**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 | PathogenicPS1,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 $\geq $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