**Supplemental TABLE 1. Genetic variants present in the Registry**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **Exon** | **Nucleotide change** | | **Amino acid change** | | **Protein domain** | | **MAF#** | | **SNP ID** | | **ACMG Classification** | | **N. of families** | **N. of subjects** | **Associated phenotype** |
| ***CALM1*** | 3 | c.161A>T | | p.N54I (p.Asn54Ile) | | EF-hand II | | **-** | | rs267607276 | | Pathogenic  (PS3,PM2,PP1,PP2,PP3,PP5) | | 2 | 14 | CPVT, UD |
| ***CALM1*** | 4 | c.247G>A | | **p.E83K (p.Glu83Lys)** | | Inter EF-hand II-III linker | | **-** | | - | | VUS  (PM2,PP2,PP3) | | 1 | 1 | LQTS/CPVT |
| ***CALM1*** | 4 | c.268T>C | | p.F90L (p.Phe90Leu) | | EF-hand III | | **-** | | rs730882253 | | Pathogenic  (PS1,PS3,PM2,PP1,PP2,PP3,  PP5) | | 1 | 6 | IVF |
| ***CALM1*** | 5 | c.293A>G | | p.N98S (p.Asn98Ser) | | EF-hand III, Ca2+-chelation loop | | **-** | | rs267607277 | | Pathogenic  (PS1,PS3,PM1,PM2,PP1,PP2,  PP3,PP5) | | 11 | 11 | LQTS, CPVT, LQTS/CPVT/UD |
| ***CALM1*** | 5 | c.293A>C | | **p.N98T (p.Asn98Thr)** | | EF-hand III, Ca2+-chelation loop | | **-** | | - | | Likely Pathogenic  (PM1,PM2,PM5,PP2,PP3) | | 1 | 1 | LQTS |
| ***CALM1*** | 5 | c.313G>A | | p.E105K (p.Glu105Lys) | | EF-hand III, Ca2+-chelating | | **-** | | rs1057523130 | | Likely Pathogenic  (PM1,PM2,PM5,PM6,PP2,PP3,PP5) | | 1 | 1 | Atypical |
| ***CALM1*** | 5 | c.314A>C | | p.E105A (p.Glu105Ala) | | EF-hand III, Ca2+-chelating | | **-** | | - | | Pathogenic  (PS3,PM1,PM2,PM5,PM6,PP2,PP3) | | 1 | 1 | LQTS/CPVT |
| ***CALM1*** | 5 | c.389A>C | | p.D130A (p.Asp130Ala) | | EF-hand IV, Ca2+-chelation loop | | **-** | | - | | Likely Pathogenic  (PM1,PM2,PM5,PM6,PP2,PP3) | | 1 | 1 | LQTS |
| ***CALM1*** | 5 | c.389A>G | | p.D130G (p.Asp130Gly) | | EF-hand IV, Ca2+-chelation loop | | **-** | | rs730882252 | | Pathogenic  PS1,PS3,PM1,PM2,PM5,PP2,  PP3,PP5) | | 3 | 3 | LQTS |
| ***CALM1*** | 5 | c.389A>T | | **p.D130V (p.Asp130Val)** | | EF-hand IV, Ca2+-chelation loop | | **-** | | - | | Pathogenic  (PS1,PM1,PM2,PM5,PM6,PP2,PP3) | | 1 | 1 | LQTS |
| ***CALM1*** | 5 | c.395A>T | | p.D132V (p.Asp132Val) | | EF-hand IV, Ca2+-chelation loop | | **-** | | rs1887113791 | | Pathogenic  (PS3,PM1,PM2,PM5,PM6,PP2,PP3,PP5) | | 2 | 2 | LQTS |
| ***CALM1*** | 5 | | c.398G>T | | **p.G133V**  **(p.Gly133Val)** | | EF-hand IV, Ca2+-chelation loop | |  | |  | | Pathogenic  (PS3,PM1,PM2,PM5,PP2,PP3) | 1 | 1 | LQTS |
