Variant: NM_000218.3(KCNQ1):c.1343C>A (p.Pro448Gln)

Version: 1.0

CA028774

219923 (ClinVar)

Gene: KCNQ1 (HGNC:3784)
Condition: long QT syndrome 1 (MONDO:0100316)
Inheritance Mode: Autosomal dominant inheritance
UUID: 9b0f0c0e-b44d-44a8-853d-9d14a712aaff
Approved on: 2025-07-01
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HGVS expressions

NM_000218.3:c.1343C>A
NM_000218.3(KCNQ1):c.1343C>A (p.Pro448Gln)
NC_000011.10:g.2588804C>A
CM000673.2:g.2588804C>A
NC_000011.9:g.2610034C>A
CM000673.1:g.2610034C>A
NC_000011.8:g.2566610C>A
NG_008935.1:g.148814C>A
ENST00000496887.7:c.986C>A
ENST00000646564.2:c.803C>A
ENST00000155840.12:c.1343C>A
ENST00000335475.6:c.962C>A
ENST00000646564.1:c.449C>A
ENST00000155840.9:c.1343C>A
ENST00000335475.5:c.962C>A
NM_000218.2:c.1343C>A
NM_181798.1:c.962C>A

Uncertain Significance

Not Met criteria codes 6

BS1 BP4 BA1 PP3 PM1 PM2

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>A is a missense variant predicted to cause substitution of proline by glutamine at amino acid 448 (p.Pro448Gln). To our knowledge, this variant has not been reported in the literature in any individuals with long QT syndrome 1. This variant is present in gnomAD v.4.1.0 at a maximum allele frequency of 0.0001538, with 14 alleles / 91008 total alleles in the South Asian 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. To our knowledge, functional assays have not been reported for this variant. The computational predictor REVEL gives a score of 0.512, 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 for donor and acceptor gain and loss, which is lower than the ClinGen Potassium Channel Arrhythmia VCEP PP3 threshold of greater than or equal to 0.2 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 due to insufficient evidence for long QT syndrome 1 based on the ACMG/AMP criteria applied, as specified by the ClinGen Potassium Channel Arrhythmia VCEP. (VCEP specifications version 1.0.0; date of approval 03/04/2025).

Not Met criteria codes

BS1	✖	This variant is present in gnomAD v.4.0.0 at a maximum allele frequency of 0.0001538, with 14 alleles / 91008 total alleles in the South Asian 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.
BP4	✖	The computational predictor REVEL gives a score of 0.512, 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.
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	The computational predictor REVEL gives a score of 0.512, 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 for donor and acceptor gain and loss, 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.
PM1	✖	This variant is not a missense substitution within the pore helix consisting of amino acids 300 to 320, which is a well-characterized functional domain required for the channel function and selectivity filter of KCNQ1 (PMID: 15649981), and has been confirmed to show an absence of likely benign or benign variants listed in gnomAD.
PM2	✖	This variant is present in gnomAD v.4.1.0 at a maximum allele frequency of 0.0001538, with 14 alleles / 91008 total alleles in the South Asian 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.

Curation History

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