Variant: NM_001005361.3(DNM2):c.1393C>T (p.Arg465Trp)

Version: 1.0

CA172098

7281 (ClinVar)

Gene: DNM2 (HGNC:1785)
Condition: centronuclear myopathy (MONDO:0018947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 5181b063-b33d-441a-9219-309d92fe0501
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HGVS expressions

NM_001005361.3:c.1393C>T
NM_001005361.3(DNM2):c.1393C>T (p.Arg465Trp)
NC_000019.10:g.10798543C>T
CM000681.2:g.10798543C>T
NC_000019.9:g.10909219C>T
CM000681.1:g.10909219C>T
NC_000019.8:g.10770219C>T
NG_008792.1:g.85465C>T
ENST00000682285.1:n.1581C>T
ENST00000683738.1:n.1720C>T
ENST00000355667.11:c.1393C>T
ENST00000389253.9:c.1393C>T
ENST00000355667.10:c.1393C>T
ENST00000359692.10:c.1393C>T
ENST00000389253.8:c.1393C>T
ENST00000408974.8:c.1393C>T
ENST00000585892.5:c.1393C>T
ENST00000587329.1:n.157C>T
ENST00000587830.2:c.649C>T
ENST00000593220.1:n.542C>T
NM_001005360.2:c.1393C>T
NM_001005361.2:c.1393C>T
NM_001005362.2:c.1393C>T
NM_001190716.1:c.1393C>T
NM_004945.3:c.1393C>T
NM_001190716.2:c.1393C>T
NM_001005360.3:c.1393C>T
NM_001005362.3:c.1393C>T
NM_004945.4:c.1393C>T

Pathogenic

Met criteria codes 4

PS3 PS4 PP3 PP1_Strong

Not Met criteria codes 3

PM2 BA1 BS1

Expert Panel

Congenital Myopathies VCEP

Criteria Specification Information

Evidence Links 0

Criteria Specification: *ClinGen Congenital Myopathies Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for DNM2 Version 1.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Congenital Myopathies VCEP

The variant NM_001005361.3:c.1393C>T in DNM2 is a missense variant predicted to cause substitution of arginine by tryptophan at amino acid 465 (p.Arg465Trp). The highest population minor allele frequency in gnomAD v4.1 is 0.000001695 (2/1180018 alleles) in the European (non-Finnish) population (PM2_Supporting, BS1, and BA1 are not met). The REVEL computational prediction analysis tool produced a score of 0.83, which is above the threshold necessary to apply PP3. This variant has been reported in at least six probands with confirmed centronuclear myopathy (PS4; PMID: 16227997, 19130742, 22613877, 26908122, 28740838, 34463354, 34595679). In addition, it segregated in five affected individuals in one family (PP1_Strong; PMID: 16227997). Functional studies have demonstrated that this variant increases GTPase activity compared to wildtype dynamin (PMIDs: 20529869, 26199319). Several knock-in mouse models with the variant have been created and show muscle defects, progressive atrophy and morphological abnormalities similar to those observed in human biopsies, and DNM2 reduction has been shown to rescue the phenotype in mice (PS3; PMIDs: 20858595, 30291191). In summary, this variant meets the criteria to be classified as pathogenic for autosomal dominant centronuclear myopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen Congenital Myopathies VCEP: PP3, PS4, PP1_Strong, PS3. (ClinGen Congenital Myopathies VCEP specifications version 1; 8/7/2024)

Met criteria codes

PS3	✔	functional studies have demonstrated that this variant increases GTPase activity compared to wildtype dynamin (PMIDs: 20529869, 26199319). Several knock-in mouse models with the variant have been created and show muscle defects, progressive atrophy and morphological abnormalities similar to those observed in human biopsies, and DNM2 reduction has been shown to rescue the phenotype in mice (PMIDs: 20858595, 30291191).
PS4	✔	This variant has been reported in six probands by Bitoun et al. 2005, who had confirmed centronuclear myopathy. This variant has also been reported in probands in at least six additional publications.
PP3	✔	The REVEL computational prediction analysis tool produced a score of 0.83, which is above the threshold necessary to apply PP3.
PP1_Strong	✔	Family three from Bitoun et al. 2005 had five affected segregations reported, meeting PP1_Strong.

Not Met criteria codes

PM2	✖	The highest population minor allele frequency in gnomAD v4.1 is 0.000001695 (2/1180018 alleles) in the European (non-Finnish) population. (PM2_Supporting, BS1, and BA1 are not met)
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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