

Variant: *NM_000252.3(MTM1):c.205C>T (p.Arg69Cys)*

Version: 1.0

CA255665 [↗](#)

11055 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance (recessive (HP:0001419))

UUID: be301769-94ba-4548-a115-923b0015cdc9

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HGVS expressions

NM_000252.3(MTM1):c.205C>T (p.Arg69Cys)

NM_000252.3:c.205C>T

NC_000023.11:g.150598660C>T

CM000685.2:g.150598660C>T

NC_000023.10:g.149767124C>T

CM000685.1:g.149767124C>T

NC_000023.9:g.149517782C>T

NG_008199.1:g.35078C>T

ENST00000684910.1:c.136+2090C>T

ENST00000685439.1:c.-3-20378C>T

ENST00000685944.1:c.205C>T

ENST00000687215.1:c.-81C>T

ENST00000687365.1:n.260C>T

ENST00000688152.1:c.205C>T

ENST00000688403.1:c.-301+29798C>T

ENST00000689314.1:c.205C>T

ENST00000689694.1:c.205C>T

ENST00000689810.1:c.205C>T

ENST00000690282.1:c.-301+29942C>T

ENST00000690351.1:c.136+2090C>T

ENST00000691232.1:c.-3-20378C>T

ENST00000691686.1:c.205C>T

ENST00000691851.1:c.205C>T

ENST00000692015.1:c.205C>T

ENST00000692638.1:c.136+2090C>T

ENST00000692852.1:c.205C>T

ENST00000692915.1:c.205C>T

ENST00000693422.1:n.266C>T

ENST00000370396.7:c.205C>T

ENST00000306167.11:n.244C>T

ENST00000370396.6:c.205C>T

ENST00000424519.1:c.205C>T

ENST00000490530.1:n.170+2090C>T

NM_000252.2:c.205C>T

NM_001376906.1:c.205C>T

NM_001376907.1:c.205C>T

NM_001376908.1:c.205C>T

Pathogenic

Met criteria codes 5

PM2_Supporting PS4_Moderate PS3
PP1_Strong PP3

Not Met criteria codes 4

BS1 BP4 BA1 PM5

Evidence Links 1

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 c.205C>T (NM_000252.3(MTM1):c.205C>T (p.Arg69Cys)) variant in MTM1 is a missense variant predicted to cause substitution of Arg by Cys at amino acid 69. The variant was found in at least 3 probands from three families with X-linked centronuclear myopathy (PS4_Moderate; PMIDs: 9285787, 15811014). The variant has been reported to segregate with X-linked centronuclear myopathy in 6 affected individuals from one family (PP1_strong; PMID: 15811014). The variant specific model in mice showed muscle weakness and low myotubularin protein concentrations, indicating that this variant impacts protein function (PS3; PMID: 22068590; Pierson et al., 2012). The computational predictor REVEL gives a score of 0.825, which is above the threshold of 0.7, set by the Congenital Myopathies VCEP, evidence that correlates with impact to MTM1 function (PP3). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). 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_Moderate, PP1_Strong, PS3, PP3, PM2_Supporting; Version 1, 8/7/2024).

Met criteria codes

PM2_Supporting		✓	This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Coverage of the region of the gene in which the variant was found is adequate.
PS4_Moderate		✓	Variant was found in three probands with X-linked centronuclear myopathy (PMID: 9285787, 15811014).
PS3		✓	<p>The variant specific model in mice showed muscle weakness and low myotubularin protein concentrations, indicating that this variant impacts protein function (PMID: 22068590; Pierson et al., 2012).</p> <p>This was a mouse model. Hemizygous male mice with the Arg69Cys mutant acquire early muscle atrophy before weakness at 2 months. The average survival time is 66 weeks. Histopathological analysis revealed small myofibers with centrally located nuclei. Myotublarin protein is very low because the nucleotide change results in skipping of exon 4 in most mRNAs, causing early termination of myotubularin translation at exon 5. Some full-length Mtm mRNA with the mutation are available, which allows for sufficient myotubularin function to match the fairly mild phenotypic presentation. The mutant mice were made with PCR mutagenesis to trigger the mutation and the DNA was subcloned into the targeting vector. The wild-type sequence was replaced with a vector. A human quadricep sample from a patient with this mutation indicated that the mutation results in the skipping of exon 4 and early truncation of the protein in humans as well. PubMed:22068590</p>
PP1_Strong		✓	

The variant has been reported to segregate with X-linked centronuclear myopathy in 6 affected individuals from one family (PP1_strong; PMID: 15811014).

PP3			The computational predictor REVEL gives a score of 0.825, which is above the threshold of 0.7, set by the Congenital Myopathies VCEP, evidence that correlates with impact to MTM1 function (PP3).
Not Met criteria codes			
BS1			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
BP4			The computational predictor REVEL gives a score of 0.825, which is above the threshold of 0.7, set by the Congenital Myopathies VCEP, evidence that correlates with impact to MTM1 function (PP3).
BA1			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PM5			There are two other variants in ClinVar at this same residue, Arg to Gly and Arg to Cys, but the former is classified as a variant of uncertain significance for X-linked centronuclear myopathy, and the later is classified as pathogenic for the condition (but by only one submitter, back in 2013, with no evidence).

Curation History

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