

Variant: *NM_001005361.3(DNM2):c.1678G>A (p.Glu560Lys)*

Version: 1.0

CA10584608 [↗](#)

246082 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: a9bd9d4c-d2fe-469a-9f52-eea34a6ea84e

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HGVS expressions

NM_001005361.3(DNM2):c.1678G>A (p.Glu560Lys)

NM_001005361.3:c.1678G>A

NC_000019.10:g.10819986G>A

CM000681.2:g.10819986G>A

NC_000019.9:g.10930662G>A

CM000681.1:g.10930662G>A

NC_000019.8:g.10791662G>A

NG_008792.1:g.106908G>A

ENST00000681972.1:n.1109G>A

ENST00000355667.11:c.1678G>A

ENST00000389253.9:c.1678G>A

ENST00000355667.10:c.1678G>A

ENST00000359692.10:c.1666G>A

ENST00000389253.8:c.1678G>A

ENST00000408974.8:c.1666G>A

ENST00000585892.5:c.1678G>A

ENST00000590787.1:n.3177G>A

ENST00000590806.5:n.3866G>A

NM_001005360.2:c.1678G>A

NM_001005361.2:c.1678G>A

NM_001005362.2:c.1666G>A

NM_001190716.1:c.1678G>A

NM_004945.3:c.1666G>A

NM_001190716.2:c.1678G>A

NM_001005360.3:c.1678G>A

NM_001005362.3:c.1666G>A

NM_004945.4:c.1666G>A

Likely Pathogenic

Met criteria codes 5

PS4

PP2

PM6

PM2_Supporting

PS3_Supporting

Not Met criteria codes 2

BP4

PP3

Expert Panel

[Congenital Myopathies VCEP](#) [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Congenital Myopathies
Expert Panel Specifications to the ACMG/AMP Variant

Evidence submitted by expert panel

Congenital Myopathies VCEP

The NM_001005361.3:c.1678G>A variant in DNM2 is a missense variant predicted to cause substitution of glutamate by lysine at amino acid 560 (p.Glu560Lys). This variant is absent from gnomAD v4.1.0 (PM2_supporting). 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). The computational predictor REVEL gives a score of 0.686, which is neither above nor below the thresholds predicting a damaging or benign impact on DNM2 function (no codes met). This variant has been reported in 2 probands with centronuclear myopathy (PS4; 1.0 pt.; PMIDs: 19122038, 22396310). This variant has been identified as a suspected de novo occurrence in one individual with centronuclear myopathy (PM6; PMID: 22396310). Membrane fission/dissociation assay using incubated DNM2 protein showed notably increased fission activity but reduced dissociation efficiency for the mutant indicating that this variant impacts protein function (PS3_supporting; PMID: 26199319). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal dominant centronuclear myopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen Congenital Myopathies VCEP: PS4, PM6, PS3_Supporting, PM2_Supporting, PP2 (ClinGen Congenital Myopathies VCEP Specifications Version 1.0.0; 5/12/2025).

Met criteria codes

PS4			This variant has been reported in 2 probands with centronuclear myopathy (including type 1 fiber predominance and ophthalmoparesis/ptosis) (PS4; 1.0 pt.; PMIDs: 19122038, 22396310).
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). Z-score for missense variants in DNM2 in gnomAD v4.1.0 is 4.87.
PM6			This variant has been identified as a suspected de novo occurrence in 1 proband (PM6; PMID: 22396310).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_supporting). Coverage of the gene in the region this variant occurs is adequate.
PS3_Supporting			Membrane fission/dissociation assay using incubated DNM2 protein showed notably increased fission activity but reduced dissociation efficiency for the mutant indicating that this variant impacts protein function (PS3_supporting; PMID: 26199319).
			The scientists utilized the different levels of DYN2 proteins and incubated them using SUPER templates for a half-hour at room temperature in conditions of GTP. Membrane fission was quantified by the release of fluorescent vesicles from SUPER template. Notably increased fission activity was seen for the p.Glu560Lys variant. Dissociation efficiency was lower for the mutant, however. PubMed:26199319 

Not Met criteria codes

BP4			The computational predictor REVEL gives a score of 0.686, which is neither above nor below the thresholds predicting a damaging or benign impact on DNM2 function (no codes met). In-silico predictions are conflicting.
PP3			The computational predictor REVEL gives a score of 0.686, which is neither above nor below the thresholds predicting a damaging or benign impact on DNM2 function (no codes met). In-silico predictions are conflicting.

Curation History 		
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