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Variant: NM_000218.3(KCNQ1):c.898G>A (p.Ala300Thr)

Version: 1.0

CA008554

3128 (ClinVar)

Gene: KCNQ1 (HGNC:3784)
Condition: long QT syndrome 1 (MONDO:0100316)
Inheritance Mode: Autosomal recessive inheritance
UUID: 41ccd0c0-c514-4656-8b37-c1f84389a648
Approved on: 2025-07-01
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HGVS expressions

NM_000218.3:c.898G>A
NM_000218.3(KCNQ1):c.898G>A (p.Ala300Thr)
NC_000011.10:g.2572963G>A
CM000673.2:g.2572963G>A
NC_000011.9:g.2594193G>A
CM000673.1:g.2594193G>A
NC_000011.8:g.2550769G>A
NG_008935.1:g.132973G>A
ENST00000496887.7:c.637G>A
ENST00000646564.2:c.478-10472G>A
ENST00000155840.12:c.898G>A
ENST00000335475.6:c.517G>A
ENST00000646564.1:c.124-10472G>A
ENST00000155840.9:c.898G>A
ENST00000335475.5:c.517G>A
NM_000218.2:c.898G>A
NM_181798.1:c.517G>A

Uncertain Significance

Met criteria codes 2

PS3 PP3

Not Met criteria codes 8

PS4 PM2 PM1 PM3 PM5 BA1 BS1 BP5

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.898G>A is a missense variant predicted to cause substitution of alanine by threonine at amino acid 300 (p.Ala300Thr). This variant is present in gnomAD v.4.1.0 at a maximum allele frequency of 0.0003167, with 59996/1613624 in the Admixed American 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. The variant is located 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. However, this variant is not rare (meeting PM2_Supporting), so it cannot be considered for PM1. This variant has been reported in at least four affected probands with a diagnosis of long QT syndrome, however, available reported details are not sufficiently specific for long QT syndrome 1, so the PP4 code is not met (PMIDs: 9641694, 27251404, 28600177, 34165182). This variant has been detected in at least 1 individual with Jervell and Lange-Nielsen syndrome who had both a long QT interval and congenital deafness. This individual was compound heterozygous for the variant and a VUS (c.1066_1071del (p.Gln356_Gln357del)) and not confirmed in trans (PMID: 34165182), so the PM3 code is not met. The computational predictor REVEL gives a score of 0.907, which is above the ClinGen Potassium Channel Arrhythmia VCEP PP3 threshold of >0.75 and predicts a damaging effect on KCNQ1 function (PP3). This variant has been shown to disrupt KCNQ1 function in two required experimental assays, including automated patch-clamp, mislocalization by immunofluorescence, and structural and functional simulation (PS3; PMIDs: 9641694, 30571187, 11087258,17999538). Please note that the variant has only been observed to cause disease in the homozygous or compound heterozygous state. 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: PS3 and PP3. (VCEP specifications version 1.0.0; date of approval 03/04/2025).

Met criteria codes

PS3	✔	This variant has been shown to disrupt KCNQ1 function in two required experimental assays, including automated patch-clamp, mislocalization by immunofluorescence, and structural and functional simulation (PS3; PMIDs: 9641694, 30571187, 11087258,17999538).
PP3	✔	The computational predictor REVEL gives a score of 0.907, which is above the ClinGen Potassium Channel Arrhythmia VCEP PP3 threshold of >0.75 and predicts a damaging effect on KCNQ1 function.

Not Met criteria codes

PS4	✖	This variant is rare and has been reported in 2 apparently unrelated probands affected with long QT syndrome 1, but they have a second variant so PM3 may be a better fit (PMIDs: 9641694, 34165182).
PM2	✖	This variant is present in gnomAD v.4.0.0 at a maximum allele frequency of 0.0003167, with 19/59996 alleles in the Admixed American population, which is higher than the ClinGen Potassium Channel Arrhythmia VCEP PM2_Supporting threshold of <0.00001.
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. However, this variant is not rare (meeting PM2_Supporting), so it cannot be considered for PM1.
PM3	✖	This variant has been detected in at least 1 individual with Jervell and Lange-Nielsen syndrome who had both a long QT interval and congenital deafness. This individual was compound heterozygous for the variant and a VUS (c.1066_1071del (p.Gln356_Gln357del)) and not confirmed in trans (0 points, PMID: 34165182), so the PM3 code is not met. This variant has also been detected in at least 2 individuals with Romano Ward syndrome who had long QT intervals, but no congenital deafness (PMIDs: 28600177, 9641694), so PM3 does not apply.

PM5			Other missense variants in the same codon, c.898G>T (p.Ala300Ser) and c.899C>A (p.Ala300Glu), have been classified as VUS by the ClinGen Potassium Channel Arrhythmia VCEP. 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 none of the variants have a predicted impact on KCNQ1 splicing.
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			This variant is present in gnomAD v.4.0.0 at a maximum allele frequency of 0.0003167, with 19/59996 alleles in the Admixed American population, which is lower than the ClinGen Potassium Channel Arrhythmia VCEP BS1 threshold of >0.0004 (BS1). This variant is reported in gnomAD v2.1.1 but not meeting the BS1 criteria.
BP5			This variant has been observed in 1 patient with an alternate molecular basis for disease with a phenotype that is not sufficiently specific (PMID: 27251404), but the other variant, SCN5A (c.1399G>T p.Ala467Ser), is a VUS in ClinVar, so BP5 is not met.

Curation History

Showing 1 to 1 of 1 rows