| ***CALM1*** | 5 | c.404G>A | | **p.G135E (p.Gly135Glu)** | | EF-hand IV, Ca2+-chelation loop | | **-** | | - | | Likely Pathogenic  (PM1,PM2,PP2,PP3) | | 1 | 1 | CPVT |
| ***CALM1*** | 6 | c.422A>G | | p.E141G (p.Glu141Gly) | | EF-hand IV, Ca2+-chelating | | **-** | | rs1887120112 | | Pathogenic  (PS1,PS3,PM1,PM2,PM5,PM6,PP2,PP3,PP5) | | 1 | 1 | LQTS |
| ***CALM1*** | 6 | c.422A>T | | p.E141V (p.Glu141Val) | | EF-hand IV, Ca2+-chelating | | **-** | | rs1887120112 | | Pathogenic  (PS3,PM1,PM2,PM5,PM6,PP2,PP3) | | 1 | 1 | LQTS |
| ***CALM1*** | 6 | c.424T>C | | **p.F142L (p.Phe142Leu)** | | EF-hand IV | | **-** | | rs1085307479 | | Pathogenic  (PS1,PS3,PM2,PM6,PP2,PP3.  PP5) | | 1 | 1 | LQTS |
| ***CALM1*** | 6 | c.426C>A | | **p.F142L (p.Phe142Leu)** | | EF-hand IV | | **-** | | rs199744595 | | Pathogenic  (PS1,PS3,PM2,PM6,PP2,PP3,  PP5) | | 1 | 1 | LQTS |
| ***CALM1*** | 6 | c.426C>G | | p.F142L (p.Phe142Leu) | | EF-hand IV | | **-** | | rs199744595 | | Pathogenic  (PS1,PS3,PM2,PM6,PP2,PP3,  PP5) | | 4 | 4 | LQTS |
| ***N.*** |  | ***18*** | | ***16*** | |  | |  | |  | |  | | ***35*** | ***52*** |  |
| ***CALM2*** |  | | c.89C>G | | **p.T30R (p.Thr30Arg)** | | EF-hand I | | **-** | | **-** | | VUS  (PM2,PP2,PP3) | 1 | 2 | CPVT |
| ***CALM2*** | *3* | c.104C>T | | **p.T35I (p.Thr35Ile)** | | EF-hand I | | 0.000003982/1 | | rs757523692 | | VUS  (PP2,PP3) | | 1 | 2 | CPVT |
| ***CALM2*** | 3 | c.136G>A | | p.E46K (p.Glu46Lys) | | EF-hand II | | **-** | | - | | Pathogenic  (PS3,PM2,PM6,PP2,PP3) | | 2 | 2 | CPVT |
| ***CALM2*** | 3 | c.172G>C | | **p.A58P**  **(p.Ala58Pro)** | | EF-hand II,  Ca2+-chelation loop | | **-** | | **-** | | Likely Pathogenic  (PM1,PM2,PP2,PP3) | | 1 | 1 | LQTS |
| ***CALM2*** | 4 | c.188C>G | | **p.T63R (p.Thr63Arg)** | | EF-hand II, Ca2+-chelation loop | | **-** | | - | | Likely Pathogenic  (PM1,PM2,PP2,PP3) | | 1 | 1 | UD |
| ***CALM2*** | 4 | c.192T>G | | **p.I64M (p.Ile64Met)** | | EF-hand II, Ca2+-chelation loop | | **-** | | - | | Likely Pathogenic  (PM1,PM2,PM6,PP2) | | 1 | 1 | Atypical |
| ***CALM2*** | 4 | c.203A>C | | **p.E68A (p.Glu68Ala)** | | EF-hand II, Ca2+-chelating | | **-** | | - | | Likely Pathogenic  (PM1,PM2,PP2,PP3) | | 1 | 2 | LQTS |
| ***CALM2*** | 4 | c.268T>C | | p.F90L (p.Phe90Leu) | | EF-hand III | | **-** | | - | | Pathogenic  (PS1,PS3,PM2,PP2,PP3) | | 1 | 1 | UD |
