Variant: NM_001040142.2(SCN2A):c.1526A>G (p.Lys509Arg)

Version: 1.0

CA318202

207086 (ClinVar)

Gene: SCN2A (HGNC:6326)
Condition: complex neurodevelopmental disorder (MONDO:0100038)
Inheritance Mode: Autosomal dominant inheritance
UUID: 20d691da-2b31-4fcc-bb92-9a9df416c0e6
Approved on: 2025-08-26
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HGVS expressions

NM_001040142.2:c.1526A>G
NM_001040142.2(SCN2A):c.1526A>G (p.Lys509Arg)
NC_000002.12:g.165315613A>G
CM000664.2:g.165315613A>G
NC_000002.11:g.166172123A>G
CM000664.1:g.166172123A>G
NC_000002.10:g.165880369A>G
NG_008143.1:g.81212A>G
ENST00000631182.3:c.1526A>G
ENST00000375437.7:c.1526A>G
ENST00000635945.1:n.1889A>G
ENST00000636071.2:c.1526A>G
ENST00000636135.1:c.1397A>G
ENST00000636384.2:c.1526A>G
ENST00000636662.2:c.*2049A>G
ENST00000636769.1:c.1526A>G
ENST00000636985.2:c.1130A>G
ENST00000637266.2:c.1526A>G
ENST00000637367.1:c.*1459A>G
ENST00000638151.1:n.1610A>G
ENST00000283256.10:c.1526A>G
ENST00000375427.4:c.1526A>G
ENST00000375437.6:c.1526A>G
ENST00000480032.4:n.1669A>G
ENST00000631182.2:c.1526A>G
NM_001040142.1:c.1526A>G
NM_001040143.1:c.1526A>G
NM_021007.2:c.1526A>G
NM_001040143.2:c.1526A>G
NM_001371246.1:c.1526A>G
NM_001371247.1:c.1526A>G
NM_021007.3:c.1526A>G

Likely Benign

Met criteria codes 2

BS1 BP4

Not Met criteria codes 6

PS1 PP3 PP4 PM1 PM5 PM2

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 SCN2A Version 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Epilepsy Sodium Channel VCEP

The filtering allele frequency (the lower threshold of the 95% CI of 21/1,613,966) of thec.1526A>G variant in SCN2A is 0.00001144 for Non-Finnish European chromosomes by gnomAD v4.1.0, which is higher than the ClinGen Epilepsy Sodium Channel Variant Curation Expert Panel threshold (>0.0002%) for BS1, and therefore meets this criterion (BS1). The computational predictor REVEL gives a score of 0.243 (REVEL threshold for BP4 supporting 0.183-0.290, PMID: 36413997), evidence that does not predict a damaging effect on SCN2A function (BP4). This missense change has been observed in one individual with seizures (PMID: 25131622). However, the inheritance and a detailed information of the phenotype is not described. In summary, this variant has been classified as likely benign for autosomal dominant complex neurodevelopmental disorder based on the ACMG/AMP criteria applied, as specified by the Epilepsy Sodium Channel Expert Panel: BS1, BP4 (version 2.0; approved 8/26/25).

Met criteria codes

BS1	✔	The filtering allele frequency (the lower threshold of the 95% CI of 21/1,613,966) of the c.1526A>G variant in SCN2A is 0.001144% (gnomAD v4.1.0) for Non-Finnish European chromosomes, which is higher than the ClinGen Epilepsy Sodium Channel Variant Curation Expert Panel threshold (>0.0002%) for BS1, and therefore meets this criterion BS1).
BP4	✔	The computational predictor REVEL gives a score of 0.243 (REVEL threshold for BP4 supporting 0.183-0.290, PMID: 36413997), evidence that does not predict a damaging effect on SCN2A function (BP4).

Not Met criteria codes

PS1	✖	NM_001040142.2(SCN2A):c.1527A>G (p.Lys509=) synonymous Likely benign SCN1A: no paralogous variants SCN3A: no P/LP variants NM_006922.4(SCN3A):c.1516AGA[1] (p.Arg507del) VUS NM_006922.4(SCN3A):c.1521A>C (p.Arg507Ser) LB NM_006922.4(SCN3A):c.1520G>A (p.Arg507Lys) LB SCN8A: NM_001330260.2(SCN8A):c.1497G>A (p.Lys499=) LB
PP3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	✖	Other phenotypes not consistent w/neurodevelopmental disorder: 0 points (for supporting 1-1.5 points) PMID: 25131622. WES in 78 patients with various neurodevelopmental disabilities. Patient 72 has the SCN2A c.1526 A>G (K509R) variant. However, the inheritance is unknown. Phenotype: only serizures, MRI findings: normal. They

described epileptic encephalopathy, early infantile, 11 (MIM# 613721) as the disease. The phenotype evidence does not meet the complex Neurodevelopmental Disorder described by Helbig et al, 2018 (PMID: 30311377)

PM1	✖	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 Expert Panel.
PM5	✖	NM_001040142.2(SCN2A):c.1527A>G (p.Lys509=) synonymous Likely benign SCN1A: no paralogous variants SCN3A: no P/LP variants NM_006922.4(SCN3A):c.1516AGA[1] (p.Arg507del) VUS NM_006922.4(SCN3A):c.1521A>C (p.Arg507Ser) LB NM_006922.4(SCN3A):c.1520G>A (p.Arg507Lys) LB SCN8A: NM_001330260.2(SCN8A):c.1497G>A (p.Lys499=) LB
PM2	✖	Allele frequency is above 0.0002% in GnomAD v4.1.0 (0.001144%)

Curation History

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