# Supplemental Material

**Data S1.**

**DNA sequencing**

Genomic DNA was extracted from EDTA blood using Agencourt Genfind v2 (Beckman Coulter). A panel targeting the 17 genes *AKAP9* (NM_005751.4), *ANK2* (NM_1148.4), *CACNA1C* (NM_000719.6), *CALM1* (NM_006888.4), *CALM2* (NM_001743.4), *CALM3* (NM_005184.2), *CAV3* (NM_033337.2), *KCNE1* (NM_000219.5), *KCNE2* (NM_172201.1), *KCNH2* (NM_000238.3), *KCNJ2* (NM_000891.2), *KCNJ5* (NM_000890.3), *KCNQ1* (NM_000218.2), *SCN4B* (NM_174934.3), *SCN5A* (NM_198056.2), *SNTA1* (NM_003098.2) and *TRDN* (NM_006073.3) was designed using DesignStudio (Illumina). NGS sample preparation and enrichment was performed using Illumina's Nextera Rapid Capture Custom Enrichment kit according to the manufacturer's recommendation. Samples were sequenced 2x150 bp on a NextSeq 500 (Illumina).

All pathogenic and likely pathogenic variants were confirmed with Sanger sequencing on an ABI3130, using a validated and accredited method in accordance with ISO15189.

**Bioinformatics pipeline**

The reads were mapped to the reference sequence (GRCh37/hg19) by BWA (Burrows-Wheeler Aligner) [21]. GATK (Genome Analysis Toolkit) was used for base quality score recalibration, indel realignment, duplicate removal and SNP and INDEL discovery [22-24]. Mean target coverage was 876X, and on average 97 % of all targeted bases had coverage greater than 20X. Variants were annotated by Annovar [25]. Filtus software was used for bioinformatic filtering [26].

**RNA-analyses**

PAXgene Blood RNA tubes were used for collection of blood samples for RNA analyses. Total RNA was extracted with PAXgene Blood RNA Kit (Qiagen). RT-PCR was performed

with OneStep RT-PCR Kit (Qiagen). Amplicons were run on 1.5 % agarose gels, DNA was extracted from individual bands using QIAquick Gel Extraction Kit (Qiagen) and Sanger sequenced on an ABI3130 (Thermo Fisher Scientific).

**Table S1. Number of drugs from CredibleMeds QTdrugs lists at time of ECG 1 and ECG 2 for 31 patients with a pathogenic or likely pathogenic variant.**

| | ECG1 | ECG2 |
|---|---|---|
| Drugs with known risk TdP | Sotalol (n=1)<br>Amiodarone (n=1)<br>Flecainide (n=1)<br>Citalopram (n=1) | Amiodarone (n=1)<br>Flecainide (n=1)<br>Citalopram (n=1) |
| Drugs with possible risk TdP | Tamoxifen (n=1)<br>Lithium (n=1) | Lithium (n=1) |
| Drugs with conditional risk TdP | Hydrochlorothiazide (n=4)<br>Furosemide (n=3)<br>Solifenacin (n=1)<br>Sertraline (n=1)<br>Pantoprazole (n=2) | Hydrochlorothiazide (n=4)<br>Furosemide (n=1)<br>Pantoprazole (n=3)<br>Solifenacin (n=1)<br>Sertraline (n=1)<br>Paroxetine (n=1) |
| Drugs with special risk for LQTS patients | Salbutamol (n=1)<br>Salmeterol (n=1)<br>Formeterol (n=1) | Salmeterol (n=1)<br>Formeterol (n=1) |

ECG=Electrocardiogram; TdP=torsades de pointes; VUS= variants of uncertain significance

