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Variant: NM_001040142.2(SCN2A):c.5317G>A (p.Ala1773Thr)

Version: 1.0

CA318033

207024 (ClinVar)

Gene: SCN2A (HGNC:6326)
Condition: complex neurodevelopmental disorder (MONDO:0100038)
Inheritance Mode: Autosomal dominant inheritance
UUID: 6069a6a1-2957-454e-9774-80e2a3fba60c
Approved on: 2024-05-07
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HGVS expressions

NM_001040142.2:c.5317G>A
NM_001040142.2(SCN2A):c.5317G>A (p.Ala1773Thr)
NC_000002.12:g.165389123G>A
CM000664.2:g.165389123G>A
NC_000002.11:g.166245633G>A
CM000664.1:g.166245633G>A
NC_000002.10:g.165953879G>A
NG_008143.1:g.154722G>A
ENST00000631182.3:c.5317G>A
ENST00000375437.7:c.5317G>A
ENST00000636071.2:c.5317G>A
ENST00000636135.1:c.*3636G>A
ENST00000636384.2:c.*3304G>A
ENST00000636662.2:c.*5840G>A
ENST00000636769.1:c.*3259G>A
ENST00000636985.2:c.4921G>A
ENST00000637266.2:c.5317G>A
ENST00000283256.10:c.5317G>A
ENST00000375427.4:c.5317G>A
ENST00000375437.6:c.5317G>A
ENST00000480032.4:n.8748G>A
ENST00000631182.2:c.5317G>A
NM_001040142.1:c.5317G>A
NM_001040143.1:c.5317G>A
NM_021007.2:c.5317G>A
NM_001040143.2:c.5317G>A
NM_001371246.1:c.5317G>A
NM_001371247.1:c.5317G>A
NM_021007.3:c.5317G>A

Pathogenic

Met criteria codes 5

PM1_Strong PM2_Supporting PS2_Moderate PS3 PS4

Expert Panel

Epilepsy Sodium Channel VCEP

Not Met criteria codes 14

PM5 BA1 BS1 BS4 BS3 BP5 BP4 BP1 BP2 PS1 PP1 PP2 PP3 PP4

Evidence Links 1

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.5317G>A (NM_001040142.2) variant in SCN2A is a missense variant predicted to cause substitution of Alanine by Threonine at amino acid 1773 (p.Ala1773Thr). This variant has been reported in 9 probands with complex neurodevelopmental disorder (PMIDs: 34758253, 33000761, 28947817, 29655203, 31440721, 31785789, 34469436, 32400968, 35431799), including as a de novo occurrence with confirmed parental relationships in 2 individual(s) (PMIDs: 31785789, 32400968) and as a de novo occurrence with assumed parental relationships in 2 individuals PMID: 33000761, 35431799). This variant is absent from gnomAD v2.1.1. Whole-cell patch-clamp recordings of voltage-gated Na+ currents in HEK293T cell in showed a significant hyperpolarizing shift in the voltage dependence of the activation curve and a depolarizing shift of steady-state fast inactivation accompanied by decreased current density indicating that this variant impacts protein function (PMIDs: 32400968, 32400968). This variant resides within a region of SCN2A 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 pathogenic for complex neurodevelopmental disorder based on the ACMG/AMP criteria applied, as specified by the ClinGen Epilepsy Sodium Channel VCEP: PS3, PS4, PS2, PM1, PM2_Supporting. (Epilepsy Sodium Channel VCEP specifications v1.0; approved 5/9/23).

Met criteria codes

PM1_Strong	✔	This variant resides within a region of SCN2A that is defined as a mutational hotspot and/or critical functional domain by the ClinGen Epilepsy Sodium Channel VCEP (PM1_Strong)
PM2_Supporting	✔	This variant is absent from gnomAD v[20210610] (PM2_Supporting)
PS2_Moderate	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in 2 individual(s) and with assumed de novo variants with neurodevelopmental phenotype in 2 individuals (PS2_Moderate) PMID: 31785789, 32400968, 33000761, and 35431799.
PS3	✔	Whole-cell patch-clamp recordings of voltage-gated Na+ currents in HEK293T cell in showed a significant hyperpolarizing shift in the voltage dependence of the activation curve and a depolarizing shift of steady-state fast inactivation accompanied by decreased current density indicating that this variant impacts protein function (PMIDs: 32400968, 32400968)(PS3_Strong) Whole-cell patch-clamp e-physiology recordings of voltage-gated Na+ currents in HEK293T cell expressing the A1773T and WT Na+ channels showed that the A1773T channel exhibited a significant hyperpolarizing shift in the voltage dependence of the activation curve and a depolarizing shift of steady-state fast inactivation accompanied by decreased current density with a half-maximal activation potential at ~10 mV the of −68.76 ± 2.01 mV for the A1773T compared to (−58.57 ± 1.40 mV) in the WT (Figure 2d). The mutant showed a longer recovery time constant τ1 from fast-inactivation compared to WT. PubMed:32400968
PS4	✔	

This variant has been reported in 9 probands meeting complex neurodevelopmental disorder. Four of these probands are de novo and counted for the PS2 criteria, leaving five probands (PS4_Strong); PMIDs: 34758253, 33000761, 28947817, 29655203, 31440721, 31785789, 34469436, 32400968, 35431799

Not Met criteria codes

PM5	✖	Another missense variant [c.5318 C>T, p.Ala1773Val] in the same codon has been reported in patients with complex neurodevelopmental disorder (PMIDs: 34992632, 28379373, 27824329, ClinVar Variation ID: 520893]. However, this variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen Epilepsy Sodium Channel VCEP (PM5 not met)
BA1	✖	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
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1	✖	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
PS1	✖	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	✖	Not applicable as more robust contraint measures are used.
PP3	✖	Not applying PP3 since this variant meets PM1_strong per VCEP specifications, but computational predictor REVEL gives a score of 0.94, which is above the threshold that correlates with impact to moderate function per the

specifications (PP3_Moderate)

PP4	✖	Accounted for under PS2/PM6/PS4

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001040142.2(SCN2A):c.5317G>A (...	Pathogenic	Complex Neurodevelopmental Disorder	2024-05-07	1.0	ClinGen Epilepsy Sodium Channel Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for SCN2A Version 1.0.0	SCN2A

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