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Variant: NM_000218.3(KCNQ1):c.1552C>T (p.Arg518Ter)

Version: 1.0

CA005894

3131 (ClinVar)

Gene: KCNQ1 (HGNC:3784)
Condition: long QT syndrome 1 (MONDO:0100316)
Inheritance Mode: Autosomal dominant inheritance
UUID: 7b0a5163-52c0-4b26-8a49-5b09cd269be6
Approved on: 2025-07-01
Published on: 2025-07-02

HGVS expressions

NM_000218.3:c.1552C>T
NM_000218.3(KCNQ1):c.1552C>T (p.Arg518Ter)
NC_000011.10:g.2768881C>T
CM000673.2:g.2768881C>T
NC_000011.9:g.2790111C>T
CM000673.1:g.2790111C>T
NC_000011.8:g.2746687C>T
NG_008935.1:g.328891C>T
ENST00000496887.7:c.1195C>T
ENST00000646564.2:c.1012C>T
ENST00000155840.12:c.1552C>T
ENST00000335475.6:c.1171C>T
ENST00000646564.1:c.658C>T
ENST00000155840.9:c.1552C>T
ENST00000335475.5:c.1171C>T
NM_000218.2:c.1552C>T
NM_181798.1:c.1171C>T

Likely Pathogenic

Met criteria codes 1

PVS1

Not Met criteria codes 6

BP4 PS3 PP3 PM3 PM2 BS1

Evidence Links 1

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.1552C>T (p.Arg518Ter) is a nonsense variant in exon 12 of 16 that introduces a premature stop codon at codon 518 and is predicted to trigger nonsense-mediated decay (PVS1). This variant is present in gnomAD v.4.1.0 at a maximum allele frequency of 0.0001737, with 205/1179992 alleles in the European (non-Finnish) population, which is lower than the ClinGen Potassium Channel Arrhythmia VCEP BS1 threshold of >0.0004 and higher than the PM2_Supporting threshold of <0.00001, so neither criterion is met. This variant has been detected in at least 2 apparently unrelated individuals with Jervell and Lange-Nielsen syndrome who had both a long QT interval and congenital deafness and harbored the variant in the homozygous state (1 pt, PMID: 29922582, PMID: 28438721, PM3), however PM3 is not met since this code requires the variant to be sufficiently rare (meeting PM2_Supporting). Additional individuals harbored the variant in the compound heterozygous state, some with autosomal recessive long QT syndrome (without congenital deafness) and others with Jervell and Lange-Nielsen syndrome (PMID: 24912595, PMID: 23392653). One individual harbored the variant in the compound heterozygous state, confirmed in trans with the NM_000218.3(KCNQ1):c.1573G>A (p.Ala525Thr) variant, which has not yet been classified by the ClinGen Potassium Channel Arrhythmia VCEP (PMID: 24912595). This variant has been shown to disrupt KCNQ1 function in at least four experimental assays, including manual patch-clamp and KCNQ1 mislocalization by immunofluorescence (PMID: 24912595, PMID: 25705178), however, PS3_Supporting is not met since the variant has already met PVS1. In summary, this variant meets the criteria to be classified as likely pathogenic for long QT syndrome 1 based on the ACMG/AMP criteria applied, as specified by the ClinGen Potassium Channel Arrhythmia VCEP: PVS1. (VCEP specifications version 1.0.0; date of approval 03/04/2025).

Met criteria codes

PVS1	✔	This is a nonsense variant located in exon 12 of 16 and introduces a premature stop codon between codons 1-581, which is predicted to lead to nonsense-mediated decay (PVS1).

Not Met criteria codes

BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✖	This variant has been shown to disrupt KCNQ1 function in at least four experimental assays, including manual patch-clamp and KCNQ1 mislocalization by immunofluorescence (PMID: 24912595, PMID: 25705178), however, PS3_Supporting is not met since the variant has already met PVS1. CHO cells transfected with variant KCNQ1 yielded no detectable current (PMID: 25705178, Figure 2E, compared to wild-type in Figure 2B). Localization is abnormal as well, with successful staining only when the cells have been permeabilized but generating no cell surface staining in the non-permeabilized state (Figure S1). PubMed:25705178
PP3	✖	The computational predictor SpliceAI gives a score of 0.1, which is below the ClinGen Potassium Channel Arrhythmia VCEP PP3 threshold of >0.5 and does not predict a damaging effect on KCNQ1 function.
PM3	✖	This variant has been detected in at least 2 apparently unrelated individuals with Jervell and Lange-Nielsen syndrome who had both a long QT interval and congenital deafness and harbored the variant in the homozygous state (1 pt, PMID: 29922582, PMID: 28438721, PM3), however PM3 is not met since this code requires the variant to be sufficiently rare (meeting PM2_Supporting). Additional individuals harbored the variant in the compound heterozygous state, some with autosomal recessive long QT syndrome (without congenital deafness) and others with Jervell and Lange-Nielsen syndrome (PMID: 24912595, PMID: 23392653). One individual harbored the variant in the compound heterozygous state, confirmed in trans with the NM_000218.3(KCNQ1):c.1573G>A (p.Ala525Thr) variant, which has not yet been classified by the ClinGen Potassium Channel Arrhythmia VCEP (PMID: 24912595).
PM2	✖	

This variant is present in gnomAD v.4.1.0 at a maximum allele frequency of 0.0001737, with 205/1179992 alleles in the European (non-Finnish) population, which is lower than the ClinGen Potassium Channel Arrhythmia VCEP BS1 threshold of >0.0004 and higher than the PM2_Supporting threshold of <0.00001, so neither criterion is met.

BS1			This variant is present in gnomAD v.4.1.0 at a maximum allele frequency of 0.0001737, with 205/1179992 alleles in the European (non-Finnish) population, which is lower than the ClinGen Potassium Channel Arrhythmia VCEP BS1 threshold of >0.0004 and higher than the PM2_Supporting threshold of <0.00001, so neither criterion is met.

Curation History 

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