| ***CALM2*** | 5 | c.287A>G | | p.D96G (p.Asp96Gly) | | EF-hand III, Ca2+-chelation loop | | **-** | | - | | Likely Pathogenic  (PM1,PM2,PM5,PM6,PP2,PP3) | | 2 | 2 | LQTS |
| ***CALM2*** | 5 | c.287A>T | | p.D96V (p.Asp96Val) | | EF-hand III, Ca2+-chelation loop | | **-** | | rs730882254 | | Pathogenic  (PS3,PM1,PM2,PM5,PM6,PP2,PP3,PP5) | | 2 | 2 | LQTS |
| ***CALM2*** | 5 | c.293A>G | | p.N98S (p.Asn98Ser) | | EF-hand III, Ca2+-chelation loop | | **-** | | rs398124647 | | Pathogenic  (PS1,PS3,PM1,PM2,PM5,PP1,PP2,PP3,PP5) | | 11 | 11 | LQTS, CPVT, IVF, LQTS/CPVT/UD |
| ***CALM2*** | 5 | c.293A>T | | p.N98I (p.Asn98Ile) | | EF-hand III, Ca2+-chelation loop | | **-** | | rs398124647 | | Pathogenic  (PS3,PM1,PM2,PM5,PM6,PP2,PP3,PP5) | | 2 | 2 | LQTS |
| ***CALM2*** | 5 | c.340G>A | | **p.G114R (p.Gly114Arg)** | | Inter EF- hand III-IV linker | | **-** | | - | | Pathogenic  (PS3,PM2,PM5,PP2,PP3) | | 1 | 3 | UD |
| ***CALM2*** | 5 | c.388G>A | | **p.D130N (p.Asp130Asn)** | | EF-hand IV, Ca2+-chelation loop | | **-** | | - | | Likely Pathogenic  (PM1,PM2,PM5,PM6,PP2) | | 1 | 1 | LQTS |
| ***CALM2*** | 5 | c.388G>T | | **p.D130Y (p.Asp130Tyr)** | | EF-hand IV, Ca2+-chelation loop | | **-** | | - | | Likely Pathogenic  (PM1,PM2,PM5,PM6,PP2,PP3) | | 1 | 1 | LQTS |
| ***CALM2*** | 5 | c.389A>G | | p.D130G (p.Asp130Gly) | | EF-hand IV, Ca2+-chelation loop | | **-** | | rs1573214163 | | Pathogenic  (PS1,PS3,PM1,PM2,PP2,PP5) | | 1 | 1 | LQTS |
| ***CALM2*** | 5 | c.389A>T | | p.D130V (p.Asp130Val) | | EF-hand IV, Ca2+-chelation loop | | **-** | | - | | Pathogenic  (PS1,PM1,PM2,PM5,PM6,PP2,PP3) | | 1 | 1 | LQTS |
| ***CALM2*** | 5 | c.394G>C | | p.D132H (p.Asp132His) | | EF-hand IV, Ca2+-chelation loop | | **-** | | - | | Pathogenic  (PS3,PM1,PM2,PM5,PM6,PP2,PP3) | | 1 | 1 | LQTS |
| ***CALM2*** | 5 | c.394G>T | | **p.D132Y (p.Asp132Tyr)** | | EF-hand IV, Ca2+-chelation loop | | **-** | | - | | Likely Pathogenic  (PM1,PM2,PM5,PP2,PP3) | | 1 | 1 | LQTS |
| ***CALM2*** | 5 | c.395A>G | | p.D132G (p.Asp132Gly) | | EF-hand IV, Ca2+-chelation loop | | **-** | | rs1687164164 | | Likely Pathogenic  (PM1,PM2,PM5,PM6,PP2,PP5) | | 3 | 4 | LQTS |
| ***CALM2*** | 5 | c.396T>G | | p.D132E (p.Asp132Glu) | | EF-hand IV, Ca2+-chelation loop | | **-** | | rs398124648 | | Pathogenic  (PS1,PS3,PM1,PM2,PM6,PP2,PP3,PP5) | | 1 | 1 | LQTS/CPVT |
