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_001040142.2(SCN2A):c.2657T>C (p.Leu886Ser)

Version: 1.0

CA317886

206972 (ClinVar)

Gene: SCN2A (HGNC:6326)
Condition: complex neurodevelopmental disorder (MONDO:0100038)
Inheritance Mode: Autosomal dominant inheritance
UUID: 7e708ed4-b2fc-4bf7-8cf3-3c83e2b68ad7
Approved on: 2025/3/25
Published on: 2025/4/24

HGVS expressions

NM_001040142.2(SCN2A):c.2657T>C (p.Leu886Ser)
NM_001040142.2:c.2657T>C
NC_000002.12:g.165344649T>C
CM000664.2:g.165344649T>C
NC_000002.11:g.166201159T>C
CM000664.1:g.166201159T>C
NC_000002.10:g.165909405T>C
NG_008143.1:g.110248T>C
ENST00000631182.3:c.2657T>C
ENST00000375437.7:c.2657T>C
ENST00000636071.2:c.2657T>C
ENST00000636135.1:c.*976T>C
ENST00000636384.2:c.*644T>C
ENST00000636662.2:c.*3180T>C
ENST00000636769.1:c.*599T>C
ENST00000636985.2:c.2261T>C
ENST00000637266.2:c.2657T>C
ENST00000673831.1:c.95T>C
ENST00000673883.1:c.95T>C
ENST00000674133.1:c.508T>C
ENST00000283256.10:c.2657T>C
ENST00000375427.4:c.2657T>C
ENST00000375437.6:c.2657T>C
ENST00000480032.4:n.2800T>C
ENST00000631182.2:c.2657T>C
NM_001040142.1:c.2657T>C
NM_001040143.1:c.2657T>C
NM_021007.2:c.2657T>C
NM_001040143.2:c.2657T>C
NM_001371246.1:c.2657T>C
NM_001371247.1:c.2657T>C
NM_021007.3:c.2657T>C

Likely Pathogenic

Met criteria codes 5

PM6 PM1 PM2_Supporting PS4_Supporting PP3_Moderate

Not Met criteria codes 21

PS1 PS2 PS3 PP1 PP2 PP4 PVS1 PM3 PM5 PM4 BA1 BS2 BS1 BS4 BS3 BP5 BP7 BP4 BP3 BP1 BP2

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 c.2657T>C variant in SCN2A is a missense variant predicted to cause a substitution of leucine by serine at amino acid 886 (p.Leu886Ser). This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 2 individuals with a complex neurodevelopmental disorder (PM6); (PMID: 3541799; internal data GeneDx). It has also been identified in an additional proband with a complex neurodevelopmental disorder (PS4_supporting) (internal data, Labcorp). This variant is absent from gnomAD v4.0) (PM2_supporting). The computational predictor REVEL gives a score of 0.971, evidence that correlates with impact to SCN2A function (PP3_moderate). This variant resides within a region of SCN2A that is defined as a mutation hotspot by the ClinGen Epilepsy Sodium Channel VCEP (PM1). In summary, this variant meets the criteria to be classified as Likely Pathogenic for autosomal dominant complex neurodevelopmental disorder based on the ACMG/AMP criteria applied, as specified by the ClinGen Epilepsy Sodium Channel VCEP: (PP3_moderate, PM1, PM6, PM2_supporting, PS4_supporting). Approved March 25, 2025.

Met criteria codes

PM6	✔	Reported de novo in one case w/ neonatal epilepsy (PMID: 35431799) (0.5 pts). Identified in the de novo state in a patient with epilepsy by a clinical lab (GeneDx) (0.5 pts). Reported de novo in one case in broad NICU cohort (PMID: 38778310) (0 pts).
PM1	✔	Located in PER 6
PM2_Supporting	✔	Absent in controls (gnomAD v:4.0)
PS4_Supporting	✔	Reported by one lab (LabCorp/Invitae) in a person with a neurodevelopmental disorder.
PP3_Moderate	✔	REVEL score = 0.971

Not Met criteria codes

PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2		✖	N/A
PP4		✖	N/A
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3		✖	N/A
PM5		✖	There are novel missense changes reported in SCN2A and paralogous genes, but since only one is classified as P/LP, does not meet threshold to apply PM5. SCN1A:p.Leu895Pro (ClinVar ID: 1367610) was classified as pathogenic in ClinVar by a clinical lab (Invitae); SCN3A:p.Leu887Phe (ClinVar ID: 1989062) was classified as a VUS by a clinical lab (Invitae); SCN2A:p.Leu886Met was classified as a VUS by a clinical lab (Invitae); SCN2A:p.Leu886Val (ClinVar ID: 2065720) was classified as a VUS by a clinical lab (Invitae)
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2		✖	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
BS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP7	✖	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
BP3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1	✖	N/A
BP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

nowing 1 to 1 of 1 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001040142.2(SCN2A):c.2657T>C (...	Likely Pathogenic	Complex Neurodevelopmental Disorder	2025-04-24	1.0	ClinGen Epilepsy Sodium Channel Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for SCN2A Version 2.0.0	SCN2A

nowing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.