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Variant: NM_001165963.4(SCN1A):c.1259C>T (p.Ala420Val)

Version: 1.0

CA303506

189996 (ClinVar)

Gene: SCN1A (HGNC:6323)
Condition: generalized epilepsy with febrile seizures plus (MONDO:0018214)
Inheritance Mode: Autosomal dominant inheritance
UUID: fd9eb26f-7592-4ee0-9836-5c77dc8d41c7
Approved on: 2024/7/30
Published on: 2025/10/23

HGVS expressions

NM_001165963.4:c.1259C>T
NM_001165963.4(SCN1A):c.1259C>T (p.Ala420Val)
NC_000002.12:g.166046888G>A
CM000664.2:g.166046888G>A
NC_000002.11:g.166903398G>A
CM000664.1:g.166903398G>A
NC_000002.10:g.166611644G>A
NG_011906.1:g.31752C>T
ENST00000689288.1:c.1259C>T
ENST00000303395.9:c.1259C>T
ENST00000635750.1:c.1259C>T
ENST00000635776.1:c.1259C>T
ENST00000636194.1:c.1259C>T
ENST00000636759.1:c.*1049C>T
ENST00000637968.1:n.1511C>T
ENST00000637988.1:c.1259C>T
ENST00000640036.1:c.1259C>T
ENST00000641575.1:c.1259C>T
ENST00000641603.1:c.1259C>T
ENST00000641996.1:c.*813C>T
ENST00000671940.1:c.1259C>T
ENST00000673490.1:n.3732C>T
ENST00000674923.1:c.1259C>T
ENST00000303395.8:c.1259C>T
ENST00000375405.7:c.1259C>T
ENST00000409050.1:c.1259C>T
ENST00000423058.6:c.1259C>T
NM_001165963.1:c.1259C>T
NM_001165964.1:c.1259C>T
NM_001202435.1:c.1259C>T
NM_006920.4:c.1259C>T
NM_001165963.2:c.1259C>T
NM_001165964.2:c.1259C>T
NM_001202435.2:c.1259C>T
NM_001353948.1:c.1259C>T
NM_001353949.1:c.1259C>T
NM_001353950.1:c.1259C>T

NM_001353951.1:c.1259C>T
NM_001353952.1:c.1259C>T
NM_001353954.1:c.1259C>T
NM_001353955.1:c.1259C>T
NM_001353957.1:c.1259C>T
NM_001353958.1:c.1259C>T
NM_001353960.1:c.1259C>T
NM_001353961.1:c.-1167C>T
NM_006920.5:c.1259C>T
NR_148667.1:n.1664C>T
NM_001165963.3:c.1259C>T
NM_001165964.3:c.1259C>T
NM_001202435.3:c.1259C>T
NM_001353948.2:c.1259C>T
NM_001353949.2:c.1259C>T
NM_001353950.2:c.1259C>T
NM_001353951.2:c.1259C>T
NM_001353952.2:c.1259C>T
NM_001353954.2:c.1259C>T
NM_001353955.2:c.1259C>T
NM_001353957.2:c.1259C>T
NM_001353958.2:c.1259C>T
NM_001353960.2:c.1259C>T
NM_001353961.2:c.-1167C>T
NM_006920.6:c.1259C>T
NR_148667.2:n.1645C>T

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PM6
PS4_Supporting PP3_Moderate

Not Met criteria codes 2

PM1 PM5

Evidence Links 0

Expert Panel

Epilepsy Sodium Channel VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Epilepsy Sodium Channel Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for SCN1A Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Epilepsy Sodium Channel VCEP

The c.1259C>T variant in SCN1A is a missense variant predicted to cause substitution of alanine by valine at amino acid 420 (p.Ala420Val). The variant has been identified as a de novo occurrence with unconfirmed parental relationships in two individuals with a consistent phenotype in the published literature (PMIDs:35696452, 26096185) (PM6_Moderate), and in one individual with seizures and intellectual disability with unknown inheritance (PMID: 22944210) (PS4_Supporting). The variant is absent from the population database, gnomAD v4.0 (PM2_Supporting). A novel missense variant at the corresponding position in the paralogous gene, SCN8A (p.Ala408Thr), has been previously reported (PMID: 26993267), however, >1 novel variant in a paralogous gene is required for PM5 (not met). The computational predictor REVEL gives a score of 0.95, which is above the threshold of 0.773, evidence that correlates with a maximum strength of PP3_Moderate. In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal dominant SCN1A-related

disorder based on the ACMG/AMP criteria applied, as specified by the ClinGen Epilepsy Sodium Channel VCEP: PM6_Moderate, PS4_Supporting, PM2_Supporting, PP3_Moderate. (version 1.0; July 23, 2024).

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.0
PM6	✔	This variant has been reported as de novo with unconfirmed parental relationships in two individuals with consistent phenotypes.
PS4_Supporting	✔	This variant was identified in one individual with epilepsy and ID, unknown inheritance.
PP3_Moderate	✔	REVEL=0.95

Not Met criteria codes

PM1	✖	Does not fall within a PER
PM5	✖	SCN8A Ala408Thr would likely reach PLP, however our specifications require >1 novel missense variant at corresponding position for paralogous genes.

Curation History

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