**Table S2. Variants of uncertain significance.**

| No. | Gene | cDNA change | Protein change | gnomAD | References | SampleID | Comments |
|---|---|---|---|---|---|---|---|
| 1 | *AKAP9* | c.815C>G | p.(Thr272Ser) | - | - | LQT0232 | c.814A>G p.(Thr272Ala) has one allele in gnomAD (1/245900) |
| 2 | *AKAP9* | c.974del | p.(Gln325Argfs*10) | - | - | LQT0082 | Loss-of-function in *AKAP9* has not previously been reported to cause LQT. |
| 3 | *AKAP9* | c.4604C>G | p.(Pro1535Arg) | 4/107712 NFE | - | LQT0376 | - |
| 4 | *AKAP9* | c.5084T>C | p.(Val1695Ala) | 1/17362 AFR | - | LQT0175 | Macaque has alanine in this position. Predicted benign. |
| 5 | *AKAP9* | c.10748C>T | p.(Ser3583Leu) | 2/112130 NFE | - | LQT0246 | 1/492 NOR alleles |
| 6 | *ANK2* | c.158G>C | p.(Gly53Ala) | 2/126490 NFE | - | LQT0171* | - |
| 7 | *ANK2* | c.2890A>G | p.(Ile964Val) | 4/125206 NFE | - | LQT0130 | Predicted benign |
| 8 | *ANK2* | c.3584G>A | p.(Gly1195Asp) | - | - | LQT0037 | - |
| 9 | *ANK2* | c.4147G>C | p.(Val1383Leu) | - | - | LQT0371 | 2/1600 alleles in Telemark inhouse database. c.4147G>A p.(Val1383Ile) and c.4147G>T p.(Val1383Phe) each has 1/245990 alleles in gnomAD |
| 10 | *ANK2* | c.4952C>A | p.(Pro1651His) | 2/245854 ALL | - | LQT0009 | Predicted benign |
| 11 | *ANK2* | c.5962A>C | p.(Met1988Leu) | - | - | LQT0442 | - |
| 12 | *CACNA1C* | c.2078C>T | p.(Pro693Leu) | - | - | LQT0078<br>LQT0482 | - |
| 13 | *CACNA1C* | c.2437G>A | p.(Gly813Arg) | 4/71678 NFE | - | LQT0118<br>LQT0143 | Highly conserved glycine. Likely benign in ClinVar |
| 14 | *CACNA1C* | c.2444C>A | p.(Ser815Tyr) | - | - | LQT0120 | - |
| 15 | *CACNA1C* | c.2654C>G | p.(Ser885Cys) | - | - | LQT0327 | Predicted benign |
| 16 | *CACNA1C* | c.2954G>T | p.(Gly985Val) | - | - | LQT0105 | - |
| 17 | *CACNA1C* | c.3080G>T | p.(Arg1027Leu) | - | - | LQT0132* | Predicted likely pathogenic. c.3079C>T p.(Arg1027Trp) has 2/246242 alleles in gnomAD |
| 18 | *CACNA1C* | c.4043C>T | p.(Thr1348Met) | 1/17240 EA | - | LQT0302 | - |
| 19 | *CACNA1C* | c.4819C>T | p.(Pro1607Ser) | 3/70458 NFE | 1 | LQT0235<br>LQT0329<br>LQT0430* | Predicted likely pathogenic. Published by Lieve et al. as pathogenic mutation in one patient [1]. |
| 20 | *CACNA1C* | c.5657G>T | p.(Gly1886Val) | - | - | LQT0471 | 7/31786 alleles in CentoMD (unclassified). 1/3930 DAN. G>A |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | p.(Gly1886Asp) in 2/30778 SA, G>C<br>p.(Gly1886Ala) in 1/111406 NFE |
| 21 | *CACNA1C* | c.6235G>A | p.(Asp2079Asn) | 7/98762 NFE | - | LQT0228<br>LQT0263 | - |
| 22 | *CALM1* | c.14T>C | p.(Leu5Pro) | - | - | LQT0233 | Reported pathogenic mutations in *CALM1* are C-terminal whereas p.(Leu5Pro) is N-terminal. |
