Variant: NM_001040142.2(SCN2A):c.5636T>C (p.Met1879Thr)

Version: 1.0

CA349039608

1478168 (ClinVar)

Gene: SCN2A (HGNC:6326)
Condition: complex neurodevelopmental disorder (MONDO:0100038)
Inheritance Mode: Autosomal dominant inheritance
UUID: 09da11a8-2597-4850-b32c-6b19d80f8377
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HGVS expressions

NM_001040142.2:c.5636T>C
NM_001040142.2(SCN2A):c.5636T>C (p.Met1879Thr)
NC_000002.12:g.165389442T>C
CM000664.2:g.165389442T>C
NC_000002.11:g.166245952T>C
CM000664.1:g.166245952T>C
NC_000002.10:g.165954198T>C
NG_008143.1:g.155041T>C
ENST00000631182.3:c.5636T>C
ENST00000375437.7:c.5636T>C
ENST00000636071.2:c.5636T>C
ENST00000636135.1:c.*3955T>C
ENST00000636384.2:c.*3623T>C
ENST00000636662.2:c.*6159T>C
ENST00000636769.1:c.*3578T>C
ENST00000636985.2:c.5240T>C
ENST00000637266.2:c.5636T>C
ENST00000283256.10:c.5636T>C
ENST00000375427.4:c.5636T>C
ENST00000375437.6:c.5636T>C
ENST00000480032.4:n.9067T>C
ENST00000631182.2:c.5636T>C
NM_001040142.1:c.5636T>C
NM_001040143.1:c.5636T>C
NM_021007.2:c.5636T>C
NM_001040143.2:c.5636T>C
NM_001371246.1:c.5636T>C
NM_001371247.1:c.5636T>C
NM_021007.3:c.5636T>C

Likely Pathogenic

Met criteria codes 5

PS3 PM6_Supporting PP3_Moderate PS4_Supporting PM2_Supporting

Expert Panel

Epilepsy Sodium Channel VCEP

Evidence Links 0

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.5636T>C variant in SCN2A is a missense variant predicted to cause substitution of methionine by threonine at amino acid 1879 (p.Met1879Thr). This variant has been reported in one individual as de novo with unconfirmed parental relationships (PMID:32750235) (PM6_Supporting), and in one individual without parental segregation (PMID: 27779742) (PS4_Supporting), both with consistent phenotypes. Another missense variant at the same position in SCN2A (p.Met1879Ile) has been reported in the literature (PMID: 34055682), however, this variant does not reach Likely Pathogenic per these criteria so was not included for PM5. This variant is absent from the population database gnomAD v4.0 (PM2_Supporting). Functional evidence has demonstrated that this variant impacts normal protein function. Specifically, heterologous expression with voltage clamping has shown a shift of at least 4.1mV in voltage dependence of inactivation (PS3). The computational predictor REVEL gives a score of 0.922, 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 likely pathogenic for autosomal dominant complex neurodevelopmental disorder based on the ACMG/AMP criteria applied, as specified by the ClinGen Epilepsy Sodium Channel VCEP: PM6_Supporting, PS4_Supporting, PM2_Supporting, PS3, PP3_Moderate. (version 1.0; March 26, 2024).

Met criteria codes

PS3	✔	In this publication (PMID: 32750235), the M1879T variant caused disturbances in channel inactivation including substantially depolarized voltage dependence of inactivation, slower time course of inactivation, and enhanced resurgent current. PS3 is applied due to Voltage dependence of inactivation as defined by FENICS ontology (https://bioportal.bioontology.org/ontologies/FENICS) being shifted shifted by at least 4.1 mV (absolute value).
PM6_Supporting	✔	A male with global developmental delay and seizures onset at 2 months. The variant is reported as de novo without mentioning confirming parentage.
PP3_Moderate	✔	REVEL=0.922
PS4_Supporting	✔	A proband with epilepsy and global developmental delay is reported in this publication, inheritance is not mentioned (PMID: 27779742).
PM2_Supporting	✔	This variant is absent from gnomAD v4.0

Curation History

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