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Variant: NM_001330260.2(SCN8A):c.2533T>C (p.Ser845Pro)

Version: 1.0

CA16042904

373333 (ClinVar)

Gene: SCN8A (HGNC:6334)
Condition: complex neurodevelopmental disorder (MONDO:0100038)
Inheritance Mode: Autosomal dominant inheritance
UUID: 384cff6d-77c4-4955-84eb-ed960c74d6dc
Approved on: 2025/8/26
Published on: 2025/12/17

HGVS expressions

NM_001330260.2(SCN8A):c.2533T>C (p.Ser845Pro)
NM_001330260.2:c.2533T>C
NC_000012.12:g.51762665T>C
CM000674.2:g.51762665T>C
NC_000012.11:g.52156449T>C
CM000674.1:g.52156449T>C
NC_000012.10:g.50442716T>C
NG_021180.2:g.176430T>C
NG_021180.3:g.177708T>C
ENST00000354534.11:c.2533T>C
ENST00000548086.3:c.380T>C
ENST00000627620.5:c.2533T>C
ENST00000636945.2:c.537T>C
ENST00000662684.1:c.2533T>C
ENST00000668547.1:c.2533T>C
ENST00000354534.10:c.2533T>C
ENST00000355133.7:c.2533T>C
ENST00000545061.5:c.2533T>C
ENST00000550891.4:n.2661T>C
ENST00000599343.5:c.2566T>C
ENST00000627620.2:c.2533T>C
NM_001177984.2:c.2533T>C
NM_014191.3:c.2533T>C
NM_001330260.1:c.2533T>C
NM_001369788.1:c.2533T>C
NM_014191.4:c.2533T>C
NM_001177984.3:c.2533T>C

Likely Pathogenic

Met criteria codes 4

PP3_Moderate PM5_Supporting PM2_Supporting PM1

Not Met criteria codes 17

PP1 PM6 PM4 BA1 BS2 BS1 BS3 BP5 BP7 BP4 BP3

Expert Panel

Epilepsy Sodium Channel VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Epilepsy Sodium Channel Expert Panel Specifications to the ACMG/AMP Variant*

BP2 PVS1 PS1 PS2 PS3 PS4

Evidence Links 0

Interpretation Guidelines for SCN8A Version 2.0.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Epilepsy Sodium Channel VCEP

The NM_001330260.2:c.2533T>C variant in SCN8A is a missense variant predicted to cause substitution of serine by proline at amino acid 845 (p.Ser845Pro). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.960, which is above the threshold of 0.773, evidence that correlates with impact to SCN8A function (PP3_Moderate). Another missense variant (c.2534C>T (p.Ser845Phe), ClinVar Variation ID: 207109) in the same codon has been classified as likely pathogenic for autosomal dominant complex neurodevelopmental disorder by the ClinGen Epilepsy Sodium Channel VCEP (PM5_Supporting). This variant resides within a region, amino acids 844-852, of SCN8A that is defined as a mutational hotspot and/or critical functional domain 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: PM1, PP3_Moderate, PM2_Supporting, PM5_Supporting. (VCEP specifications version 2.0.0; approved 8/26/25).

Met criteria codes

PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.960, which is above the threshold of 0.773, evidence that correlates with impact to SCN8A function (PP3_Moderate).
PM5_Supporting	✔	Another missense variant (c.2534C>T (p.Ser845Phe), ClinVar Variation ID: 207109) in the same codon has been classified as likely pathogenic for autosomal dominant complex neurodevelopmental disorder by the ClinGen Epilepsy Sodium Channel VCEP (PM5_Supporting).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PM1	✔	This variant resides within a region, amino acids 844-852, of SCN8A that is defined as a mutational hotspot and/or critical functional domain by the ClinGen Epilepsy Sodium Channel VCEP (PM1).

Not Met criteria codes

PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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
BS3		✖	To our knowledge, functional assays have not been reported for this variant.
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
BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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		✖	To our knowledge, functional assays have not been reported for this variant.
PS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001330260.2(SCN8A):c.2533T>C (...	Likely Pathogenic	Complex Neurodevelopmental Disorder	2025-12-17	1.0	ClinGen Epilepsy Sodium Channel Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for SCN8A Version 2.0.0	SCN8A

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