

Variant: NM_000252.3(MTM1):c.1210G>A (p.Glu404Lys)

Version: 1.0

CA10539219 [↗](#)

530855 (ClinVar) [↗](#)

Gene: MTM1 ([HGNC:4534](#))

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

Inheritance Mode: X-linked inheritance

UUID: 4555c90b-b9d2-4159-a35d-5cd69bc61fee

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HGVS expressions

NM_000252.3(MTM1):c.1210G>A (p.Glu404Lys)

NM_000252.3:c.1210G>A

NC_000023.11:g.150657977G>A

CM000685.2:g.150657977G>A

NC_000023.10:g.149826450G>A

CM000685.1:g.149826450G>A

NC_000023.9:g.149577108G>A

NG_008199.1:g.94404G>A

ENST00000684910.1:c.*743G>A

ENST00000685439.1:c.865G>A

ENST00000685944.1:c.1210G>A

ENST00000686212.1:n.812G>A

ENST00000687215.1:c.*965G>A

ENST00000688152.1:c.*654G>A

ENST00000688403.1:c.466G>A

ENST00000689314.1:c.1255G>A

ENST00000689694.1:c.1210G>A

ENST00000689810.1:c.*859G>A

ENST00000690282.1:c.466G>A

ENST00000690351.1:c.*862G>A

ENST00000691232.1:c.865G>A

ENST00000691482.1:n.2225G>A

ENST00000691686.1:c.1210G>A

ENST00000691851.1:c.1053+8076G>A

ENST00000692015.1:c.997G>A

ENST00000692638.1:c.*1015G>A

ENST00000692852.1:c.1021G>A

ENST00000692915.1:c.*1356G>A

ENST00000370396.7:c.1210G>A

ENST00000306167.11:n.1077G>A

ENST00000370396.6:c.1210G>A

NM_000252.2:c.1210G>A

NM_001376906.1:c.1210G>A

NM_001376907.1:c.1099G>A

NM_001376908.1:c.1210G>A

Pathogenic

Met criteria codes 6

PM2_Supporting

PS3_Supporting

PS4_Very Strong

PP1

PP3

PP4

Evidence Links 0

Expert Panel

Congenital Myopathies VCEP

Criteria Specification Information

[Criteria Specification:](#) ClinGen Congenital Myopathies Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for MTM1 Version 1.0.0

[Criteria Specification Approval History](#)

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Congenital Myopathies VCEP

The NM_000252.3(MTM1):c.1210G>A variant in MTM1 is a missense variant predicted to cause substitution of glutamic acid by lysine at amino acid 404 (p.Glu404Lys). This variant has been reported in 10 probands meeting X-linked centronuclear myopathy (PS4_VeryStrong; PMIDs: 19084976, 33164942, 25957634, 9285787, 38544359, 38259611, 12467749, 30902907, 17005396). At least one patient with this variant displayed muscle biopsy with rounded muscle fibers with a single centrally located nucleus surrounded by a halo devoid of contractile elements, but containing mitochondria, which is highly specific for X-linked centronuclear myopathy (PP4; PMID: 17005396). The variant has been reported to segregate with disease in 4 affected individuals from 2 families (PP1; PMIDs: 17005396, 33164942). The variant is absent from gnomAD v.4.1.0 (PM2_Supporting). Immunofluorescence and western blot assays in COS cells (fibroblast-like cells derived from monkey kidney) showed unstable protein with aggregates in the cytoplasm and near the nucleus, probably in the Golgi, and very low myotubularin levels on western blot, indicating that this variant impacts protein function (PS3_Supporting; PMID: 12118066). The computational predictor REVEL gives a score of 0.759, which is above the threshold of 0.7 evidence that correlates with impact to MTM1 function (PP3). In summary, this variant meets the criteria to be classified as pathogenic for X-linked centronuclear myopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen Congenital Myopathies VCEP: PS4_VeryStrong, PS3_Supporting, PM2_Supporting, PP1, PP3, PP4 (ClinGen Congenital Myopathies VCEP specifications version 1.0.0; 2/20/2025).

Met criteria codes

PM2_Supporting



The variant is absent from gnomAD v.4.1.0. (PM2_Supporting).

PS3_Supporting



Immunofluorescence and western blot assays in COS cells (fibroblast-like cells derived from monkey kidney) showed unstable protein with aggregates in the cytoplasm and near the nucleus, probably in the Golgi, and very low myotubularin levels on western blot (data not shown) indicating that this variant impacts protein function (PMID 12118066)(PS3_Supporting).

PS4_Very Strong



This variant has been reported in 10 probands meeting X-linked centronuclear myopathy (PS4_Strong; PMIDs: 19084976, 33164942, 25957634, 9285787, 38544359, 38259611, 12467749, 30902907, 17005396).

PP1



The variant has been reported to segregate with disease in 4 affected individuals from 2 families (PP1_Supporting; PMIDs: 17005396, 33164942)

PP3



The computational predictor REVEL gives a score of 0.759, which is above the threshold of 0.7, evidence that correlates with impact to MTM1 function (PP3_Supporting).

PP4

At least one patient with this variant displayed muscle biopsy with rounded muscle fibers with a single centrally located nucleus surrounded by a halo devoid of contractile elements, but containing mitochondria, which is highly specific for X-linked centronuclear myopathy (PP4_Supporting, PMIDs 17005396).

Curation History [↗](#)

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