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Variant: NM_001005361.3(DNM2):c.1852G>A (p.Ala618Thr)

Version: 1.0

CA404041079

449326 (ClinVar)

Gene: DNM2 (HGNC:1785)
Condition: centronuclear myopathy (MONDO:0018947)
Inheritance Mode: Autosomal dominant inheritance
UUID: aa115c72-331e-4f61-9a5b-aa1abd9bb9e7
Approved on: 2024/8/7
Published on: 2024/10/1

HGVS expressions

NM_001005361.3:c.1852G>A
NM_001005361.3(DNM2):c.1852G>A (p.Ala618Thr)
NC_000019.10:g.10823858G>A
CM000681.2:g.10823858G>A
NC_000019.9:g.10934534G>A
CM000681.1:g.10934534G>A
NC_000019.8:g.10795534G>A
NG_008792.1:g.110780G>A
ENST00000681972.1:n.1283G>A
ENST00000355667.11:c.1852G>A
ENST00000389253.9:c.1852G>A
ENST00000355667.10:c.1852G>A
ENST00000359692.10:c.1840G>A
ENST00000389253.8:c.1852G>A
ENST00000408974.8:c.1840G>A
ENST00000585892.5:c.1852G>A
ENST00000590787.1:n.3351G>A
ENST00000590806.5:n.4040G>A
ENST00000593203.1:n.635G>A
NM_001005360.2:c.1852G>A
NM_001005361.2:c.1852G>A
NM_001005362.2:c.1840G>A
NM_001190716.1:c.1852G>A
NM_004945.3:c.1840G>A
NM_001190716.2:c.1852G>A
NM_001005360.3:c.1852G>A
NM_001005362.3:c.1840G>A
NM_004945.4:c.1840G>A

Pathogenic

Met criteria codes 6

PS3_Moderate PS2 PS4 PP2 PP3 PM2_Supporting

Not Met criteria codes 3

BA1 BS1 BP4

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 c.1852G>A (p.Ala618Thr) variant in DNM2 is a missense variant predicted to cause substitution of Alanine by Threonine at amino acid 618. This variant is absent from gnomAD v4.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.818, which is above the threshold of 0.7, evidence that correlates with impact to DNM2 function (PP3). DNM2, in which the variant was identified, is defined by the ClinGen Congenital Myopathies VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). This variant has been reported in four probands with features of centronuclear myopathy, two of which were de novo with parental relationships confirmed (PS4, PS2; PMIDs:17932957, 28357410, 34463354, 32154989). In vitro assays showed an increase in GTPase activity and oligomer stability indicating that this variant impacts protein function (PMIDs: 26199319, 20700106, 34744632)(PS3_Moderate). 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: PS4, PS2, PS3_Moderate, PM2_Supporting, PP2, PP3 (ClinGen Congenital Myopathies VCEP specifications version 1; 8/7/2024).

Met criteria codes

PS3_Moderate	✔	In vitro assays showed an increase in GTPase activity and oligomer stability indicating that this variant impacts protein function (PMIDs: 26199319, 20700106, 34744632)(PS3_M).
PS2	✔	This variant has been reported as de novo observations with parental relationships confirmed in two probands with features of centronuclear myopathy (PS2; PMIDs:17932957, 32154989).
PS4	✔	This variant has been reported in four probands with features of centronuclear myopathy, two of which were de novo with parental relationships confirmed (PS4, PS2; PMIDs:17932957, 28357410, 34463354, 32154989).
PP2	✔	DNM2, in which the variant was identified, is defined by the ClinGen Congenital Myopathies VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease. The missense Z-score in gnomAD v2.1.1 is 3.48 which is above the threshold (3.09) set by the Congenital Myopathies VCEP.
PP3	✔	The computational predictor REVEL gives a score of 0.818, which is above the threshold of 0.7, evidence that correlates with impact to DNM2 function.
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).

Not Met criteria codes

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
BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 1 of 1 rows

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