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Variant: NM_006922.4(SCN3A):c.2624T>C (p.Ile875Thr)

Version: 1.0

CA16043377

373960 (ClinVar)

Gene: SCN3A (HGNC:6328)
Condition: developmental and epileptic encephalopathy (MONDO:0100062)
Inheritance Mode: Autosomal dominant inheritance
UUID: 2ec0b468-966c-4f4a-8b2b-75d4a680b3f1
Approved on: 2024/5/9
Published on: 2024/5/9

HGVS expressions

NM_006922.4:c.2624T>C
NM_006922.4(SCN3A):c.2624T>C (p.Ile875Thr)
NC_000002.12:g.165130238A>G
CM000664.2:g.165130238A>G
NC_000002.11:g.165986748A>G
CM000664.1:g.165986748A>G
NC_000002.10:g.165694994A>G
NG_042289.1:g.78851T>C
ENST00000706067.1:c.2573T>C
ENST00000283254.12:c.2624T>C
ENST00000638473.1:c.*465T>C
ENST00000639244.1:c.2573T>C
ENST00000640652.1:c.2573T>C
ENST00000658209.1:c.722T>C
ENST00000668657.1:c.2486T>C
ENST00000283254.11:c.2624T>C
ENST00000360093.7:c.2624T>C
ENST00000409101.7:c.2477T>C
ENST00000440431.6:c.2477T>C
NM_001081676.1:c.2477T>C
NM_001081677.1:c.2477T>C
NM_006922.3:c.2624T>C
NM_001081676.2:c.2477T>C
NM_001081677.2:c.2477T>C

Pathogenic

Met criteria codes 5

PM2_Supporting PM6 PM1 PS3 PS2_Very Strong

Not Met criteria codes 4

BA1 PP3 BS1 BP4

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 SCN3A Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Epilepsy Sodium Channel VCEP

The c.2624T>C variant in SCN3A is a missense variant predicted to cause substitution of isoleucine by threonine at amino acid 875 (p.Ile875Thr). The variant has been identified as a de novo occurrence with confirmed parental relationships in at least 4 individual(s) with DEE (PMIDs: 29740860, 29466837) (PS2_Very Strong) and as a de novo occurrance with unconfirmed parental relationship in a least 2 individuals with DEE (PMIDs: 29286531, 28191890) (PM6_Moderate), with additional case evidence available in the literature. The variant is absent from gnomAD v2.1.1 (PM2_Supporting). Studies have observed that when expressed in mammalian cells in culture, this variant causes a gain-of-function effect on the mutant channels as evidenced by a significant leftward/hyperpolarized shift in the voltage dependence of activation, an increase in the persistent/inactivating current, and a rightward/depolarizing shift in the voltage of inactivation (PS3; PMID: 29466837). In summary, this variant meets the criteria to be classified as pathogenic for autosomal dominant developmental and epilepstic encephalopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen Epilepsy Sodium Channel VCEP: PS2_VS, PM6_Moderate, PM2_Supporting, PS3. (Version 1; July 7, 2023).

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1.
PM6	✔	This variant has been identified as de novo with confirmed parental relationships in at least 2 patients with consistent phenotypes.
PM1	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✔	Heterologous expression with voltage clamping showed a difference that exceeded the threshold for Strong in multiple biophysical parameters: Voltage dependence of activation shifted 10.9mV (WT -26.2; mutant -37.1), threshold 2.2mV. Voltage dependence of inactivation shifted 9.7mV (WT 10.2, mutant 19.9), threshold 4.1mV. Persistant current (WT 2.6, mutant 18.0) >135% of WT. Voltage dependence of activation shifted 10.9mV (WT -26.2; mutant -37.1), threshold 2.2mV. Voltage dependence of inactivation shifted 9.7mV (WT 10.2, mutant 19.9), threshold 4.1mV. Persistant current (WT 2.6, mutant 18.0) >135% of WT. PubMed:29466837
PS2_Very Strong	✔	This variant has been identified as de novo via trio exome sequencing in at least 4 patients with consistent phenotypes.

Not Met criteria codes

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	The in-silico REVEL score for this variant is 0.976 which meets the criteria for PP3_Moderate but was not applied as PM1_Strong was already reached.

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

Curation History

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