| ***CALM2*** | 5 | c.397G>A | | **p.G133S (p.Gly133Ser)** | | EF-hand IV, Ca2+-chelation loop | | **-** | | - | | Likely Pathogenic  (PM1,PM2,PM6,PP2,PP3) | | 1 | 1 | LQTS |
| ***CALM2*** | 5 | c.400G>A | | p.D134N (p.Asp134Asn) | | EF-hand IV, Ca2+-chelation loop | | **-** | | rs398124650 | | Likely Pathogenic  (PM1,PM2,PM5,PP2,PP3,PP5) | | 1 | 2 | LQTS/CPVT |
| ***CALM2*** | 5 | c.400G>C | | p.D134H (p.Asp134His) | | EF-hand IV, Ca2+-chelation loop | | **-** | | rs398124650 | | Pathogenic  (PS3,PM1,PM2,PM5,PM6,PP2,PP3,PP5) | | 1 | 1 | LQTS |
| ***CALM2*** | 5 | | c.404G>T | | **p.G135V**  **(p.Gly135Val)** | | EF-hand IV, Ca2+-chelation loop | | **-** | | - | | Likely Pathogenic  (PM1,PM2,PM5,PP2,PP3) | 1 | 1 | UD |
| ***CALM2*** | 5 | c.407A>C | | p.Q136P (p.Gln136Pro) | | EF-hand IV, Ca2+-chelation loop | | **-** | | rs398124649 | | Pathogenic  (PS3,PM1,PM2,PM5,PP2,PP3) | | 1 | 1 | LQTS/CPVT |
| ***CALM2*** | 5 | c.414C>G | | p.N138K (p.Asn138Lys) | | EF-hand IV, Ca2+-chelation loop | | **-** | | rs1553431702 | | Pathogenic  (PS1,PS3,PM1,PM2,PM6,PP2) | | 1 | 1 | LQTS |
| ***CALM2*** | 5 | c.421G>A | | **p.E141K (p.Glu141Lys)** | | EF-hand IV, Ca2+-chelating | | **-** | | - | | Pathogenic  (PS3,PM1,PM2,PM5,PM6,PP2,PP3) | | 1 | 1 | LQTS |
| ***CALM2*** | 6 | c.422A>G | | p.E141G (p.Glu141Gly) | | EF-hand IV, Ca2+-chelating | | **-** | | - | | Pathogenic  (PS1,PS3,PM1,PM2,PM5,PM6,PP2,PP3) | | 1 | 1 | LQTS |
| ***CALM2*** | 6 | c.423G>C | | **p.E141D (p.Glu141Asp)** | | EF-hand IV, Ca2+-chelating | | **-** | | - | | Likely Pathogenic  (PM1,PM2,PM5,PM6,PP2,PP3) | | 1 | 1 | LQTS |
| ***N.*** |  | ***30*** | | ***30*** | |  | |  | |  | |  | | ***46*** | ***53*** |  |
| ***CALM3*** | 4 | c.281A>C | | p.D94A (p.Asp94Ala) | | EF-hand III, Ca2+-chelation loop | | **-** | | rs1060502608 | | Likely Pathogenic  (PM1,PM2,PM6,PP2,PP3,PP5) | | 1 | 1 | LQTS |
| ***CALM3*** | 5 | c.286G>C | | p.D96H (p.Asp96His) | | EF-hand III, Ca2+-chelation loop | | **-** | | rs1060502607 | | Likely Pathogenic  (PM1,PM2,PM5,PM6,PP2,PP3,PP5) | | 2 | 2 | LQTS |
| ***CALM3*** | 5 | c.307G>A | | **p.A103T (p.Ala103Thr)** | | EF-hand III | | 0.000004609/1 | | rs147880865 | | VUS  (PM5,PP2) | | 1 | 1 | LQTS |
| ***CALM3*** | 5 | c.308C>T | | p.A103V (p.Ala103Val) | | EF-hand III | | **-** | | rs1568666713 | | Likely Pathogenic  (PS3,PM2,PP2,PP3) | | 1 | 2 | CPVT |
