The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000218.3(KCNQ1):c.1032G>A (p.Ala344=)

Version: 1.0

CA005005

3135 (ClinVar)

Gene: KCNQ1 (HGNC:3784)
Condition: long QT syndrome 1 (MONDO:0100316)
Inheritance Mode: Autosomal dominant inheritance
UUID: c959f6f1-1316-4a0b-a82e-622e7817c145
Approved on: 2025-07-01
Published on: 2025-07-02

HGVS expressions

NM_000218.3:c.1032G>A
NM_000218.3(KCNQ1):c.1032G>A (p.Ala344=)
NC_000011.10:g.2583545G>A
CM000673.2:g.2583545G>A
NC_000011.9:g.2604775G>A
CM000673.1:g.2604775G>A
NC_000011.8:g.2561351G>A
NG_008935.1:g.143555G>A
ENST00000496887.7:c.771G>A
ENST00000646564.2:c.588G>A
ENST00000155840.12:c.1032G>A
ENST00000335475.6:c.651G>A
ENST00000646564.1:c.234G>A
ENST00000155840.9:c.1032G>A
ENST00000335475.5:c.651G>A
NM_000218.2:c.1032G>A
NM_181798.1:c.651G>A

Pathogenic

Met criteria codes 5

PM2_Supporting PS4 PS3 PP4 PP3

Not Met criteria codes 3

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.1032G>A is a synonymous variant (p.Ala344=) predicted to affect KCNQ1 mRNA splicing. The computational splicing predictor SpliceAI gives scores of 0.49 for donor gain and 0.38 for donor loss, which are higher than the ClinGen Potassium Channel Arrhythmia VCEP PP3 threshold of greater than or equal to 0.2 and predict that the variant disrupts KCNQ1 splicing (PP3). The variant is observed at an extremely low frequency in the population with a maximum allele frequency (gnomAD 4.1.0) of 0.000001701, with 2 in 1,175,668 individuals of European (non-Finnish) ancestry (PM2_Supporting). Functional studies have been performed on this variant and meet criteria with demonstrated deleterious effects on electrophysiology and RNA metabolism (PS3, PMID: 29857160, 10477533, 17292394). There are 23 reported probands in the literature with a clinical diagnosis of Long QT syndrome (PS4; PMID: 26118460, PMID: 21810471, PMID: 9654228, PMID: 29497013, PMID: 17292394). An additional case reports provides specific details that are highly specific for a diagnosis of Long QT syndrome in an individual with the variant who had a significantly prolonged QTc at rest and exercise-triggered events (PP4, PMID: 21810471). In summary, this variant meets the criteria to be classified as pathogenic for long QT syndrome 1 based on the ACMG/AMP criteria applied, as specified by the ClinGen Potassium Channel Arrhythmia VCEP: PS3, PS4, PM2_Supporting, PP3, and PP4. (VCEP specifications version 1.0.0; date of approval 03/04/2025).

Met criteria codes

PM2_Supporting	✔	in gnomAD 4.0 present in 2 in 1,175,668 individuals of European (non-Finnish) ancestry or 0.000001701 which is 0.0001701% This is less than the 0.001% cut off set by KCNQ1 VCEP and is met
PS4	✔	PS4 is Met by > 6 probands.
PS3	✔	PMID: 29857160 counts for 1 electrophysiology PMID: 10477533 counts for 1 RNA metabolism PMID: 17292394 counts for 1 RNA metabolism and 1 electrophysiology Total: 2 RNA metabolism and 2 electrophysiology is STRONG per KCNQ1 VCEP PS3 criteria
PP4	✔	Patient’s phenotype or family history is highly specific for a disease with a single genetic etiology. QT prolongation above 480ms AND Swimming-associated events OR Treadmill stress test result (PMID: 21699858) OR T-wave morphology characteristic of LQT1 (PMID: 7586261, 29141844) PMID: 21810471 – 2011, Identification and functional characterization of KCNQ1 mutations around the exon 7-intron 7 junction affecting the splicing process (Tsuji et al, Horie senior author). Proband with QTc 558 resting and 615 during exercise
PP3	✔	The computational splicing predictor SpliceAI gives scores of 0.49 for donor gain and 0.38 for donor loss, which are higher than the ClinGen Potassium Channel Arrhythmia VCEP PP3 threshold of greater than or equal to 0.2 and predict that the variant disrupts KCNQ1 splicing (PP3).

Not Met criteria codes

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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