Variant: NM_000218.3(KCNQ1):c.590C>T (p.Pro197Leu)

Version: 1.0

CA007671

191476 (ClinVar)

Gene: KCNQ1 (HGNC:3784)
Condition: long QT syndrome 1 (MONDO:0100316)
Inheritance Mode: Autosomal dominant inheritance
UUID: 16790749-f8e7-4d2b-9702-736d6283cb02
Approved on: 2025-07-01
Published on: 2025-07-02

HGVS expressions

NM_000218.3:c.590C>T
NM_000218.3(KCNQ1):c.590C>T (p.Pro197Leu)
NC_000011.10:g.2570740C>T
CM000673.2:g.2570740C>T
NC_000011.9:g.2591970C>T
CM000673.1:g.2591970C>T
NC_000011.8:g.2548546C>T
NG_008935.1:g.130750C>T
ENST00000496887.7:c.329C>T
ENST00000646564.2:c.478-12695C>T
ENST00000155840.12:c.590C>T
ENST00000335475.6:c.209C>T
ENST00000646564.1:c.124-12695C>T
ENST00000155840.9:c.590C>T
ENST00000335475.5:c.209C>T
ENST00000496887.6:c.329C>T
NM_000218.2:c.590C>T
NM_181798.1:c.209C>T

Uncertain Significance

Met criteria codes 1

PP3

Not Met criteria codes 11

BS1 BS3 BP4 PS1 PS3 PS4 PM1 PM5 PM2 BA1 PP4

Evidence Links 3

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.590C>T is a missense variant predicted to cause replacement of proline with leucine at position 197. This residue is conserved across the 5 human KCNQ paralogues (https://www.cardiodb.org/paralogue_annotation/gene.php?name=KCNQ1) and another missense variant in the same codon, NM_000218.3(KCNQ1):c.589C>T (p.Pro197Ser), has been investigated in connection with long QT syndrome 1 (PMID: 29532034) but has been classified as a variant of uncertain significance for long QT syndrome 1 by the ClinGen Potassium Channel Arrhythmia VCEP, so PM5 is not yet met. This variant is present in gnomAD v.4.1.0 at a maximum allele frequency of 0.00004576, with 54 / 1179994 in the European non-FInnish population, which is higher than the ClinGen Potassium Channel Arrhythmia VCEP PM2_Supporting threshold of <0.00001, but lower than the BS1 threshold of >0.0004, so neither criterion is met. This variant has been reported in the cardiovascular disorder literature, however, the available clinical details are not sufficient for inclusion in PS4, so the PS4_Supporting code is not yet met. The computational predictor REVEL gives a score of 0.965, which is above the ClinGen Potassium Channel Arrhythmia VCEP PP3 threshold of >0.75 and predicts a damaging effect on KCNQ1 function (PP3). The variant demonstrates 60-70% of wild-type cell surface trafficking by flow cytometry (PMID: 29532034), but 140-150% of wild-type peak current density (PMID: 29532034, PMID: 30571187), which is not compatible with a proposed role as a disease-causing variant for long QT syndrome 1, so the PS3 code is not met. In summary, this variant meets the criteria to be classified as a variant of uncertain significance for long QT syndrome 1 based on the ACMG/AMP criteria applied, as specified by the ClinGen Potassium Channel Arrhythmia VCEP: PP3. (VCEP specifications version 1.0.0; date of approval 03/04/2025).

Met criteria codes

PP3	✔	REVEL = 0.965 (>0.75).

Not Met criteria codes

BS1	✖	Maximum allele frequency in any of the 5 subcontinental subpopulations in gnomAD of does not exceed 0.04%.
BS3	✖	This variant exhibits 147% of wild-type activity when co-expressed with KCNE1 in CHO cells (PMID: 30571187, Figure 6), which is not compatible with a proposed role in causing long QT syndrome 1. PubMed:30571187 The Meiler lab experimental/structural/functional simulation (http://servers.meilerlab.org/servers/show?s_id=29) classifies this variant as dysfunctional for IKs, V_1/2, and □_deactivation but normal for □_activation. PubMed:29021305 The variant demonstrates ~60-70% of wild-type cell surface trafficking by flow cytometry, but 140-150% of wild-type peak current density (PMID: 29532034, Figure 1). PubMed:29532034
BP4	✖	REVEL = 0.965 (>0.25).
PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✖	The variant demonstrates 60-70% of wild-type cell surface trafficking by flow cytometry (PMID: 29532034), but 140-150% of wild-type peak current density (PMID: 29532034, PMID: 30571187), which is not compatible with a proposed role as a disease-causing variant for long QT syndrome 1, so the PS3 code is not met. The Meiler lab experimental/structural/functional simulation (http://servers.meilerlab.org/servers/show?s_id=29) classifies this variant as dysfunctional for IKs, V_1/2, and □_deactivation but normal for □_activation (PMID: 29021305). This variant exhibits 147% of wild-type activity when co-expressed with KCNE1 in CHO cells (PMID: 30571187, Figure 6), which is not compatible with a proposed role in causing long QT syndrome 1. PubMed:30571187 The Meiler lab experimental/structural/functional simulation (http://servers.meilerlab.org/servers/show?s_id=29) classifies this variant as dysfunctional for IKs, V_1/2, and □_deactivation but normal for □_activation.

PubMed:29021305

The variant demonstrates ~60-70% of wild-type cell surface trafficking by flow cytometry, but 140-150% of wild-type peak current density (PMID: 29532034, Figure 1). PubMed:29532034

PS4	ℹ	✖	No carriers are described in the literature in sufficient phenotypic detail to evaluate this.
PM1	ℹ	✖	Variant is not in the pore helix (amino acids 300-320).
PM5	ℹ	✖	This residue is conserved across the 5 human KCNQ1 paralogues (https://www.cardiodb.org/paralogue_annotation/gene.php?name=KCNQ1) and another missense variant in the same codon, NM_000218.3(KCNQ1):c.589C>T (p.Pro197Ser), has been investigated in connection with long QT syndrome 1 (PMID: 29532034), however this variant has been classified as a variant of uncertain significance for long QT syndrome 1 by the ClinGen Potassium Channel Arrhythmia VCEP, so PM5 is not yet met.
PM2		✖	Maximum allele frequency of 0.00004576 in the European non-Finnish subpopulation in gnomAD v4.1.0 exceeds 0.001%, so PM2_Supporting is not met.
BA1	ℹ	✖	Maximum allele frequency in any of the 5 subcontinental subpopulations in gnomAD does not exceed 0.4%.
PP4	ℹ	✖	No carriers are described in the literature in sufficient phenotypic detail to meet this.

Curation History

Showing 1 to 1 of 1 rows