

*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:** 2025-03-25

**Published on:** 2025-04-24

### *HGVS expressions*

**NM\_001040142.2:c.2657T>C**

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

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

- PM1
- PM6
- PS4\_Supporting
- PM2\_Supporting
- PP3\_Moderate

Not Met criteria codes 21

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

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

PM1		✓	Located in PER 6
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).
PS4_Supporting		✓	Reported by one lab (LabCorp/Invitae) in a person with a neurodevelopmental disorder.
PM2_Supporting		✓	Absent in controls (gnomAD v:4.0)
PP3_Moderate		✓	REVEL score = 0.971









#### Not Met criteria codes

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)

<b>PM4</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BA1</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BS2</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BS1</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BS4</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BS3</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP4</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP3</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP1</b>			N/A
<b>BP2</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP5</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP7</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>PS1</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>PS2</b>			

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

<b>PS3</b>	 	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>PP1</b>	 	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>PP2</b>		N/A
<b>PP4</b>		N/A
<b>PVS1</b>	 	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History [↗](#)

Showing 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.