Variant: NM_000218.3(KCNQ1):c.817C>T (p.Leu273Phe)

Version: 1.0

CA008331

3119 (ClinVar)

Gene: KCNQ1 (HGNC:3784)
Condition: long QT syndrome 1 (MONDO:0100316)
Inheritance Mode: Autosomal dominant inheritance
UUID: f829d50f-363d-46be-a5ac-eb425492a343
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HGVS expressions

NM_000218.3:c.817C>T
NM_000218.3(KCNQ1):c.817C>T (p.Leu273Phe)
NC_000011.10:g.2572882C>T
CM000673.2:g.2572882C>T
NC_000011.9:g.2594112C>T
CM000673.1:g.2594112C>T
NC_000011.8:g.2550688C>T
NG_008935.1:g.132892C>T
ENST00000496887.7:c.556C>T
ENST00000646564.2:c.478-10553C>T
ENST00000155840.12:c.817C>T
ENST00000335475.6:c.436C>T
ENST00000646564.1:c.124-10553C>T
ENST00000155840.9:c.817C>T
ENST00000335475.5:c.436C>T
ENST00000496887.6:c.556C>T
NM_000218.2:c.817C>T
NM_181798.1:c.436C>T

Likely Pathogenic

Met criteria codes 5

PS3 PP3 PP4 PM2_Supporting PS4_Moderate

Not Met criteria codes 2

PP1 PM5

Evidence Links 1

Expert Panel

Potassium Channel Arrhythmia VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Potassium Channel Arrhythmia Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for KCNQ1 Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Potassium Channel Arrhythmia VCEP

NM_000218.3(KCNQ1):c.817C>T is a missense variant in KCNQ1 that replaces leucine with phenylalanine at codon 273. This variant is present in gnomAD v.4.1.0 at a maximum allele frequency of 0.000007627, with 9 alleles / 1180016 total alleles in the European (non-Finnish) population, which is lower than the ClinGen Potassium Channel Arrhythmia VCEP PM2_Supporting threshold of <0.00001 (PM2_Supporting). This variant is rare and has been reported in at least 5 apparently unrelated probands affected with long QT syndrome 1 (PMID: 8528244, PMID: 25645639, PMID: 27920829, PMID: 24372464, PMID: 37449562, PS4_Moderate). This variant has been reported in at least one affected proband exhibiting QTc prolongation above 480 milliseconds and an exercise-associated event, which together are highly specific for long QT syndrome 1 (PP4, PMID: 24372464). The variant has been reported to segregate with long QT syndrome 1 through the proband and 3 affected family members from one family, however, one member had QTc less than 480 ms and was excluded from counting, so PP1 has not been met (PMID: 28249770). Another missense variant NM_000218.3(KCNQ1):c.817C>G (p.Leu273Val) in the same codon has been observed in relation to Long QT Syndrome, however the PM5 has not been considered to avoid circularity. The computational predictor REVEL gives a score of 0.924, which is above the ClinGen Potassium Channel Arrhythmia VCEP PP3 threshold of >0.75 and predicts a damaging effect on KCNQ1 function (PP3). This variant has been shown to disrupt KCNQ1 function in at least five experimental assays, including Manual patch-clamp and Experimental/Structural/Functional Simulation (PS3; PMID: 9323054, PMID: 29451064, PMID: 29167462, PMID: 29021305, PMID: 11278406). In summary, this variant meets the criteria to be classified as likely pathogenic for long QT syndrome 1 based on the ACMG/AMP criteria applied, as specified by the ClinGen Potassium Channel Arrhythmia VCEP: PS3, PS4_Moderate, PM2_Supporting, PP3, and PP4. (VCEP specifications version 1.0.0; date of approval 03/04/2025).

Met criteria codes

PS3	✔	This variant has been shown to disrupt KCNQ1 function in at least five experimental assays, including Manual patch-clamp and Experimental/Structural/Functional Simulation (PS3; PMID: 9323054, PMID: 29451064, PMID: 29167462, PMID: 29021305, PMID: 11278406). Co-expression of wild-type or mutant KCNQ1 with KCNE1 shows decreased current amplitude for mutant channels (Figure 4). **PubMed:11278406**
PP3	✔	The computational predictor REVEL gives a score of 0.924, which is above the ClinGen Potassium Channel Arrhythmia VCEP PP3 threshold of >0.75 and predicts a damaging effect on KCNQ1 function. The computational splicing predictor SpliceAI gives a score of 0.01 for acceptor loss, which is lower than the ClinGen Potassium Channel Arrhythmia VCEP threshold of >0.5 and does not strongly predict that the variant disrupts the splicing of KCNQ1.
PP4	✔	This variant has been reported in at least one affected proband exhibiting QTc prolongation above 480 milliseconds and an exercise-associated event, which together are highly specific for long QT syndrome 1 (PP4, PMID: 24372464).
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a maximum allele frequency of 0.000007627, with 9 alleles / 1180016 total alleles in the European (non-Finnish) population, which is lower than the ClinGen Potassium Channel Arrhythmia VCEP PM2_Supporting threshold of <0.00001 (PM2_Supporting).
PS4_Moderate	✔	This variant is rare and has been reported in at least 5 apparently unrelated probands affected with long QT syndrome 1 (PMID: 8528244, PMID: 25645639, PMID: 27920829, PMID: 24372464, PMID: 37449562, PS4_Moderate).

Not Met criteria codes

PP1	✖	The variant has been reported to segregate with long QT syndrome 1 through the proband and 3 affected family members from one family, however, one member had QTc less than 480 ms and was excluded from counting, so PP1 has not been met (PMID: 28249770).

PM5		✖	Another missense variant NM_000218.3(KCNQ1):c.817C>G (p.Leu273Val) in the same codon has been classified as a VUS for Long QT Syndrome by the ClinGen Potassium Channel Arrhythmia VCEP, however, PM5 has not been considered for this variant in order to avoid circularity.

Curation History

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