| ***CALM3*** | 5 | c.340G>T | | p.G114W (p.Gly114Trp) | | Inter EF- hand III-IV linker | | **-** | | - | | Pathogenic  (PS3,PM2,PM5,PP2,PP3) | | 1 | 2 | CPVT |
| ***CALM3*** | 5 | c.388G>A | | **p.D130N (p.Asp130Asn)** | | EF-hand IV, Ca2+-chelation loop | | **-** | | - | | Likely Pathogenic  (PM1,PM2,PM5,PM6,PP2) | | 1 | 1 | LQTS |
| ***CALM3*** | 5 | c.389A>G | | p.D130G (p.Asp130Gly) | | EF-hand IV, Ca2+-chelation loop | | **-** | | rs1599759554 | | Pathogenic  (PS1,PS3,PM1,PM2,PM5,PP1,PP2,PP3,PP5) | | 2 | 6 | LQTS |
| ***CALM3*** | 5 | c.390C>G | | **p.D130E (p.Asp130Glu)** | | EF-hand IV, Ca2+-chelation loop | | **-** | | - | | Likely Pathogenic  (PM1,PM2,PM5,PM6,PP2,PP3) | | 1 | 1 | LQTS |
| ***CALM3*** | 5 | c.396T>A | | p.D132E (p.Asp132Glu) | | EF-hand IV, Ca2+-chelation loop | | **-** | | rs1064796271 | | Pathogenic  (PS1,PS3,PM1,PM2,PM5,PM6,PP2,PP3,PP5) | | 1 | 1 | CPVT |
| ***CALM3*** | 5 | c.414T>G | | **p. N138K (p.Asn138Lys)** | | EF-hand IV, Ca2+-chelation loop | | **-** | | - | | Pathogenic  (PS3,PM1,PM2,PP1,PP2,BP4) | | 1 | 14 | LQTS |
| ***CALM3*** | 5 | c.421G>A | | p.E141K (p.Glu141Lys) | | EF-hand IV, Ca2+-chelating | | **-** | | rs1599759598 | | Pathogenic  (PS1,PS3,PM1,PM2,PM5,PP2,PP3) | | 1 | 1 | LQTS |
| ***CALM3*** | 6 | c.422A>G | | **p.E141G (p.Glu141Gly)** | | EF-Hand IV, Ca2+-chelating | | **-** | | rs1555814427 | | Pathogenic  (PS3,PM1,PM2,PM5,PM6,PP2,PP3,PP5) | | 1 | 1 | LQTS |
| ***CALM3*** | 6 | c.426T>G | | p.F142L (p.Phe142Leu) | | EF-Hand IV | | **-** | | - | | Pathogenic  (PS1,PS3,PM2,PM6,PP2,PP3) | | 1 | 1 | LQTS |
| ***CALM3*** | 6 | c.426T>A | | **p.F142L (p.Phe142Leu)** | | EF-Hand IV | | **-** | | - | | Pathogenic  (PS1,PS3,PM2,PM6,PP2,PP3) | | 1 | 1 | LQTS |
| ***N.*** |  | ***14*** | | ***13*** | |  | |  | |  | |  | | ***16*** | ***35*** |  |
| ***Total*** |  | **62** | | **59** | |  | |  | |  | |  | | 97 | 140 |  |

Amino acid changes occurring in 2 of the 3 *CALM* genes are highlighted in light grey. Newly identified *CALM* variants are indicated in bold. # Minor allele frequencies (MAF) were assessed for each variant in all publicly available exome/genome databases. The dash indicates no MAF reported.

VUS = variant of uncertain significance; LQTS = long QT syndrome; CPVT = catecholaminergic polymorphic ventricular tachycardia; IVF = idiopathic ventricular fibrillation; UD = uncertain diagnosis; SCD = sudden cardiac death