

Variant: NM_001005361.3(DNM2):c.1102G>A (p.Glu368Lys)

Version: 1.0

CA118661 [↗](#)

7282 (ClinVar) [↗](#)

Gene: DNM2 ([HGNC:1785](#))

Condition: centronuclear myopathy ([MONDO:0018947](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: f50ef19f-b4a3-4934-9f09-07949b4c0cc2

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HGVS expressions

NM_001005361.3(DNM2):c.1102G>A (p.Glu368Lys)

NM_001005361.3:c.1102G>A

NC_000019.10:g.10793829G>A

CM000681.2:g.10793829G>A

NC_000019.9:g.10904505G>A

CM000681.1:g.10904505G>A

NC_000019.8:g.10765505G>A

NG_008792.1:g.80751G>A

ENST00000682285.1:n.1290G>A

ENST00000682524.1:n.1290G>A

ENST00000683738.1:n.1290G>A

ENST00000355667.11:c.1102G>A

ENST00000389253.9:c.1102G>A

ENST00000355667.10:c.1102G>A

ENST00000359692.10:c.1102G>A

ENST00000389253.8:c.1102G>A

ENST00000408974.8:c.1102G>A

ENST00000585892.5:c.1102G>A

ENST00000587830.2:c.358G>A

ENST00000591701.5:n.462G>A

NM_001005360.2:c.1102G>A

NM_001005361.2:c.1102G>A

NM_001005362.2:c.1102G>A

NM_001190716.1:c.1102G>A

NM_004945.3:c.1102G>A

NM_001190716.2:c.1102G>A

NM_001005360.3:c.1102G>A

NM_001005362.3:c.1102G>A

NM_004945.4:c.1102G>A

Pathogenic

Met criteria codes **6**

PS4 PP2 PP3 PS3_Moderate

PS2_Very Strong PM2_Supporting

Not Met criteria codes **2**

Expert Panel

Congenital Myopathies VCEP [↗](#)

Criteria Specification Information

BA1 BS1

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 NM_001005361.3:c.1102G>A variant in DNM2 is a missense variant predicted to cause substitution of glutamic acid by lysine at amino acid 368 (p.Glu368Lys). This variant is absent from gnomAD v4.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.799, 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 at least 6 probands with centronuclear myopathy (PS4; PMIDs: 16227997, 22613877, 25501959, 27159402, 33124102). Of those 6 individuals, the variant was identified as a de novo occurrence with confirmed parental relationships in at least 3 of those individuals with centronuclear myopathy (PS2_VeryStrong; PMIDs: 16227997, 27159402, 33124102). Oligomerization in Sf9 cells showed defective autoinhibition of self-assembly, indicating that this variant impacts protein function (PMID: 26199319). Additionally, GTPase activity in Sf9 cells was between 2-2.5-fold higher than wild-type DNM2 (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: PS2_VeryStrong, PS4, PS3_Moderate, PM2_Supporting, PP2, PP3. (ClinGen Congenital Myopathies VCEP Specifications Version 1.0; 10/25/2024)

Met criteria codes

PS4			This variant has been reported in at least 6 probands with centronuclear myopathy (PS4; PMIDs: 16227997, 22613877, 25501959, 27159402, 33124102).
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 (PP2).
PP3			The computational predictor REVEL gives a score of 0.799, which is above the threshold of 0.7, evidence that correlates with impact to DNM2 function (PP3).
PS3_Moderate			Oligomerization in Sf9 cells showed defective autoinhibition of self-assembly, indicating that this variant impacts protein function (PMID: 26199319). Additionally, GTPase activity in Sf9 cells was between 2-2.5-fold higher than wild-type DNM2 (PS3_Moderate).
PS2_Very Strong			The variant was identified as a de novo occurrence with confirmed parental relationships in at least 3 individuals with centronuclear myopathy (PS2_VeryStrong; PMIDs: 16227997, 27159402, 33124102).
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



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