| 23 | *KCNH2* | c.889C>T | p.(Pro297Ser) | 4/14522 NFE | 2-4 | LQT0161<br>LQT0199* | Found in one LQT case by Kapa et al.[2] and in one young sudden unexplained death case by Winkel et al.[3]. Reported as potential false positive by Giudicessi et al. [4]. This is a poorly covered region in exomes. |
| 24 | *KCNH2* | c.2653C>T | p.(Arg885Cys) | 10/25116 FIN | 5-7 | LQT0162 | 2/15875 alleles in CentoMD (unclassified). Reported as pathogenic by Berge et al.[5], and as VUS by Amendola et al. [6] and Dorschner et al.[7] Predicted likely pathogenic. |
| 25 | *KCNH2* | c.3118A>G | p.(Ser1040Gly) | - | 8 | LQT0312<br>LQT0334<br>LQT0344<br>LQT0430* | 1/492 NOR alleles. Found in one sudden infant death syndrome case by Arnestad et al.[8]. |
| 26 | *SCN4B* | c.34G>A | p.(Ala12Thr) | 3/108260 NFE | - | LQT0171* | VUS in ClinVar. Predicted benign. Localized to exon 1, whereas all reported pathogenic variants in *SCN4B* are in exon 4 and 5. |
| 27 | *SCN5A* | c.3707A>C | p.(Lys1236Thr) | - | - | LQT0064 | Predicted likely deleterious. Other variants affecting the same codon, p.(Lys1236Arg) and p.(Lys1236Asn) have each been reported in one patient with Brugada syndrome [9,10]. |
| 28 | *SCN5A* | c.3430_3434del | p.(Met1144Glnfs*4) | - | - | LQT0273 | Most, but not all, loss-of-function variants in *SCN5A* result in Brugada syndrome. |
| 29 | *SCN5A* | c.4501C>G | p.(Leu1501Val) | 5/112248 NFE | 11-14 | LQT0217*<br>LQT0359 | Likely pathogenic in ClinVar. Pathogenic in CentoMD. Predicted to introduce a cryptic splice site, but mRNA analyses show only partially |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | disrupted splicing (Figure S1). Reported previously in both LQT- and Brugada syndrome patients. |
| 30 | *SCN5A* | c.5579G>A | p.(Arg1860Lys) | - | - | LQT0123<br>LQT0199*<br>LQT0360 | Another variant affecting the same codon, p.(Arg1860Ser), is reported in an LQT case who also harbored the known pathogenic *KCNQ1* (p.Arg243Cys) [15]. |
| 31 | *SNTA1* | c.205G>A | p.(Glu69Lys) | 0/ | - | LQT0148 | VUS in ClinVar |
| 32 | *SNTA1* | c.759T>A | p.(Asp253Glu) | 18/126524 NFE | - | LQT0132* | VUS in ClinVar. 3/31714 alleles in CentoMD (unclassified) |
| 33 | *KCNH2* | c.1475A>G | p.(His492Arg) | - | - | LQT0203 | Predicted likely pathogenic. Other variant affecting the same codon, p.(His492Tyr) has been reported to cause a milder LQT phenotype [16]. |
| 34 | *KCNH2* | c.2738C>T | p.(Ala913Val) | 22/9116 FIN (1 hom) | 1, 17-20 | LQT0217* | Uncertain and likely pathogenic in ClinVar.4/15875*2 alleles in CentoMD (uncertain). Conflicting results from *in vitro* functional testing. Predicted to introduce a cryptic splice site. It is our opinion that this variant is too common to be a highly penetrant pathogenic mutation, but it could be a risk factor. |

