Variant: NM_000218.3(KCNQ1):c.1343C>T (p.Pro448Leu)

Version: 1.0

CA005629

67027 (ClinVar)

Gene: KCNQ1 (HGNC:3784)
Condition: long QT syndrome 1 (MONDO:0100316)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3a055e81-1d7d-4937-95ee-7f63f47352e6
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HGVS expressions

NM_000218.3:c.1343C>T
NM_000218.3(KCNQ1):c.1343C>T (p.Pro448Leu)
NC_000011.10:g.2588804C>T
CM000673.2:g.2588804C>T
NC_000011.9:g.2610034C>T
CM000673.1:g.2610034C>T
NC_000011.8:g.2566610C>T
NG_008935.1:g.148814C>T
ENST00000496887.7:c.986C>T
ENST00000646564.2:c.803C>T
ENST00000155840.12:c.1343C>T
ENST00000335475.6:c.962C>T
ENST00000646564.1:c.449C>T
ENST00000155840.9:c.1343C>T
ENST00000335475.5:c.962C>T
NM_000218.2:c.1343C>T
NM_181798.1:c.962C>T

Uncertain Significance

Met criteria codes 1

BS4_Supporting

Not Met criteria codes 10

BS2 BS1 BS3 BP4 PS1 PS3 PS4 PP3 PM2 PM5

Evidence Links 0

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.1343C>T is a missense variant ithat substitutes proline with leucine at codon 448 (p.Pro448Leu). This variant is present in gnomAD v.4.1.0 at a maximum allele frequency of 0.00005254, with 62 alleles / 1,179,942 total alleles 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 at least 1 proband affected with long QT syndrome 1, however, the requirement for 2 unrelated probands has not been reached so the PS4_Supporting code is not yet met (PMID: 23392653, PMID: 19716085, PMID: 25854863). The variant has been observed in a family with long QT syndrome but fails to segregate with the disease phenotype in at least 1 affected member (PMID: 23392653; BS4_Supporting). The computational predictor REVEL gives a score of 0.592, which is below the ClinGen Potassium Channel Arrhythmia VCEP PP3 threshold of >0.75 but higher than the BP4 threshold of <0.25 and does not strongly predict a damaging effect on KCNQ1 function. The computational splicing predictor SpliceAI gives a score of 0.00, which is lower than the ClinGen Potassium Channel Arrhythmia VCEP PP3 threshold of >0.5 and does not strongly predict a damaging effect on KCNQ1 splicing. 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: BS4_Supporting. (VCEP specifications version 1.0.0; date of approval 03/04/2025).

Met criteria codes

BS4_Supporting	✔	The variant has been observed in a family with long QT syndrome but fails to segregate with the disease phenotype in at least 1 affected member (PMID: 23392653; BS4_Supporting).

Not Met criteria codes

BS2	✖	At least four unaffected individuals have been reported harboring the p.Pro448Leu variant in the heterozygous state, however, the BS2 code is not considered appropriate because full penetrance is not expected for long QT syndrome 1.
BS1	✖	This variant is present in gnomAD v.4.1.0 at a maximum allele frequency of 0.00005254, with 62 alleles / 1,179,942 total alleles 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.
BS3	✖	The Meiler Lab functional impact predictor (http://servers.meilerlab.org/servers/show?s_id=29) was unable to generate functional predictions for this variant due to limitations of the model preventing assessment of secondary structure at this position (PMID: 29021305), so BS3_Supporting is not met.
BP4	✖	The computational predictor REVEL gives a score of 0.592, which is below the ClinGen Potassium Channel Arrhythmia VCEP PP3 threshold of >0.75 but higher than the BP4 threshold of <0.25 and does not strongly predict a damaging effect on KCNQ1 function. The computational splicing predictor SpliceAI gives a score of 0.00, which is lower than the ClinGen Potassium Channel Arrhythmia VCEP PP3 threshold of >0.5 and does not strongly predict a damaging effect on KCNQ1 splicing.
PS1	✖	The equivalent codon of the paralogue KCNQ3 encodes leucine, so PS1_Moderate was not considered.
PS3	✖	The Meiler Lab functional impact predictor (http://servers.meilerlab.org/servers/show?s_id=29) was unable to generate functional predictions for this variant due to limitations of the model preventing assessment of secondary structure at this position (PMID: 29021305), so PS3_Supporting is not met.
PS4	✖	

This variant is rare and has been reported in at least 1 proband affected with long QT syndrome 1, however, the requirement for 2 unrelated probands has not been reached so the PS4_Supporting code is not yet met (PMID: 23392653, PMID: 19716085, PMID: 25854863).

PP3	✖	The computational predictor REVEL gives a score of 0.592, which is below the ClinGen Potassium Channel Arrhythmia VCEP PP3 threshold of >0.75 but higher than the BP4 threshold of <0.25 and does not strongly predict a damaging effect on KCNQ1 function. The computational splicing predictor SpliceAI gives a score of 0.00, which is lower than the ClinGen Potassium Channel Arrhythmia VCEP PP3 threshold of >0.5 and does not strongly predict a damaging effect on KCNQ1 splicing.
PM2	✖	This variant is present in gnomAD v.4.1.0 at a maximum allele frequency of 0.00005254, with 62 alleles / 1,179,942 total alleles 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.
PM5	✖	Two other missense variants in the same codon, NM_000218.3(KCNQ1):c.1343C>A (p.Pro448Gln) and NM_000218.3(KCNQ1):c.1343C>G (p.Pro448Arg), have been investigated in relation to long QT syndrome 1, but neither has been classified yet by the ClinGen Potassium Channel Arrhythmia VCEP. In addition, the equivalent codon of the paralogue KCNQ3 encodes leucine, so the conservation is not sufficient to consider the PM5 code.

Curation History

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