

Variant: NM_000252.3(MTM1):c.614C>T (p.Pro205Leu)

Version: 1.0

CA271909 [↗](#)

158987 (ClinVar) [↗](#)

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

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

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

UUID: 63ca0364-f7f7-4ed4-8127-18f4feff245f

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HGVS expressions

NM_000252.3:c.614C>T

NM_000252.3(MTM1):c.614C>T (p.Pro205Leu)

NC_000023.11:g.150641354C>T

CM000685.2:g.150641354C>T

NC_000023.10:g.149809827C>T

CM000685.1:g.149809827C>T

NC_000023.9:g.149560485C>T

NG_008199.1:g.77781C>T

ENST00000684910.1:c.*147C>T

ENST00000685439.1:c.269C>T

ENST00000685944.1:c.614C>T

ENST00000686212.1:n.216C>T

ENST00000687215.1:c.*369C>T

ENST00000688152.1:c.*58C>T

ENST00000688403.1:c.-131C>T

ENST00000689314.1:c.659C>T

ENST00000689694.1:c.614C>T

ENST00000689810.1:c.*263C>T

ENST00000690282.1:c.-131C>T

ENST00000690351.1:c.*266C>T

ENST00000691232.1:c.269C>T

ENST00000691482.1:n.1629C>T

ENST00000691686.1:c.614C>T

ENST00000691851.1:c.614C>T

ENST00000692015.1:c.401C>T

ENST00000692638.1:c.*419C>T

ENST00000692852.1:c.614C>T

ENST00000692915.1:c.*821C>T

ENST00000370396.7:c.614C>T

ENST00000306167.11:n.481C>T

ENST00000370396.6:c.614C>T

ENST00000490530.1:n.553C>T

NM_000252.2:c.614C>T

NM_001376906.1:c.614C>T

NM_001376907.1:c.503C>T

NM_001376908.1:c.614C>T

Pathogenic

Met criteria codes 5

- PS3_Moderate
- PP3
- PM2_Supporting
- PM6
- PS4

Not Met criteria codes 4

- BA1
- BP4
- BS1
- PM1

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 c.614C>T variant in MTM1 is a missense variant predicted to cause substitution of proline by leucine at amino acid 205. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.968, which is above the Congenital Myopathies VCEP threshold of 0.7, evidence that correlates with impact to MTM1 function (PP3). This variant has been reported in at least ten individuals with centronuclear myopathy (PS4; PMIDs: 28685322, 11793470, 8640223, 15725586, 10063835). This variant has been identified as a de novo occurrence with unconfirmed parental relationships in one individual with X-linked centronuclear myopathy. (PM6; PMID: 10063835). A phosphatase assay using recombinant human myotubularin as a fusion protein in E. coli, showed that the mutation dramatically reduced phosphatase activity, indicating that this variant may impact protein function (PS3_Moderate; PMID: 10900271). 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, PM6, PS3_Moderate, PP3, PM2_Supporting. (Congenital Myopathies VCEP specifications version 1; 8/7/2024)

Met criteria codes

PS3_Moderate			A phosphatase assay using recombinant human myotubularin as a fusion protein in E. coli showed that the mutation dramatically reduced phosphatase activity, indicating that this variant impacts protein function (PS3_supporting; PMID: 10900271). Upgraded to moderate because the assay is specific and robust.
PP3			The computational predictor REVEL gives a score of 0.968, which is above the Congenital Myopathies VCEP threshold of 0.7, evidence that correlates with impact to MTM1 function (PP3). This variant is also predicted to be damaging by several in-silico predictors.
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Coverage of the gene in the region in which this variant is found is adequate.
PM6			One patient from Austria was a suspected de novo case. The patient presented with severe myotubular myopathy.
PS4			This variant has been reported in at least ten individuals from ten families with x-linked centro-nuclear myopathy (PS4; PMIDs: 28685322, 11793470, 8640223, 15725586, 10063835).

Not Met criteria codes

BA1			This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Coverage of the gene in the region in which this variant is found is adequate.
BP4			The computational predictor REVEL gives a score of 0.968, which is above the Congenital Myopathies VCEP threshold of 0.7, evidence that correlates with impact to MTM1 function (PP3). This variant is also predicted to be damaging by several in-silico predictors.
BS1			This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Coverage of the gene in the region in which this variant is found is adequate.
PM1			I would propose that the region in which this variant is found be considered a hot spot point as it is associated with a CpG dinucleotide, considered a frequent hot spot location. Also, in ClinVar, lots of variants in this region are noted to be pathogenic (at residues 189-205, including Asn189Ser, Tyr192Cys, Leu194Pro, Thr197Ile, Tyr198His, Tyr198Ser, and Val204Gly).

Curation History 		
Showing 1 to 1 of 1 rows		

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