# *Variant: NM_000218.3(KCNQ1):c.1343C>G (p.Pro448Arg)*

Version: 1.0

*CA005620*

*67026 (ClinVar)*

**Gene**: KCNQ1 (HGNC:3784)
**Condition**: long QT syndrome 1 (MONDO:0100316)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** 01cd0b19-0176-4062-8c84-fcd29d25b1b9
**Approved on**: 2025-07-01
**Published on**: 2025-07-02

## *HGVS expressions*

**NM_000218.3:c.1343C>G**
NM_000218.3(KCNQ1):c.1343C>G (p.Pro448Arg)
NC_000011.10:g.2588804C>G
CM000673.2:g.2588804C>G
NC_000011.9:g.2610034C>G
CM000673.1:g.2610034C>G
NC_000011.8:g.2566610C>G
NG_008935.1:g.148814C>G
ENST00000496887.7:c.986C>G
ENST00000646564.2:c.803C>G
ENST00000155840.12:c.1343C>G
ENST00000335475.6:c.962C>G
ENST00000646564.1:c.449C>G
ENST00000155840.9:c.1343C>G
ENST00000335475.5:c.962C>G
NM_000218.2:c.1343C>G
NM_181798.1:c.962C>G

**Benign**

**Met criteria codes** 3

PP1 BA1 BP5

**Not Met criteria codes** 12

BS1 BS4 BS3 PP3 PP4 PS1 PS4 PM1 PM3 PM5 PM2 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.1343C>G (p.Pro448Arg) is a missense variant predicted to cause substitution of proline by arginine at amino acid 448 (p.Pro448Arg). This variant has been reported as a polymorphism that is present in approximately 20% of Asian individuals (PMID: 11997281). This variant is present in gnomAD v.4.1.0 at a maximum allele frequency of 0.09851, with 4408 alleles / 44746 total alleles and 203 homozygotes in the East Asian population, which is higher than the ClinGen Potassium Channel Arrhythmia VCEP BA1 threshold of >0.004 (BA1). The variant has been reported to segregate with long QT syndrome 1 through the proband and 3 affected family members from one family (PP1; PMID: 17597962). This variant has been observed in 1 patient with an alternate molecular basis for disease with a phenotype that is not sufficiently specific (BP5; PMID 15242738). Functional studies have been performed on this variant (PMIDs: 15051636, 15242738), but it does not yet meet the criteria for PS3/BS3. In summary, this variant meets the criteria to be classified as benign for long QT syndrome 1 based on the ACMG/AMP criteria applied, as specified by the ClinGen Potassium Channel Arrhythmia VCEP: BA1, BP5, and PP1. (VCEP specifications version 1.0.0; date of approval 03/04/2025).**

**Met criteria codes**

| | | |
|---|---|---|
| **PP1** | ✔ | The variant has been reported to segregate with long QT syndrome 1 through the proband and 3 affected family members from one family (PP1; PMID: 17597962). |
| **BA1** | ✔ | This variant is present in gnomAD v.4.0.0 at a maximum allele frequency of 0.09851, with 4408 alleles / 44746 total alleles and 203 homozygotes in the East Asian population, which is higher than the ClinGen Potassium Channel Arrhythmia VCEP BA1 threshold of >0.004. |
| **BP5** | ✔ | This variant has been observed in 1 patient with an alternate molecular basis for disease with a phenotype that is not sufficiently specific (BP5; PMID 15242738). |

**Not Met criteria codes**

| | | |
|---|---|---|
| **BS1** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **BS4** | ✖ | The variant has been observed in a family with long QT syndrome but fails to segregate with the disease phenotype in at least 1 affected member (PMID: 15242738), but the phenotype is not sufficient to apply BS4. |
| **BS3** | ✖ | This variant has been shown to have a non-deleterious impact on KCNQ1 function in an electrophysiology assay (PMID: 15242738, 15051636), but was not shown to have a statistical significance, so BS3 is not met. |
| **PP3** | ✖ | The computational predictor REVEL gives a score of 0.594, 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 0.0 for donor and acceptor gain and loss, 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. |
| **PP4** | ✖ | This variant has been reported in at least one affected proband 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: 17597962). |
| **PS1** | ✖ | There is no other missense variant that encodes the same amino acid substitution in this codon of KCNQ1. There is also not the same missense substitution in the equivalent codon of the paralogue KCNQ2. |

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|---|---|---|---|
| **PS4** | | ✖ | In order to be evaluated for this criterion, the variant must be rare (not meet BS1). |
| **PM1** | | ✖ | This variant is not 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. |
| **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 homozygous for the variant (PM3= 0 points, PMID 28595573), but phase is unknown so PM3 is not yet met. |
| **PM5** | | ✖ | Two missense variants are present in ClinVar at the same codon, but this amino acid is not conserved across all 5 human KCNQ paralogues. Poor conservation (ineligibility for PM5) is defined whenever 1 or more KCNQ's show a different amino acid at the position. |
| **PM2** | | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **BP4** | | ✖ | The computational predictor REVEL gives a score of 0.594, 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. |

## Curation History

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