

Variant: NM_000252.3(MTM1):c.575A>G (p.Tyr192Cys)

Version: 1.0

CA271902 [↗](#)

158984 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 6455990a-f06d-4552-9f48-1ac04ed57b89

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HGVS expressions

NM_000252.3(MTM1):c.575A>G (p.Tyr192Cys)

NM_000252.3:c.575A>G

NC_000023.11:g.150641315A>G

CM000685.2:g.150641315A>G

NC_000023.10:g.149809788A>G

CM000685.1:g.149809788A>G

NC_000023.9:g.149560446A>G

NG_008199.1:g.77742A>G

ENST00000684910.1:c.*108A>G

ENST00000685439.1:c.230A>G

ENST00000685944.1:c.575A>G

ENST00000686212.1:n.177A>G

ENST00000687215.1:c.*330A>G

ENST00000688152.1:c.*19A>G

ENST00000688403.1:c.-170A>G

ENST00000689314.1:c.620A>G

ENST00000689694.1:c.575A>G

ENST00000689810.1:c.*224A>G

ENST00000690282.1:c.-170A>G

ENST00000690351.1:c.*227A>G

ENST00000691232.1:c.230A>G

ENST00000691482.1:n.1590A>G

ENST00000691686.1:c.575A>G

ENST00000691851.1:c.575A>G

ENST00000692015.1:c.362A>G

ENST00000692638.1:c.*380A>G

ENST00000692852.1:c.575A>G

ENST00000692915.1:c.*782A>G

ENST00000370396.7:c.575A>G

ENST00000306167.11:n.442A>G

ENST00000370396.6:c.575A>G

ENST00000490530.1:n.514A>G

NM_000252.2:c.575A>G

NM_001376906.1:c.575A>G

NM_001376907.1:c.464A>G

NM_001376908.1:c.575A>G

Likely Pathogenic

Met criteria codes 5

PP1_ModeratePS4PP3PM2_SupportingPS3_Supporting

Not Met criteria codes 3

BA1BS1BP4

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:c.575A>G variant in MTM1 is a missense variant predicted to cause substitution of tyrosine by cysteine at amino acid 192. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.946, which is above the threshold of 0.7, evidence that correlates with impact to MTM1 function (PP3). This variant has been reported in 5 probands with centronuclear myopathy (PS4_Strong; PMID: 20434914, http://dx.doi:10.1016/j.nmd.2014.06.056, ClinVar SCV: SCV000634492.8, Invitae). The variant has been reported to segregate with X-linked centronuclear myopathy in at least 3 affected family members from 2 families (PP1_Moderate; http://dx.doi:10.1016/j.nmd.2014.06.056, ClinVar SCV: SCV000634492.8, Invitae). Myotubularin level was lower in cells from one patient compared to control. Semi-quantitative analysis compared to GAPDH level suggested a decrease of about 7 times compared to control (PS3_Supporting; PMID: 20434914). 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: PS4, PP1_Moderate, PS3_Supporting, PM2_Supporting, PP3. (Congenital Myopathies VCEP specifications version 1; 8/7/2024)

Met criteria codes

PP1_Moderate

✓

Segregated in at least 3 family members (doi:10.1016/j.nmd.2014.06.056, ClinVar SCV: SCV000634492.8, Invitae)

PS4

✓

Detected in at 5 probands with centronuclear myopathy (PMID: 20434914, doi:10.1016/j.nmd.2014.06.056, Invitae, ClinVar SCV: SCV000634492.8)

PP3

✓

The computational predictor REVEL gives a score of 0.946, which is above the threshold of 0.7, evidence that correlates with impact to MTM1 function

PM2_Supporting

✓

This variant is absent from gnomAD v4.1.0

PS3_Supporting

✓

Myotubularin level was lower in cells from one patient compared to control. Semi-quantitative analysis compared to GAPDH level suggested a decrease of about 7 times compared to control (PMID: 20434914)

Not Met criteria codes

BA1

✗

This variant is absent from gnomAD v4.1.0

BS1			This variant is absent from gnomAD v4.1.0
BP4			The computational predictor REVEL gives a score of 0.946, which is above the threshold of 0.7, evidence that correlates with impact to MTM1 function

Curation History 

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