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Variant: NM_000218.3(KCNQ1):c.217C>A (p.Pro73Thr)

Version: 1.0

CA006724

53031 (ClinVar)

Gene: KCNQ1 (HGNC:3784)
Condition: long QT syndrome 1 (MONDO:0100316)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3575e5d9-e92d-4853-b029-e517871f979b
Approved on: 2025-07-01
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HGVS expressions

NM_000218.3:c.217C>A
NM_000218.3(KCNQ1):c.217C>A (p.Pro73Thr)
NC_000011.10:g.2445315C>A
CM000673.2:g.2445315C>A
NC_000011.9:g.2466545C>A
CM000673.1:g.2466545C>A
NC_000011.8:g.2423121C>A
NG_008935.1:g.5325C>A
ENST00000496887.7:c.24-68C>A
ENST00000646564.2:c.217C>A
ENST00000155840.12:c.217C>A
ENST00000155840.9:c.217C>A
ENST00000496887.6:c.24-68C>A
NM_000218.2:c.217C>A

Uncertain Significance

Met criteria codes 2

BP5 PS4_Moderate

Not Met criteria codes 7

BP4 BS1 BS3 PP1 PP3 PS3 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.217C>A (p.Pro73Thr) is a missense variant that causes substitution of proline with threonine at amino acid 73. This variant is present in gnomAD v.4.1.0 at a maximum allele frequency of 0.0002533, with 287 alleles / 1132988 total alleles in the European non-Finnish 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. This variant is rare and has been reported in at least 4

apparently unrelated probands affected with long QT syndrome 1 (PS4_Moderate; PMID: 15840476, PMID: 19716085, PMID: 22949429, PMID: 24606995, PMID: 20851114). The variant has been reported to segregate with long QT syndrome 1 through a proband and 1 affected family member (PMID: 26743238), which is not sufficient to meet PP1. This variant has been observed in 1 patient with an alternate molecular basis for disease (NM_000335.5(SCN5A):c.1231G>A (p.Val411Met)) with a phenotype that matches long QT syndrome 3 (BP5; PMID: 28588847, PMID: 23098067). This variant has also been observed in 1 patient with additional variants in KCNQ1 present both in cis (NM_000218.3(KCNQ1):c.502G>A (p.Gly168Arg)) and in trans (listed as p.Asp454Thrfs*7) providing an alternate molecular basis for disease (PMID: 24667783), however, BP5 is only applicable when the phenotypes match another form of LQTS. The computational predictor REVEL gives a score of 0.566, 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 0.01 for donor gain, 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. The Meiler Lab functional impact predictor (http://servers.meilerlab.org/servers/show?s_id=29) was unable to generate a prediction of functional impact for this variant due to a limitation of the model and the unavailability of secondary structure at this residue (PMID: 29021305), so neither PS3_Supporting nor BS3_Supporting was met. 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: PS4_Moderate, BP5. (VCEP specifications version 1.0.0; date of approval 03/04/2025).

Met criteria codes

BP5	✔	This variant has been observed in 1 patients with an alternate molecular basis for disease (NM_000335.5(SCN5A):c.1231G>A (p.Val411Met)) with a phenotype that matches long QT syndrome 3 (BP5; PMID: 28588847, PMID: 23098067). This variant has also been observed in 1 patient with additional variants in KCNQ1 present both in cis (NM_000218.3(KCNQ1):c.502G>A (p.Gly168Arg)) and in trans (listed as p.Asp454Thrfs*7) providing an alternate molecular basis for disease (PMID: 24667783), however, BP5 is only applicable when the phenotypes match another form of LQTS. The variant has also been observed in 1 proband with sudden cardiac death who carried the NM_000238.4(KCNH2):c.87C>A (p.Phe29Leu), however, additional phenotype details were not available (PMID: 29598884).
PS4_Moderate	✔	This variant is rare and has been reported in 4 apparently unrelated probands affected with long QT syndrome 1 (PS4_Moderate; PMID: 19716085).

Not Met criteria codes

BP4	✖	The computational predictor REVEL gives a score of 0.566, 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 0.01 for donor gain, 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.
BS1	✖	This variant is present in gnomAD v.4.0.0 at a maximum allele frequency of 0.0002533, with 287 alleles / 1132988 total alleles in the European non-Finnish 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.
BS3	✖	The Meiler Lab functional impact predictor (http://servers.meilerlab.org/servers/show?s_id=29) was unable to generate a prediction of functional impact for this variant due to a limitation of the model and the unavailability of secondary structure at this residue (PMID: 29021305), so neither PS3_Supporting nor BS3_Supporting were met.

PP1		✖	The variant has been reported to segregate with long QT syndrome 1 through the proband and 1 affected family member (PMID: 26743238), which is not sufficient to meet PP1.
PP3		✖	The computational predictor REVEL gives a score of 0.566, 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 0.01 for donor gain, 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.
PS3		✖	The Meiler Lab functional impact predictor (http://servers.meilerlab.org/servers/show?s_id=29) was unable to generate a prediction of functional impact for this variant due to a limitation of the model and the unavailability of secondary structure at this residue (PMID: 29021305), so neither PS3_Supporting nor BS3_Supporting were met.
PM2		✖	This variant is present in gnomAD v.4.0.0 at a maximum allele frequency of 0.0002533, with 287 alleles / 1132988 total alleles in the European non-Finnish 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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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000218.3(KCNQ1):c.217C>A (p.Pro...	Uncertain Significance	Long QT Syndrome 1	2025-07-01	1.0	ClinGen Potassium Channel Arrhythmia Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for KCNQ1 Version 1.0.0	KCNQ1

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