Variant: NM_001040142.2(SCN2A):c.1399G>A (p.Ala467Thr)

Version: 1.0

CA1939819

452471 (ClinVar)

Gene: SCN2A (HGNC:6326)
Condition: complex neurodevelopmental disorder (MONDO:0100038)
Inheritance Mode: Autosomal dominant inheritance
UUID: 1884e5f2-7fc9-4150-8381-123c9f745b24
Approved on: 2025-06-24
Published on: 2025-06-24

HGVS expressions

NM_001040142.2:c.1399G>A
NM_001040142.2(SCN2A):c.1399G>A (p.Ala467Thr)
NC_000002.12:g.165315486G>A
CM000664.2:g.165315486G>A
NC_000002.11:g.166171996G>A
CM000664.1:g.166171996G>A
NC_000002.10:g.165880242G>A
NG_008143.1:g.81085G>A
ENST00000631182.3:c.1399G>A
ENST00000375437.7:c.1399G>A
ENST00000635945.1:n.1762G>A
ENST00000636071.2:c.1399G>A
ENST00000636135.1:c.1270G>A
ENST00000636384.2:c.1399G>A
ENST00000636662.2:c.*1922G>A
ENST00000636769.1:c.1399G>A
ENST00000636985.2:c.1003G>A
ENST00000637266.2:c.1399G>A
ENST00000637367.1:c.*1332G>A
ENST00000638151.1:n.1483G>A
ENST00000283256.10:c.1399G>A
ENST00000375427.4:c.1399G>A
ENST00000375437.6:c.1399G>A
ENST00000424833.5:c.1399G>A
ENST00000480032.4:n.1542G>A
ENST00000631182.2:c.1399G>A
NM_001040142.1:c.1399G>A
NM_001040143.1:c.1399G>A
NM_021007.2:c.1399G>A
NM_001040143.2:c.1399G>A
NM_001371246.1:c.1399G>A
NM_001371247.1:c.1399G>A
NM_021007.3:c.1399G>A

Met criteria codes 2

Expert Panel

Benign

BP4 **BA1**

Not Met criteria codes 13

PM1 **PM5** **PM6** **PM2** **BS4** **BS3** **PS1** **PS2** **PS3** **PS4** **BP2** **PP1** **PP3**

Evidence Links 0

Epilepsy Sodium Channel VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Epilepsy Sodium Channel Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for SCN2A Version 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Epilepsy Sodium Channel VCEP

The NM_001040142.2(SCN2A):c.1399G>A variant in SCN2A is a missense variant predicted to cause substitution of Alanine by Threonine at amino acid 467 (p.Ala467Thr). The highest population minor allele frequency in gnomAD 4.1.0 is 0.01501% (9/59978 alleles) in the Admixed American population, which is higher than the ClinGen Epilepsy Sodium Channel VCEP threshold (>0.01%) for BA1, and therefore meets this criterion (BA1). The computational predictor REVEL gives a score of 0.269, (which is below the threshold of 0.290), evidence that does not predict a damaging effect on SCN2A function (BP4). In summary, this variant meets the criteria to be classified as benign for autosomal dominant complex neurodevelopmental disorder based on the ACMG/AMP criteria applied, as specified by the ClinGen Epilepsy Sodium Channel VCEP: BP4, BA1. (Specification Version 2.0.0; 1/7/2025).

Met criteria codes

BP4	ℹ	✓	The computational predictor REVEL gives a score of 0.269, (which is below the threshold of 0.290), evidence that does not predict a damaging effect on SCN2A function (BP4).
BA1	ℹ	✓	The highest population minor allele frequency in gnomAD 4.1.0 is 0.01501% (9/59978 alleles) in the Admixed American population, which is higher than the ClinGen Epilepsy Sodium Channel VCEP threshold (>0.01%) for BA1, and therefore meets this criterion (BA1).

Not Met criteria codes

PM1	ℹ	✗	This variant does not reside within a region of SCN2A that is defined as a mutational hotspot or critical functional domain by the ClinGen Epilepsy Sodium Channel VCEP.
PM5	ℹ	✗	5 different missense variants (SCN2A c.1399G>A p.Ala467Pro, SCN2A c.1393G>T p.Ala467Ser, SCN2A c.1400C>T p.Ala467Val, SCN1A c.1393A>G p.Thr465Ala, and SCN3A c.1397C>T p.Ser466Leu,) in the same or paralogous codon have been reported (ClinVar IDs: 2500543, 983216, 1318705, 1352508, and 3371473). However, these variants have not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen Epilepsy Sodium Channel VCEP.
PM6	ℹ	✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2		✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	To our knowledge, functional assays have not been reported for this variant.
PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	ℹ	✖	To our knowledge, functional assays have not been reported for this variant.
PS4	ℹ	✖	This variant has been reported in one family and two additional probands meeting criteria for a complex neurodevelopmental disorder. However, PS4_Moderate cannot be applied because this variant is present in control populations (gnomAD, PMID 29635106, 38059254).
BP2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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