

Variant: *NM_001330260.2(SCN8A):c.4892T>C*
(p.Ile1631Thr)

Version: 1.0

[CA384880453](#)

[691254 \(ClinVar\)](#)

Gene: SCN8A ([HGNC:6334](#))

Condition: complex neurodevelopmental disorder ([MONDO:0100038](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: ea04729d-f891-485e-9f88-7aabaf604695

Approved on: 2025-09-23

Published on: 2025-12-17

HGVS expressions

NM_001330260.2:c.4892T>C

NM_001330260.2(SCN8A):c.4892T>C (p.Ile1631Thr)

NC_000012.12:g.51806378T>C

CM000674.2:g.51806378T>C

NC_000012.11:g.52200162T>C

CM000674.1:g.52200162T>C

NC_000012.10:g.50486429T>C

NG_021180.2:g.220143T>C

NG_021180.3:g.221421T>C

ENST00000354534.11:c.4892T>C

ENST00000627620.5:c.4892T>C

ENST00000636945.2:c.2956T>C

ENST00000662684.1:c.4892T>C

ENST00000668547.1:c.4769T>C

ENST00000354534.10:c.4892T>C

ENST00000355133.7:c.4769T>C

ENST00000545061.5:c.4769T>C

ENST00000599343.5:c.4925T>C

ENST00000627620.2:c.4892T>C

NM_001177984.2:c.4769T>C

NM_014191.3:c.4892T>C

NM_001330260.1:c.4892T>C

NM_001369788.1:c.4769T>C

NM_014191.4:c.4892T>C

NM_001177984.3:c.4769T>C

Likely Pathogenic

Met criteria codes **5**

PP3_Moderate

PS4_Moderate

PS2_Supporting

PM5_Supporting

PM2_Supporting

Not Met criteria codes **2**

PS1

PM1

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 SCN8A Version 2.0.0*

Evidence submitted by expert panel



Epilepsy Sodium Channel VCEP

The NM_001330260.2:c.4892T>C in SCN8A is a missense variant predicted to change Ile to Thr at codon 1631 (p.Ile1631Thr). The variant is absent from population databases (gnomAD v4.1; PM2_Supporting). The computational predictor REVEL gives a score of 0.98 which is higher than the threshold set >0.75 (PP3_Moderate). This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with Complex Neurodevelopmental Disorder (ClinVar Variation ID: 691254; PS2_Supporting). This variant has been identified in one patient with focal epilepsy in infancy without familial testing (Labcorp Genetics (formerly Invitae). Four different missense variants, in the same codon and in the paralogous gen SCN2A, have been reported in patients with Complex Neurodevelopmental Disorder (ClinVar Variation IDs: 3635210, 427167, 2020237, 835364, PM5_Supporting). This variant has been reported in 2 probands meeting Complex Neurodevelopmental Disorder criteria (ClinVar Variation ID: 691254, Labcorp Genetics (formerly Invitae); PS4_Moderate). In summary, this variant has been classified as likely pathogenic for autosomal dominant complex neurodevelopmental disorder based on the ACMG/AMP criteria applied, as specified by the Epilepsy Sodium Channel Expert Panel: PM2_Supporting, PS2_Supporting, PM5_Supporting, PP3_Moderate, PS4_Moderate (specifications v2.0; September 23, 2025).





