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# *Variant: NM_000252.3(MTM1):c.690G>T (p.Trp230Cys)*

Version: 1.0

*CA415256307*

*4475856 (ClinVar)*

**Gene**: MTM1 (HGNC:4534)
**Condition**: centronuclear myopathy (MONDO:0018947)
**Inheritance Mode**: X-linked inheritance
**UUID:** 0e7e4644-f85d-408c-9ff6-97a3442c196e
**Approved on**: 2025/11/10
**Published on**: 2025/12/9

## *HGVS expressions*

**NM_000252.3(MTM1):c.690G>T (p.Trp230Cys)**
**NM_000252.3:c.690G>T**
NC_000023.11:g.150645694G>T
CM000685.2:g.150645694G>T
NC_000023.10:g.149814167G>T
CM000685.1:g.149814167G>T
NC_000023.9:g.149564825G>T
NG_008199.1:g.82121G>T
ENST00000684910.1:c.*223G>T
ENST00000685439.1:c.345G>T
ENST00000685944.1:c.690G>T
ENST00000686212.1:n.292G>T
ENST00000687215.1:c.*445G>T
ENST00000688152.1:c.*134G>T
ENST00000688403.1:c.-55G>T
ENST00000689314.1:c.735G>T
ENST00000689694.1:c.690G>T
ENST00000689810.1:c.*339G>T
ENST00000690282.1:c.-55G>T
ENST00000690351.1:c.*342G>T
ENST00000691232.1:c.345G>T
ENST00000691482.1:n.1705G>T
ENST00000691686.1:c.690G>T
ENST00000691851.1:c.690G>T
ENST00000692015.1:c.477G>T
ENST00000692638.1:c.*495G>T
ENST00000692852.1:c.679-4022G>T
ENST00000692915.1:c.*897G>T
ENST00000370396.7:c.690G>T
ENST00000306167.11:n.557G>T
ENST00000370396.6:c.690G>T
ENST00000490530.1:n.629G>T
NM_000252.2:c.690G>T
NM_001376906.1:c.690G>T
NM_001376907.1:c.579G>T
NM_001376908.1:c.690G>T

**Likely Pathogenic**

**Met criteria codes** 5

PS3_Supporting | PM2_Supporting | PM5_Supporting | PS4_Moderate | PP3

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 NM_000252.3:c.690G>T (p.Trp230Cys) variant in MTM1 is a missense variant predicted to cause substitution of tryptophan by cysteine at amino acid 230. This variant is absent from gnomAD v4.1.0 (PM2_supporting). The computational predictor REVEL gives a score of 0.901, which is above the Congenital Myopathies VCEP threshold of 0.7, evidence that correlates with impact to MTM1 function (PP3). Another missense variant (c.688T>C, p.Trp230Arg) [VCV000092677] in the same codon has been classified as likely pathogenic for X-linked centronuclear myopathy by the ClinGen Congenital Myopathies VCEP indicating that this residue may be critical to MTM1 function (PM5_Supporting). This variant has been reported in 3 male probands with features of myotubular myopathy (PS4_moderate; PMIDs: 10063835, 12522554, VCEP internal contributor). Expression-level evidence in HEK293 cells showed significantly reduced expression of the mutant protein indicating that this variant impacts protein stability and likely protein function (PMID: 37101954; PS3_supporting). In summary, this variant meets the criteria to be classified as likely pathogenic for X-linked centronuclear myopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen Congenital Myopathies VCEP: PM2_supporting, PP3, PM5_supporting, PS4_moderate, PS3_supporting (VCEP Specifications Version 1.0.0; 11/10/2025).**

**Met criteria codes**

| | |
|---|---|
| **PS3_Supporting** ✔ | Expression analysis in HEK293 cells showed significantly reduced expression of MTM1 protein in the mutant compared to the wild-type indicating that this variant impacts protein function (PS3_supporting; PMID: 37101954).<br><br>Expression analysis was done via western blot for total protein-containing lysate from HEK293T cells transfected by corresponding plasmids. The loading control was GADPH, and the probing of the band for GADPH was done at 37 kDA. The wild-type and mutants were seen below 75 kDA, the anticipated length. The mutant p.Trp230Cys shows low expression of MTM1 compared to the wild-type. PubMed:37101954 |
| **PM2_Supporting** ✔ | This variant is absent from gnomAD v4.1.0 (PM2_supporting). Coverage of the gene is this region is adequate. |
| **PM5_Supporting** ✔ | Another missense variant (c.688T>C, p.Trp230Arg) [VCV000092677] in the same codon has been classified as likely pathogenic for X-linked centronuclear myopathy by the ClinGen Congenital Myopathies VCEP indicating that this residue may be critical to MTM1 function (PM5_Supporting). |
| **PS4_Moderate** ✔ | This variant has been reported in 3 probands with features of centronuclear myopathy (PS4_moderate; PMIDs: 10063835, 12522554; Beggs Laboratory, Boston Children’s Hospital). |
| **PP3** ✔ | |

The computational predictor REVEL gives a score of 0.901, which is above the Congenital Myopathies VCEP threshold of 0.7, evidence that correlates with impact to MTM1 function (PP3). Computational predictors consistently suggest a harmful impact (ie. damaging by SIFT, probably damaging by PolyPhen, deleterious by LRT, disease causing by MutationTaster). The variant is not predicted to impact splicing (highest SpliceAI score is 0.09 for acceptor gain).

## Curation History

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