Variant: NM_021007.3:c.2558G>A

Version: 1.0

CA210022

194555 (ClinVar)

Gene: SCN2A (HGNC:6326)
Condition: complex neurodevelopmental disorder (MONDO:0100038)
Inheritance Mode: Autosomal dominant inheritance
UUID: 5d586db8-4e92-4b7d-90c4-cef438f74e45
Approved on: 2024-05-09
Published on: 2024-05-09

HGVS expressions

NM_021007.3:c.2558G>A
NC_000002.12:g.165342465G>A
CM000664.2:g.165342465G>A
NC_000002.11:g.166198975G>A
CM000664.1:g.166198975G>A
NC_000002.10:g.165907221G>A
NG_008143.1:g.108064G>A
ENST00000631182.3:c.2558G>A
ENST00000375437.7:c.2558G>A
ENST00000636071.2:c.2558G>A
ENST00000636135.1:c.*877G>A
ENST00000636384.2:c.*545G>A
ENST00000636662.2:c.*3081G>A
ENST00000636769.1:c.*500G>A
ENST00000636985.2:c.2162G>A
ENST00000637266.2:c.2558G>A
ENST00000674133.1:c.409G>A
ENST00000283256.10:c.2558G>A
ENST00000375427.4:c.2558G>A
ENST00000375437.6:c.2558G>A
ENST00000480032.4:n.2701G>A
ENST00000631182.2:c.2558G>A
NM_001040142.1:c.2558G>A
NM_001040143.1:c.2558G>A
NM_021007.2:c.2558G>A
NM_001040142.2:c.2558G>A
NM_001040143.2:c.2558G>A
NM_001371246.1:c.2558G>A
NM_001371247.1:c.2558G>A

Pathogenic

Met criteria codes 5

PS2 PS3 PM1 PP3_Moderate PM2_Supporting

Evidence Links 1

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 c.2558G>A variant in SCN2A is a missense variant predicted to cause subsitution of arginine by glutamine at amino acid 853 (p.Arg853Gln). This variant has been identified as a de novo occurrence with confirmed parental relationships in at least 4 individual(s) identified in the published literature (PMIDs: 23935176 , 23934111, 31139143, 28708303], with additional evidence published reports available (PS2). It is absent from gnomAD v2.1.1 (PM2_Supporting). Heterologous expression assay with voltage clamping showed a decrease in peak current of 51%, which is below the threshold of 72.1%, evidence that correlates with PS3. It is a missense variant that resides within a pathogenic enriched region that is defined as a mutational hotspot (PM1). The computational predictor REVEL gives a score of 0.95, which is above the threshold of 0.773, evidence that correlates with a maximum strength of PP3_Moderate. In summary, this variant meets the criteria to be classified as PATHOGENIC for AUTOSOMAL DOMINANT COMPLEX NEURODEVELOPMENTAL DISORDER based on the ACMG/AMP criteria applied, as specified by the ClinGen Epilepsy Sodium Channel VCEP: PS2, PS3, PP3_Moderate, PM2_Supporting. (Epilepsy Sodium Channel VCEP specifications version 1.0)

Met criteria codes

PS2	✔	This variant was identified as de novo, with maternity and paternity confirmed, in at least 4 individuals with consistent phenotypes in the published literature.
PS3	✔	Heterologous expression with voltage clamping showed decreased peak current, 51% of wildtype. This exceeds the threshold of <72.7% for PS3. Peak current 51% of WT **PubMed:31558572**
PM1	✔	Variant is located within a pathogenic enriched region.
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.95, which is above the threshold of 0.773, evidence that correlates with a maximum strength of PP3_Moderate.
PM2_Supporting	✔	Absent from gnomAD v2.1.1

Curation History

Showing 1 to 1 of 1 rows