Variant: NM_001040142.2(SCN2A):c.3007C>A (p.Leu1003Ile)

Version: 1.0

CA122775

12881 (ClinVar)

Gene: SCN2A (HGNC:6326)
Condition: complex neurodevelopmental disorder (MONDO:0100038)
Inheritance Mode: Autosomal dominant inheritance
UUID: 12afe231-b4eb-4d58-9a00-5ab7e3098777
Approved on: 2024-10-22
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HGVS expressions

NM_001040142.2:c.3007C>A
NM_001040142.2(SCN2A):c.3007C>A (p.Leu1003Ile)
NC_000002.12:g.165354279C>A
CM000664.2:g.165354279C>A
NC_000002.11:g.166210789C>A
CM000664.1:g.166210789C>A
NC_000002.10:g.165919035C>A
NG_008143.1:g.119878C>A
ENST00000631182.3:c.3007C>A
ENST00000375437.7:c.3007C>A
ENST00000636071.2:c.3007C>A
ENST00000636135.1:c.*1326C>A
ENST00000636384.2:c.*994C>A
ENST00000636662.2:c.*3530C>A
ENST00000636769.1:c.*949C>A
ENST00000636985.2:c.2611C>A
ENST00000637266.2:c.3007C>A
ENST00000673831.1:c.753C>A
ENST00000673883.1:c.572C>A
ENST00000674133.1:c.858C>A
ENST00000283256.10:c.3007C>A
ENST00000375427.4:c.3007C>A
ENST00000375437.6:c.3007C>A
ENST00000480032.4:n.3150C>A
ENST00000631182.2:c.3007C>A
NM_001040142.1:c.3007C>A
NM_001040143.1:c.3007C>A
NM_021007.2:c.3007C>A
NM_001040143.2:c.3007C>A
NM_001371246.1:c.3007C>A
NM_001371247.1:c.3007C>A
NM_021007.3:c.3007C>A

Uncertain Significance

Met criteria codes 2

PS4_Supporting PM2_Supporting

Not Met criteria codes 16

PS1 PS2 PS3 PP1 PP3 PM1 PM5 PM6 BA1 BS2 BS1 BS4 BS3 BP4 BP2 BP5

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 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Epilepsy Sodium Channel VCEP

The NM_001040142.2(SCN2A):c.3007C>A (p.Leu1003Ile) variant in SCN2A is a missense variant predicted to cause substitution of leucine by isoleucine at amino acid 1003 (p.Leu1003Ile). This variant has been reported in one family meeting phenotypic criteria for Complex Neurodevelopmental Disorder (MONDO:0100038 (PS4_Supporting; PMID 15048894). In this family, the variant was reported to segregate with Complex Neurodevelopmental Disorder (MONDO:0100038) in two meioses (father with two affected children). This does not meet the threshold of three meioses to apply PP1 (PMID 15048894). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). In summary, this variant meets the criteria to be classified as a variant of uncertain significance for Complex Neurodevelopmental Disorder (MONDO:0100038) based on the ACMG/AMP criteria applied, as specified by the ClinGen Epilepsy Sodium Channel VCEP: PM2_Supporting, PS4_Supporting. (ClinGen Epilepsy Sodium Channel Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for SCN2A Version 1.0.0; approved 10/22/2024).

Met criteria codes

PS4_Supporting	✔	This variant has been reported in 1 family meeting phenotypic criteria for Complex Neurodevelopmental Disorder (MONDO:0100038) (PS4_Supporting; PMID 15048894).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

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.
PP1	✖	The variant has been reported to segregate with Complex Neurodevelopmental Disorder (MONDO:0100038) in 2 meioses from 1 family (father with 2 affected children). This does not meet the threshold of 3 meioses to apply PP1 (PMID 15048894).

PP3	ℹ	✖	The computational predictor REVEL gives a score of 0.643, which is neither above nor below the thresholds predicting a damaging or benign impact on SCN2A function.
PM1	ℹ	✖	This variant does not reside within a region of SCN2A that is defined as a mutational hotspot or critical functional domain by the ClinGen Epilepsy Sodium Channel VCEP.
PM5	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	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		✖	To our knowledge, functional assays have not been reported for this variant.
BP4	ℹ	✖	The computational predictor REVEL gives a score of 0.643, which is neither above nor below the thresholds predicting a damaging or benign impact on SCN2A function.
BP2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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