Variant: NM_001040142.2(SCN2A):c.4782G>C (p.Trp1594Cys)

Version: 1.0

CA16603919

383825 (ClinVar)

Gene: SCN2A (HGNC:6326)
Condition: complex neurodevelopmental disorder (MONDO:0100038)
Inheritance Mode: Autosomal dominant inheritance
UUID: 6cd56d8c-7204-4ecb-b20d-06066ea55d7a
Approved on: 2024-11-26
Published on: 2025-02-20

HGVS expressions

NM_001040142.2:c.4782G>C
NM_001040142.2(SCN2A):c.4782G>C (p.Trp1594Cys)
NC_000002.12:g.165386976G>C
CM000664.2:g.165386976G>C
NC_000002.11:g.166243486G>C
CM000664.1:g.166243486G>C
NC_000002.10:g.165951732G>C
NG_008143.1:g.152575G>C
ENST00000631182.3:c.4782G>C
ENST00000375437.7:c.4782G>C
ENST00000636071.2:c.4782G>C
ENST00000636135.1:c.*3101G>C
ENST00000636384.2:c.*2769G>C
ENST00000636662.2:c.*5305G>C
ENST00000636769.1:c.*2724G>C
ENST00000636985.2:c.4386G>C
ENST00000637266.2:c.4782G>C
ENST00000283256.10:c.4782G>C
ENST00000375427.4:c.4782G>C
ENST00000375437.6:c.4782G>C
ENST00000480032.4:n.8213G>C
ENST00000631182.2:c.4782G>C
NM_001040142.1:c.4782G>C
NM_001040143.1:c.4782G>C
NM_021007.2:c.4782G>C
NM_001040143.2:c.4782G>C
NM_001371246.1:c.4782G>C
NM_001371247.1:c.4782G>C
NM_021007.3:c.4782G>C

Likely Pathogenic

Met criteria codes 6

PP3_Moderate PS1_Moderate PS4_Moderate PM2_Supporting PM6 PM5_Supporting

Expert Panel

Epilepsy Sodium Channel VCEP

Not Met criteria codes 10

BA1 BS2 BS1 BP4 BP3 BP2 PS2 PS3 PP1 PM1

Evidence Links 0

Criteria Specification Information

- **Criteria Specification:** *ClinGen Epilepsy Sodium Channel Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for SCN2A Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Epilepsy Sodium Channel VCEP

The c.4782G>C variant in SCN2A is a missense variant predicted to cause substitution of tryptophan by cysteine at amino acid 1594 (p.Trp1594Cys). The variant has been identified in multiple individuals meeting criteria for complex neurodevelopmental disorder (PS4, PM6)(PMID: 34004075, internal lab contributors). It is absent from the population database gnomAD v2.1.1 and v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.924, which is above the threshold of 0.773, evidence that correlates with a maximum strength of PP3_Moderate. The same amino acid change (p.Trp1594Cys), resulting from a different nucleotide change[c.4782G>T](PMID: 35365919, PMID: 23603762) is classified as likely pathogenic for complex neurodevelopmental disorder by the ClinGen Epilepsy Sodium Channel VCEP(PS1_Moderate). Additionally, another missense variant in the same codon c.4780T>A, p.Trp1594Arg reaches likely pathogenic based on current criteria (PM5_Supporting). 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: PS4_Moderate, PM6, PS1_Moderate, PM2_Supporting, PP3_Moderate, PM5_Supporting. (version 1.0; November 26, 2024).

Met criteria codes

PP3_Moderate	✔	REVEL 0.924
PS1_Moderate	✔	SCN2A p.W1594C c.4782G>T occurs in the same gene with the same amino acid change, but has a different c.(G>T). This variant has been reported as de novo in 2 cases in the literature (PM6_Moderate), is absent in gnomAD v2 and v4 (PM2_Supporting), and has a REVEL score of 0.924 (PP3_Moderate). In sum, this variant is classified as a VLP using the current VCEP guidelines (v1.0.0). See details below from literature and VCI page for details. There are no other variants reported in paralogous genes for this amino acid position.
PS4_Moderate	✔	Observed in 1 case at ambry genetics. Female proband w/ congenital seizures (day 1 onset), global delay, unspecified dysmorphic features, and hypotonia. Family history unknown. Singleton case, no parental testing. Panel testing. PS4 +1 point = PS4_Moderate
PM2_Supporting	✔	Absent in gnomAD v2 and v4
PM6	✔	Observed in 2 de novo cases. 1. Observed at GeneDx one patient w/ infantile refractory seizures. De novo, but parentage not confirmed. PM6 +0.5 points 2. PMID: 34004075 reports 8month old F. Generalized tonic seizures developed at 1 day of age and spasms from 3 months of age. Diagnosed with Ohtahara syndrome at 3 months of age. WES revealed a de novo missense mutation in the SCN2A gene (c.4782G>C; p.Trp1594Cys). PM6 +0.5 Total +1 point = moderate
PM5_Supporting	✔	SCN2A p.W1594R c.4780T>A occurs in the same gene with a different amino acid change. This variant has been reported as de novo in 3 cases in the literature and at a clinical laboratory (PM6_Moderate), is absent in gnomAD v2

and v4 (PM2_Supporting), and has a REVEL score of 0.968. In total, this variant gets to Likely Pathogenic using the current VCEP guidelines (v1.0.0). See details below from literature and VCI page for details. There are no other variants reported in paralogous genes for this amino acid position.

Not Met criteria codes

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
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
PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✖	No experimental evidence reported
PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	Amino acid position not eligible for PM1 (using updating PM1 11/2024 alignment)

Curation History

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