

Variant: NM_001005361.3(DNM2):c.1948G>A (p.Glu650Lys)

Version: 1.0

CA404041406 [↗](#)

931135 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 0e6c1bc9-e28b-4dbe-b2be-5d199e96fd13

Approved on: 2024/8/7

Published on: 2024/10/1

HGVS expressions

NM_001005361.3(DNM2):c.1948G>A (p.Glu650Lys)

NM_001005361.3:c.1948G>A

NC_000019.10:g.10825111G>A

CM000681.2:g.10825111G>A

NC_000019.9:g.10935787G>A

CM000681.1:g.10935787G>A

NC_000019.8:g.10796787G>A

NG_008792.1:g.112033G>A

ENST00000681972.1:n.1379G>A

ENST00000355667.11:c.1948G>A

ENST00000389253.9:c.1948G>A

ENST00000355667.10:c.1948G>A

ENST00000359692.10:c.1936G>A

ENST00000389253.8:c.1948G>A

ENST00000408974.8:c.1936G>A

ENST00000585892.5:c.1948G>A

ENST00000590806.5:n.4136G>A

ENST00000593203.1:n.731G>A

NM_001005360.2:c.1948G>A

NM_001005361.2:c.1948G>A

NM_001005362.2:c.1936G>A

NM_001190716.1:c.1948G>A

NM_004945.3:c.1936G>A

NM_001190716.2:c.1948G>A

NM_001005360.3:c.1948G>A

NM_001005362.3:c.1936G>A

NM_004945.4:c.1936G>A

Likely Pathogenic

Met criteria codes **5**

PS3_Supporting

PP2

PS4

PM2_Supporting

PP1_Moderate

Evidence Links **0**

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 c.1948G>A (NM_001005361.3(DNM2):c.1948G>A (p.Glu650Lys)) variant in DNM2 is a missense variant predicted to cause substitution of glutamic acid by lysine at amino acid 650. This variant has been reported in 7 probands from 3 families all meeting phenotypic criteria and six having ptosis (PS4; PMIDs: 19623537, 24465259, 31655408). The variant has been reported to segregate with centronuclear myopathy in 4 affected individuals from one family (PP1_Moderate; PMID: 19623537). This variant is absent from gnomAD v4.1 (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). An in-vitro cell culture in muscle cells showed increased GTPase activity indicating that this variant impacts protein function (PMID: 26199319, PS3_Supporting). 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, PP1_Moderate, PP2, PM2_Supporting, PS3_Supporting. (ClinGen Congenital Myopathies VCEP specifications version 1; 8/7/2024)

Met criteria codes

PS3_Supporting			An in-vitro cell culture in muscle cells showed increased GTPase activity indicating that this variant impacts protein function (PMID: 26199319, PS3_Supporting).
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 the gene is 3.48 for missense variants.
PS4			This variant has been reported in 7 probands from 3 families meeting phenotypic criteria distal weakness and ptosis (PS4; PMIDs: 24465259, 19623537; https://doi.org/10.21203/rs.2.1852/v1).
PM2_Supporting			This variant is absent from gnomAD v2.1.1 (PM2_Supporting). Coverage of the gene in the region in which the variant is found is adequate.
PP1_Moderate			The variant has been reported to segregate with centronuclear myopathy in 4 affected individuals from one family (PP1_moderate; PMID: 19623537).

Curation History [↗](#)

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