* These patients harbored two VUS each

Predicted benign: Consistently predicted benign by SIFT, MutationTaster, PolyPhen-2 and Revel (accessed 24.01.2018)

Predicted likely pathogenic: Consistently predicted likely pathogenic/deleterious or pathogenic/deleterious by SIFT, MutationTaster, PolyPhen-2 and Revel (accessed 24.01.2018)

NOR The Norwegian 1000 genomes project http://kreftgenomikk.no/en/1000genomes/ (accessed 04.01.2016)

DAN 2,000 Danes WES (Diabetes Type 2 Study accessed through AlaMut software (accessed 24.01.2018)

gnomAD categories FIN=Finnish population, NFE=Non-Finnish European population, EA=East Asian population, AFR=African population

gnomAD=Genome Aggregation Database, VUS= Variants of uncertain significance

**Table S3. Demographics of 41 patients with variants of uncertain significance (VUS) at time of first ECG with QTc ≥ 500 ms ("ECG 1").**

| | Total (n=444) | VUS (n=41) | Negative genetic test (n=403) | P- value |
|---|---|---|---|---|
| Age (years) | 63 ± 14 | 62 ± 15 | 63 ± 14 | 0.73 |
| Female sex | 274 (62 %) | 21 (51 %) | 253 (63 %) | 0.18 |
| Heart rate (beats/min) | 77 (39-100) | 76 (48-98) | 78 (39-100) | 0.81 |
| QRS duration (ms) | 94 ± 12 | 95 ± 11 | 93 ± 12 | 0.56 |
| QTc (ms) | 512 (500-669) | 510 (500-639) | 512 (500-669) | 0.39 |
| Hypokalemia | 121/419 (30 %) | 17/39 (44 %) | 104/380 (27 %) | 0.09 |
| Number of QT-prolonging drugs | 1 (0-5) | 1 (0-5) | 1 (0-5) | 0.94 |
| Number of QT-prolonging conditions * | 1 (0-4) | 1 (0-3) | 1 (0-4) | 0.55 |
| Pro-QTc score | 2.8 ± 1.6 | 2.9 ± 1.6 | 2.8 ± 1.6 | 0.68 |

*Female sex, electrolyte disturbances and medication not included.

ECG=Electrocardiogram; QTc=corrected QT interval; VUS=Variants of uncertain significance

**Table S4. Number of drugs from CredibleMeds QTdrugs lists at time of ECG 1 and ECG 2 for 41 patients with VUS.**

| | ECG1 | ECG2 |
|---|---|---|
| Drugs with known risk TdP | Amiodarone (n=3)<br>Citalopram (n=4)<br>Escitalopram (n=1)<br>Ciprofloxacin (n=1)<br>Propofol (n=1) | Citalopram (n=3)<br>Amiodarone (n=2)<br>Escitalopram (n=4) |
| Drugs with possible risk TdP | Venlafaxine (n=1)<br>Mirtazapine (n=1)<br>Lithium (n=1)<br>Risperidone (n=1)<br>Tacrolimus (n=1)<br>Aripiprazole (n=1) | Venlafaxine (n=2)<br>Promethazine (n=1)<br>Mirtazapine (n=4)<br>Tacrolimus (n=1)<br>Aripiprazole (n=1)<br>Lithium (n=1)<br>Risperidone (n=1) |
| Drugs with conditional risk TdP | Furosemide (n=6)<br>Pantoprazole (n=3)<br>Hydrochlorothiazide (n=1)<br>Metoclopramide (n=1)<br>Metronidazole (n=2)<br>Amitriptyline (n=1)<br>Hydroxyzine (n=2)<br>Paroxetine (n=1)<br>Quetiapine (n=1)<br>Amisulpride (n=1) | Quetiapine (n=2)<br>Furosemide (n=4)<br>Hydrochlorothiazide (n=5)<br>Solifenacin (n=2)<br>Pantoprazole (n=8)<br>Metoclopramide (n= 1)<br>Sertraline (n=1)<br>Amisulpride (n=1) |
| Drugs with special risk for LQTS patients | Salbutamol (n=4)<br>Formeterol (n=1)<br>Noradrenaline (n=1) | Salmeterol (n=1)<br>Formeterol (n=1) |

