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Variant: NM_001330260.2(SCN8A):c.3953A>G (p.Asn1318Ser)

Version: 1.0

CA384904367

694309 (ClinVar)

Gene: SCN8A (HGNC:6334)
Condition: complex neurodevelopmental disorder (MONDO:0100038)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3d72f96d-dfa8-4992-81f0-bf6b4b511a81
Approved on: 2024/5/9
Published on: 2024/5/9

HGVS expressions

NM_001330260.2(SCN8A):c.3953A>G (p.Asn1318Ser)
NM_001330260.2:c.3953A>G
NC_000012.12:g.51786552A>G
CM000674.2:g.51786552A>G
NC_000012.11:g.52180336A>G
CM000674.1:g.52180336A>G
NC_000012.10:g.50466603A>G
NG_021180.2:g.200317A>G
NG_021180.3:g.201595A>G
ENST00000354534.11:c.3953A>G
ENST00000548086.3:c.1747A>G
ENST00000627620.5:c.3953A>G
ENST00000636945.2:c.2017A>G
ENST00000662684.1:c.3953A>G
ENST00000668547.1:c.3830A>G
ENST00000354534.10:c.3953A>G
ENST00000355133.7:c.3830A>G
ENST00000545061.5:c.3830A>G
ENST00000548086.1:n.204A>G
ENST00000599343.5:c.3986A>G
ENST00000627620.2:c.3953A>G
NM_001177984.2:c.3830A>G
NM_014191.3:c.3953A>G
NM_001330260.1:c.3953A>G
NM_001369788.1:c.3830A>G
NM_014191.4:c.3953A>G
NM_001177984.3:c.3830A>G

Likely Pathogenic

Met criteria codes 4

PS2 PP3_Moderate PM6_Supporting PM2_Supporting

Not Met criteria codes 2

PM1 PM5

Expert Panel

Epilepsy Sodium Channel VCEP

Criteria Specification Information

Evidence Links 0

Criteria Specification: *ClinGen Epilepsy Sodium Channel Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for SCN8A Version 1.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Epilepsy Sodium Channel VCEP

The c.3953A>G variant in SCN8A is a missense variant predicted to cause substitution of asparagine by serine at amino acid 1318 (p.Asn1318Ser). This variant has been reported as de novo with confirmed parental relationships in 2 individuals (PMID: 30968951, 31672125) and de novo with unconfirmed parental relationships in 1 individual (PMID: 35230384) with consistent phenotypes (PS2, PM6_Supporting). A novel missense variant at the same position in the paralogous gene, SCN1A (p.Asn1338Thr) has been reported as pathogenic, however, two novel missense variants are required to meet PM5_Supporting so this criterion was not applied. This variant is absent from the population database, gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.832, which is above the threshold of 0.773, evidence that correlates with a 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: PS2, PM6_Supporting, PM2_Supporting, PP3_Moderate (version 1.0; approved 5/23/23).

Met criteria codes

PS2	✔	This variant was identified in PMID: 30968951. The variant was ascertained via gene panel; de novo with maternity and paternity confirmed (PS2 applied in paper) in proband with ataxia and epilepsy. The variant was identified via trio exome sequencing which identified de novo variant in female proband of Chinese ancestry with early infantile epileptic encephalopathy (PMID: 31672125).
PP3_Moderate	✔	REVEL=0.832
PM6_Supporting	✔	The variant was identified de novo in a proband with neurodevelopmental disorder with Chinese ancestry (PMID: 35230384).
PM2_Supporting	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	novel missense variant in paralogous gene, SCN1A p.Asn1338Thr - PMID: 24901346, 25356970, 26795593. However, two novel missense variants in paralogous gene are required to meet PM5_Supporting.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001330260.2(SCN8A):c.3953A>G (...	Likely Pathogenic	Complex Neurodevelopmental Disorder	2024-05-09	1.0	ClinGen Epilepsy Sodium Channel Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for SCN8A Version 1.0.0	SCN8A

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