.78082	0.00366986
chr1:152193851	C	T	2.78082	0.00366986
chr7:116146074	C	G	2.14597	0.00381398
chr7:99032517	G	A	3.70656	0.00402111
chr6:74493432	A	C	1.91645	0.00415683
chr3:48628014	G	A	2.4046	0.00431782
chr18:23866185	G	C	2.46532	0.00437971
chr19:6921868	G	A	2.33433	0.00443082
chr14:24458162	G	C	1.99838	0.00451111
chr6:44310854	G	A	1.88772	0.00484897

Supplemental Table 4: Adjusted (age, sex, PC1, PC2) Single Marker Association Analysis of Amino Acid Coding Variants (top 40 associations shown)

VAR	REF	ALT	OR	P
chr6:150239484	C	T	18,1709	0.000105436
chr1:95330372	G	A	0,350351	0.000443721
chr19:56953963	G	A	2,4011	0.000596752
chr19:44352666	G	A	2,43525	0.000648654
chr12:50537815	A	G	0,41656	0.000653268
chr6:44310854	G	A	2,36373	0.0011631
chr7:96747192	T	C	10,0409	0.00116564
chr2:188343497	T	C	0,395691	0.00118595
chr2:24387178	G	GC	0,113015	0.0012937
chr2:54858253	G	T	24,5248	0.0014664
chr18:23866185	G	C	2,9824	0.00160308
chr10:100183570	G	C	4,04521	0.00160939
chr10:18270341	A	G	25,0109	0.00161702
chr18:33557466	A	G	2,50801	0.00161838
chr7:7561580	T	C	3,55193	0.00167564
chr1:71536574	G	C	0,188113	0.00183705
chr6:155153307	G	A	8,18871	0.00196063
chr3:49138810	T	C	4,11894	0.00235651
chr3:40231383	C	T	4,04926	0.00246135
chr14:64469828	C	T	3,67347	0.00262524
chr19:56953585	T	C	0,477608	0.00263689
chr10:129899922	T	C	8,92982	0.00292462
chr10:129903094	G	T	8,92982	0.00292462
chr4:120241902	T	C	2,44246	0.00304786
chr3:32031615	A	C	2,55056	0.00311311
chr3:32031622	T	C	2,55056	0.00311311
chr3:32031643	A	G	2,55056	0.00311311
chr14:64604595	G	A	4,09292	0.00311635
chr19:21477431	T	C	0,497901	0.00326929
chr9:123932039	C	A	31,4565	0.00372184
chr14:96871104	G	A	0,401887	0.00386664
chr18:21511034	C	A	2,27632	0.00387669
chr3:81698130	T	C	2,14124	0.00390468
chr17:2202323	T	C	6,55127	0.00392808
chr7:107217020	G	A	4,23551	0.00415154
chr22:32589090	C	T	2,5181	0.00422525
chr3:19574945	A	G	0,263914	0.00424109
chr12:113565933	G	A	4,12793	0.00430506
chr19:36168914	T	C	2,25673	0.00438453
chr6:74493432	A	C	2,09441	0.00438584

Supplemental Table 5: Genes with significant associations between diLQT cases and drug exposed controls or ESP controls according to aggregated rare variant analysis

Gene	VT p-values		SKAT p-values	
	diLQTS cases (n=65) vs. drug-exposed controls (n=148)	diLQTS cases (n=65) vs. ESP Controls (n=515)	diLQTS cases (n=65) vs. drug-exposed controls (n=148)	diLQTS cases (n=65) vs. ESP Controls (n=515)
KCNE1	0.0005	0.0033	0.0002	0.005
ACN9	0.0005	0.0006	0.0008	8.96E-05
ZNF667	8.4E-05	0.0407	0.5050	0.9900
STOX1	0.01	0.01	0.0006	0.211
REPL2	0.03	0.015	0.0002	0.0008
RAET1G	0.0022	0.4500	0.0002	0.0155
CD24	0.3333	0.5385	0.0001	0.0016

Genes that reached a significance level of $p<0.001$ comparing the diLQT cases vs. the drug-exposed controls and replicated comparing the or diLQTS cases vs. the ESP controls ($p<0.05$) using variable threshold (VT) or sequence kernel association tests (SKAT)

diLQTS, drug induced long QT syndrome; ESP, exome sequencing project

Supplemental Table 6: *In-silico* Assessment of Predicted Rare Variant Function in *KCNE1* and *ACN9*

CHR	POS	REF	ALT	Function	Gene	rsID	Amino Acids	Protein Position	PolyPhen2	SIFT	Grantham Score	PhastCons	GERP	Gene	Alleles ESP4300 EA
7	96747192	T	C	missense	*ACN9*	62624461	PHE,LEU	F53L	possibly-damaging	DAMAGING	22	1.000	4.970	ACN9	T=8386/ C=214
7	96810397	C	T	missense	*ACN9*	34146273	THR,ILE	T83I	benign	TOLERATED	89	0.078	0.675	ACN9	C=8600 / T=0
21	35821680	C	T	missense	*KCNE1*	1805128	ASP,ASN	D85N	possibly-damaging	DAMAGING	23	0.011	4.240	KCNE1	C=8485 / T=105
21	35821707	C	T	missense	*KCNE1*	74315445	ASP,ASN	D76N	probably-damaging	TOLERATED	23	0.892	5.160	KCNE1	C=8599 / T=1
21	35821640	C	T	missense	*KCNE1*	150454912	ARG,GLN	R98Q	probably-damaging	DAMAGING	43	0.904	4.940	KCNE1	C=8599 / T=1

ESP4300 EA, exome sequencing project of 4300 European Americans from the ESP6500

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