

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 PS4_Supporting PM1

PM2_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 0.000008994, 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).
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).
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).
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).

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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