ECG=Electrocardiogram; TdP=torsades de pointes; VUS= variants of uncertain significance

**Table S5. Demographics of 23 patients with *KCNQ1* p.(Gln530*) compared to 8 patients with pathogenic or likely pathogenic variants at time of first ECG with QTc ≥ 500 ms ("ECG 1").**

| | Total (n=31) | *KCNQ1* p.(Gln530*) (n=23) | Pathogenic or likely pathogenic variant (n=8) | P- value |
|---|---|---|---|---|
| Age (years) | 63 ± 17 | 67 ± 16 | 50 ± 16 | 0.01 |
| Female sex | 20 (65 %) | 17 (74 %) | 3 (38 %) | 0.08 |
| Heart rate (beats/min) | 66 (41-97) | 69 (41-97) | 63 (49-86) | 0.41 |
| QRS duration (ms) | 88 ± 10 | 88 ± 10 | 89 ± 10 | 0.74 |
| QTc (ms) | 511 (501-577) | 510 (501-577) | 513 (502-535) | 0.95 |
| Hypokalemia | 3/22 (14 %) | 3/17 (18 %) | 0/5 (0 %) | 0.72 |
| Number of QT- prolonging drugs | 0 (0-2) | 1 (0-2) | 0 (0-2) | 0.24 |
| Number of QT-prolonging conditions * | 0 (0-1) | 0 (0-1) | 0 (0-1) | 0.64 |
| Pro-QTc score | 1.7 ± 1.0 | 1.9 ± 0.9 | 1.1 ± 1.0 | 0.046 |

*Female sex, electrolyte disturbances and medication not included

ECG=Electrocardiogram; QTc=corrected QT interval

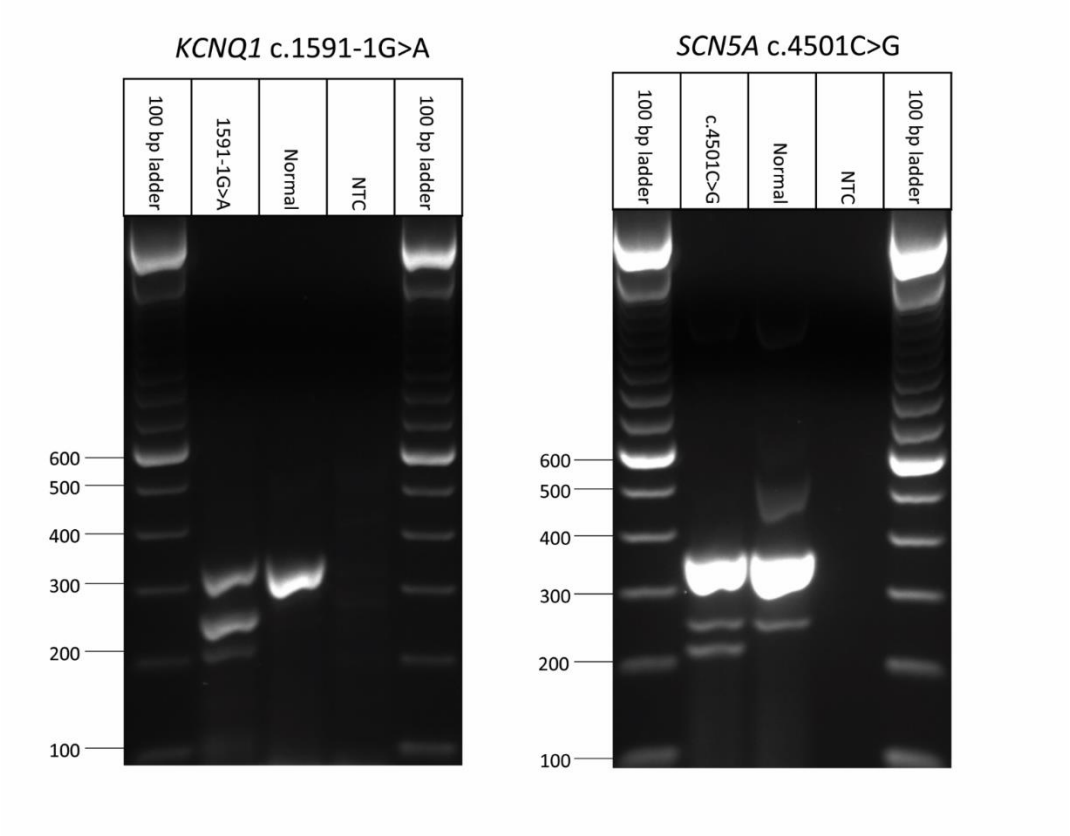
**Table S6. Uncorrected QT duration, QTc Bazett, QTc Fredericia and QTc Framingham at time of first ECG with QTc ≥ 500 ms ("ECG 1").**

