Variant: NM_001040142.2(SCN2A):c.3043G>A (p.Asp1015Asn)

Version: 1.0

CA10612411

331730 (ClinVar)

Gene: SCN2A (HGNC:6326)
Condition: complex neurodevelopmental disorder (MONDO:0100038)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8266754d-3fb0-4c99-9635-ead230befadc
Approved on: 2024-11-26
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HGVS expressions

NM_001040142.2:c.3043G>A
NM_001040142.2(SCN2A):c.3043G>A (p.Asp1015Asn)
NC_000002.12:g.165354315G>A
CM000664.2:g.165354315G>A
NC_000002.11:g.166210825G>A
CM000664.1:g.166210825G>A
NC_000002.10:g.165919071G>A
NG_008143.1:g.119914G>A
ENST00000631182.3:c.3043G>A
ENST00000375437.7:c.3043G>A
ENST00000636071.2:c.3043G>A
ENST00000636135.1:c.*1362G>A
ENST00000636384.2:c.*1030G>A
ENST00000636662.2:c.*3566G>A
ENST00000636769.1:c.*985G>A
ENST00000636985.2:c.2647G>A
ENST00000637266.2:c.3043G>A
ENST00000673831.1:c.789G>A
ENST00000673883.1:c.608G>A
ENST00000674133.1:c.894G>A
ENST00000283256.10:c.3043G>A
ENST00000375427.4:c.3043G>A
ENST00000375437.6:c.3043G>A
ENST00000480032.4:n.3186G>A
ENST00000631182.2:c.3043G>A
NM_001040142.1:c.3043G>A
NM_001040143.1:c.3043G>A
NM_021007.2:c.3043G>A
NM_001040143.2:c.3043G>A
NM_001371246.1:c.3043G>A
NM_001371247.1:c.3043G>A
NM_021007.3:c.3043G>A

Likely Benign

Met criteria codes 4

PS4_Supporting BS1 BP4 PM6_Supporting

Not Met criteria codes 11

PS1 PS3 BA1 PP1 PP3 PM1 PM5 PM2 BS2 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:c.3043G>A variant in SCN2A is a missense variant predicted to cause substitution of Aspartic Acid by Asparagine at amino acid 1015 (p.Asp1015Asn). This variant has been reported in one proband meeting phenotypic criteria for Complex Neurodevelopmental Disorder (MONDO:0100038) (PS4_Supporting; PMID 30564305); however, this variant was inherited from a parent whose affected status is unknown. This variant was also found to occur de novo in one proband meeting criteria for Complex Neurodevelopmental Disorder (MONDO:0100038) with unconfirmed parental relationships (PM6_Supporting; PMID 35431799). The minor allele frequency in the European (non-Finnish) genetic ancestry group in gnomAD v4.1.0 is 0.000006780 (0.0007%, or 8/1179964 alleles), which is higher than the ClinGen Epilepsy Sodium Channel threshold (>0.0002%) for BS1, and therefore meets this criterion (BS1). The computational predictor REVEL gives a score of 0.287, which is below the threshold of 0.290, evidence that does not predict a damaging effect on SCN2A function (BP4). In summary, this variant meets the criteria to be classified as likely benign for autosomal dominant Complex Neurodevelopmental Disorder. Although there are both pathogenic and benign types of evidence for this variant, the pathogenic evidence is not considered inconsistent with the final classification. ACMG/AMP criteria applied, as specified by the ClinGen Epilepsy Sodium Channel VCEP: PS4_Supporting, PM6_Supporting, BP4, BS1. (Epilepsy Sodium Channel VCEP Specifications version 1.0.0; Approved 1/26/2024).

Met criteria codes

PS4_Supporting	✔	This variant has been reported in one proband meeting phenotypic criteria for Complex Neurodevelopmental Disorder (MONDO:0100038) (PS4_Supporting; PMID 30564305).
BS1	✔	The minor allele frequency in the European (non-Finnish) genetic ancestry group in gnomAD v4.1.0 is 0.000006780 (0.0007%, or 8/1179964 alleles), which is higher than the ClinGen Epilepsy Sodium Channel threshold (>0.0002%) for BS1, and therefore meets this criterion. Other genetic ancestry groups (East Asian and South Asian) have higher allele frequencies but do not meet the ClinGen Epilepsy Sodium Channel threshold of ≥5 alleles to meet this criterion (BS1).
BP4	✔	The computational predictor REVEL gives a score of 0.287, which is below the threshold of 0.290, evidence that does not predict a damaging effect on SCN2A function (BP4).
PM6_Supporting	✔	This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual meeting phenotypic criteria for Complex Neurodevelopmental Disorder (MONDO:0100038) (PM6_Supporting; PMID 35431799).

Not Met criteria codes

PS1	✖	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.
BA1	✖	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
PP3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	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	✖	Two different missense variants, c.3043G>C (p.Asp1015His) and c.3043G>T (p.Asp1015Tyr), in the same codon have been reported in ClinVar (ClinVar IDs: 2068042, 1036643). However, these variants have not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen Epilepsy Sodium Channel VCEP.
PM2	✖	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
BP2	✖	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

Curation History

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