# *Variant: NM_001165963.4(SCN1A):c.2303C>T (p.Pro768Leu)*

Version: 1.0

## *CA303333*

## *189929 (ClinVar)*

**Gene**: SCN1A (HGNC:6323)
**Condition**: Dravet syndrome (MONDO:0100135)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** df4f3335-b54c-49a2-8016-9bbc4979399e
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## *HGVS expressions*

**NM_001165963.4:c.2303C>T**
NM_001165963.4(SCN1A):c.2303C>T (p.Pro768Leu)
NC_000002.12:g.166041343G>A
CM000664.2:g.166041343G>A
NC_000002.11:g.166897853G>A
CM000664.1:g.166897853G>A
NC_000002.10:g.166606099G>A
NG_011906.1:g.37297C>T
ENST00000689288.1:c.*339C>T
ENST00000303395.9:c.2303C>T
ENST00000635750.1:c.2270C>T
ENST00000635776.1:c.2270C>T
ENST00000636194.1:c.2270C>T
ENST00000636759.1:c.*2093C>T
ENST00000637968.1:n.2555C>T
ENST00000637988.1:c.2270C>T
ENST00000640036.1:c.2270C>T
ENST00000641575.1:c.2267C>T
ENST00000641603.1:c.2303C>T
ENST00000641996.1:c.*1857C>T
ENST00000671940.1:c.*246C>T
ENST00000673490.1:n.4776C>T
ENST00000674923.1:c.2303C>T
ENST00000303395.8:c.2303C>T
ENST00000375405.7:c.2270C>T
ENST00000409050.1:c.2219C>T
ENST00000423058.6:c.2303C>T
NM_001165963.1:c.2303C>T
NM_001165964.1:c.2219C>T
NM_001202435.1:c.2303C>T
NM_006920.4:c.2270C>T
NM_001165963.2:c.2303C>T
NM_001165964.2:c.2219C>T
NM_001202435.2:c.2303C>T
NM_001353948.1:c.2303C>T
NM_001353949.1:c.2270C>T
NM_001353950.1:c.2270C>T

NM_001353951.1:c.2270C>T
NM_001353952.1:c.2270C>T
NM_001353954.1:c.2267C>T
NM_001353955.1:c.2267C>T
NM_001353957.1:c.2219C>T
NM_001353958.1:c.2219C>T
NM_001353960.1:c.2216C>T
NM_001353961.1:c.-156C>T
NM_006920.5:c.2270C>T
NR_148667.1:n.2675C>T
NM_001165963.3:c.2303C>T
NM_001165964.3:c.2219C>T
NM_001202435.3:c.2303C>T
NM_001353948.2:c.2303C>T
NM_001353949.2:c.2270C>T
NM_001353950.2:c.2270C>T
NM_001353951.2:c.2270C>T
NM_001353952.2:c.2270C>T
NM_001353954.2:c.2267C>T
NM_001353955.2:c.2267C>T
NM_001353957.2:c.2219C>T
NM_001353958.2:c.2219C>T
NM_001353960.2:c.2216C>T
NM_001353961.2:c.-156C>T
NM_006920.6:c.2270C>T
NR_148667.2:n.2656C>T

**Likely Pathogenic**

**Met criteria codes** 4

**PS4_Moderate** **PM6** **PP3_Moderate** **PM2_Supporting**

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 SCN1A Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Epilepsy Sodium Channel VCEP***

**The c.2303C>T (NM_001165963.4) variant in SCN1A is a missense variant predicted to cause substitution of proline by leucine at amino acid 768 (p.Pro768Leu). This variant has been reported in one patient meeting phenotypic criteria for Dravet syndrome with unknown inheritance (PMID: 35074891; PS4_SUPPORTING) and in another patient also meeting phenotypic criteria for Dravet syndrome as a de novo occurrence with unconfirmed parental relationships (PMID: 20431604; PM6). This variant is absent from gnomAD v2 and v3 (PM2_SUPPORTING). The computational predictor REVEL gives a score of 0.927 which is above the threshold of 0.773 but under 0.932, evidence that correlates with impact to SCN1A function (PMID: 36413997; PP3_MODERATE). In summary, this variant has been classified as likely pathogenic for autosomal dominant Dravet syndrome based on the ACMG/AMP criteria applied, as specified by the Epilepsy Sodium Channel VCEP: PM6, PS4_SUPPORTING, PM2_SUPPORTING, PP3_MODERATE (version 1.0, approved 7/11/23).**

**Met criteria codes**

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|---|---|---|---|
| **PS4_Moderate** | ℹ | ✓ | In this paper (PMID: 35074891), they performed a retrospective multicenter cohort study comprising data from 1,018 patients with SCN1A-positive Dravet syndrome and patients with GEFS+ consecutively referred for genetic testing (March 2001-June 2020). The p.Pro768Leu variant, referred to as p.P768L, was found in the training cohort in one Italian patient diagnosed with Dravet syndrome with first seizure onset at 3 months old (patient # 241 in supplementary eTable1). No inheritance information was provided. The variant was noted in two additional papers, but evidence from these papers was not scored as we could not confirm the alternate nomenclature of the variant was in fact the variant of interest (PMID: 24168886, 30921204). |
| **PM6** | ℹ | ✓ | The authors in this paper (PMID: 20431604) sequenced all 26 coding exons of SCN1A in 63 Chinese patients with Dravet syndrome and their parents where available. The c.2303C>T variant was seen in patient # 16 in Table 1 (but the protein change noted by the authors is W768X) and it was said to be de novo without any mention of paternity/maternity confirmation. The cDNA numbering was based on GenBank sequence AB093548 and this is correct, whereas the protein residue numbering was based on P35498. In this protein sequence there is a Proline and not Tryptophan at position 768, hence it appears that the error is in the protein nomenclature. This is confirmed by looking at patient # 17 in Table 1 who had the c.2303_2306dupGACC (which starts at the same cDNA position as the variant in this spreadsheet) whose protein change is indicated as P768fsX772 i.e. there is a Proline at this position. |
| **PP3_Moderate** | ℹ | ✓ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **PM2_Supporting** | ℹ | ✓ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |

Curation History

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