| Patients | # of patients | Heart rate (beats/min) | Uncorrected QT duration (ms) | QTc Bazett (ms) | QTc Fredericia (ms) | QTc Framingham (ms) |
|---|---|---|---|---|---|---|
| Participants | 475 | 77 (39-100) | 456 (392-698) | 512 (500-669) | 493 (462-631) | 489 (452-631) |
| Non-participants | 258 | 81 (48-100) | 448 (392-730) | 515 (500-634) | 495 (462-786) | 489 (452-761) |
| Pathogenic or likely pathogenic variants | 31 | 66 (41-97) | 488 (400-698) | 511 (501-577) | 500 (469-616) | 498 (459-627) |
| VUS | 41 | 76 (48-98) | 464 (396-592) | 510 (500-639) | 497 (465-623) | 494 (455-614) |
| Negative genetic test | 403 | 78 (39-100) | 456 (392-650) | 512 (500-669) | 493 (462-631) | 488 (452-631) |
| VUS and negative genetic test | 444 | 77 (39-100) | 456 (392-650) | 512 (500-669) | 493 (462-631) | 489 (452-631) |
| *KCNQ1* p.(Gln530*) | 23 | 69 (41-97) | 480 (400-698) | 510 (501-577) | 500 (469-615) | 496 (459-627) |
| Pathogenic or likely pathogenic variants other than *KCNQ1* p.(Gln530*) | 8 | 63 (49-86) | 493 (432-568) | 513 (502-535) | 500 (487-615) | 500 (479-539) |
| P- value for participants vs non-participants | | <0.01 | | 0.17 | 0.56 | 0.26 |
| P- value for pathogenic or likely pathogenic variants vs VUS and negative genetic test | | <0.01 | | 0.50 | 0.18 | 0.10 |

| | | | | | | |
|---|---|---|---|---|---|---|
| P- value for VUS vs negative genetic test | | 0.81 | | 0.39 | 0.35 | 0.32 |
| P- value for *KCNQ1* p.(Gln530*) vs pathogenic or likely pathogenic variants other than *KCNQ1* p.(Gln530*) | | 0.41 | | 0.95 | 0.55 | 0.41 |

ECG=Electrocardiogram; QTc=corrected QT interval; VUS= variants of uncertain significance

**Figure S1. RT-PCR of KCNQ1 c.1591-1G>A and SCN5A c.4501C>G.**




*KCNQ1* c.1591-1G>A affects the canonical acceptor splice site of exon 13 / intron 12. RT-PCR showed skipping of exon 13 from the mature mRNA. No production of normal mRNA from the mutated allele was observed by studying a marker variant (heterozygous c.1638G>A in exon 13). *SCN5A* c.4501C>G produced an aberrant transcript where 100 bp from the 3'-end of exon 25 and the first 4 bp of exon 26 had been excluded. The fainter band of the shorter, mutated transcript compared to normal, full-length transcript indicates that normal the mutated allele also produces some normal transcript. bp=base pairs; RT-PCR=Reverse transcription polymerase chain reaction.

**Supplemental References:**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