Met criteria codes

PP3_Moderate	 	The computational predictor REVEL gives a score of 0.98, which is higher than the threshold set >0.75 (PP3_Moderate). Although is ≥ 0.932 (Strong, PMID: 36413997) strength should be capped at Moderate.
PS4_Moderate	 	Note 2: In instances of very rare variants where case-control studies may not reach statistical significance, the prior observation of the variant in multiple unrelated patients with the same phenotype, and its absence in controls, may be used as moderate level of evidence. Patient from Labcorp Genetics (formerly Invitae) with focal epilepsy in infancy Patient from Department of Genetics, Rouen University Hospital, France with Intellectual disability, Seizure, Autism
PS2_Supporting	 	This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with Complex Neurodevelopmental Disorder in the Department of Genetics, Rouen University Hospital, France (PS2_Supporting; ClinVar Variation ID: 691254). Labcorp (Invitae) identified the variant in one individual with focal epilepsy in infancy, no familial testing was completed.
PM5_Supporting	 	NM_001330260.2(SCN8A):c.4893C>G (p.Ile1631Met) ClinVar Variation ID: 3635210 (Submitted by Labcorp (formerly Invitae) Classified: LP (7 points) Met: PM2_Supporting: absent from gnomAD v4.1 PP3_Moderate: REVEL 0.86 (0.773-0.932) PS2_Moderate: 2 points: 1 de novo case Complex Neurodevelopmental Disorder from GeneDx. It is published too at Supplementary Table 1, related to de novo variants (ID - 94273 - Variant in GRCh37 (chr12-52200163 C>G)) from PMID: 33057194, 35982159). GeneDx specified: Male proband 42y at time of testing via trio exome, variant was de novo (confirmed). Phenotype: GTC seizures at 6mo, simple partial at 6y, auditory and visual hallucinations, mild ID, dolichocephaly, bitemporal narrowing, big ears, overweight. Labcorp (Invitae) has identified de variant as de novo with parentage confirmed in one individual with focal epilepsy in infancy. PS4_Moderate: GeneDx variant and Labcorp (Invitae) variant. 2 points NM_001330260.2(SCN8A):c.4892T>A (p.Ile1631Asn) ClinVar Variation ID: 427167 (Submitted by GeneDx) Classified: VUS (3 points) Met: PM2_Supporting: absent from gnomAD v4.1 PP3_Moderate: REVEL 0.98 (capped at Moderate) Not met: PM5: other VUS variants PM6: Unclear if de novo because only proband was tested. Female proband 6y at time of testing via an epilepsy panel of 53 genes (sequencing and del/dup analysis). Phenotype: Reported history of seizures and developmental delay ***Paralogous Genes*** aa 1631 in SCN8A = 1640 in SCN2A *GeneDx SCN2A NM_021007 c.4919T>A (p.Ile1640Asn) 2-months-old male at time of

testing, trio exome, variant was de novo (confirmed) Phenotype of seizures, polymicrogyria, ventriculomegaly, jerks, apnea, bradycardia, colpocephaly, and concern for pituitary insufficiency. PM2_supporting, PP3_mod, PS2_supporting NM_001040142.2(SCN2A):c.4918A>C (p.Ile1640Leu) ClinVar Variation ID: 2020237 (Submitted by Labcorp Genetics (formerly Invitae) Classified: VUS (3 points) Met: PM2_Supporting: absent from gnomAD v4.1 PP3_Moderate: REVEL 0.8 (0.773-0.932) It has been identified in one individual w/ history consistent with BFNIS. No segregation NM_001040142.2(SCN2A):c.4918A>T (p.Ile1640Phe) ClinVar Variation ID: 835364 - Submitted by Labcorp and CENTOGENE Classified: LP (6 points) Met: PM2_Supporting: absent from gnomAD v4.1 PP3_Moderate: REVEL 0.8 (0.773-0.932) PS2_supporting PMID: 30619928 Table 2 and 32712949 table S2 variant reported but without segregation. ClinVar says it is de novo but there is no supporting data Labcorp Genetics (formerly Invitae) identified the variant as de novo (with parentage confirmed) in individual w/ neonatal seizures. PS4_Moderate: 2 points. both patients by both submitters. Developmental and epileptic encephalopathy

PM2_Supporting   This variant is absent from gnomAD v4.1 (PM2_Supporting).

Not Met criteria codes

- | | | |
|------------|---|---|
| PS1 |   | No Same amino acid change as a previously established pathogenic variant regardless of nucleotide No identical Pathogenic and Likely Pathogenic variants in SCN1A, SCN2A, SCN3A |
| PM1 |   | This variant does not reside within a region of SCN8A that is defined as a PER by the ClinGen Epilepsy Sodium Channel Expert Panel. |

Curation History



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