Variant: NM_000218.3(KCNQ1):c.958C>T (p.Pro320Ser)

Version: 1.0

CA008910

67130 (ClinVar)

Gene: KCNQ1 (HGNC:3784)
Condition: long QT syndrome 1 (MONDO:0100316)
Inheritance Mode: Autosomal dominant inheritance
UUID: bd615d9c-f6ab-4dfc-ac84-670e9fc3918b
Approved on: 2025-07-01
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HGVS expressions

NM_000218.3:c.958C>T
NM_000218.3(KCNQ1):c.958C>T (p.Pro320Ser)
NC_000011.10:g.2583471C>T
CM000673.2:g.2583471C>T
NC_000011.9:g.2604701C>T
CM000673.1:g.2604701C>T
NC_000011.8:g.2561277C>T
NG_008935.1:g.143481C>T
ENST00000496887.7:c.697C>T
ENST00000646564.2:c.514C>T
ENST00000155840.12:c.958C>T
ENST00000335475.6:c.577C>T
ENST00000646564.1:c.160C>T
ENST00000155840.9:c.958C>T
ENST00000335475.5:c.577C>T
NM_000218.2:c.958C>T
NM_181798.1:c.577C>T

Uncertain Significance

Met criteria codes 4

PP3 PM2_Supporting PM1 PS4_Supporting

Not Met criteria codes 6

PS3 PP1 PM5 BA1 BS1 BP4

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.958C>T is a missense variant predicted to cause substitution of proline by serine at amino acid 320 (p.Pro320Ser). This variant is rare and has been reported in 2 apparently unrelated probands affected with long QT syndrome 1 (PS4_Supporting; PMID: 23392653, PMID: 32383558). This variant is absent in gnomAD v.2.1.1, but present in gnomAD v4.1.0 at a maximum allele frequency of 0.0000008994, with 1 allele / 1,111,812 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 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 (PM1). The computational predictor REVEL gives a score of 0.98, which is above the ClinGen Potassium Channel Arrhythmia VCEP PP3 threshold of >0.75 and predicts a damaging effect on KCNQ1 function (PP3). 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: PS4_Supporting, PM2_Supporting, PM1, PP3. (VCEP specifications version 1.0.0; date of approval 03/04/2025).

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.98, which is above the ClinGen Potassium Channel Arrhythmia VCEP PP3 threshold of >0.75 and predicts a damaging effect on KCNQ1 function (PP3).
PM2_Supporting	✔	This variant is absent in gnomAD v.2.1.1, but present in gnomAD v4.0.0 at a maximum allele frequency of 8.994e-7, with 1 allele/1111812 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).
PM1	✔	This variant is 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 (PM1).
PS4_Supporting	✔	This variant is rare and has been reported in 2 apparently unrelated probands affected with long QT syndrome 1 (PS4_Supporting; PMID: 23392653, PMID: 32383558).

Not Met criteria codes

PS3	✖	This variant has been shown to disrupt KCNQ1 function in one experimental assay, Experimental Functional Simulation (PMID 35442947), but has not yet been reported in other functional studies to meet PS3 at any level.
PP1	✖	Six family members carry this variant, but none with enough clinical detail to count (PMID: 23392653).
PM5	✖	Another missense variant in the same codon, c.959C>A (p.Pro320His), has been classified as likely pathogenic for long QT syndrome 1 by the ClinGen Potassium Channel Arrhythmia VCEP, while no benign missense variants have been identified in this codon. This residue has been confirmed to be highly conserved across all 5 human KCNQ paralogues, and SpliceAI has been used to confirm that neither variant has a predicted impact on KCNQ1 splicing. Not scoring this data for PM5 so as not to double-count with PM1.
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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