

Variant: *NM_000138.5(FBN1):c.1468G>T (p.Asp490Tyr)*

Version: 1.0

CA392343534 [↗](#)

549019 (ClinVar) [↗](#)

Gene: FBN1 ([HGNC:2200](#))

Condition: Marfan syndrome ([MONDO:0007947](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: c2666e7c-694f-4748-8c27-3fba06e4f2f6

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HGVS expressions

NM_000138.5:c.1468G>T

NM_000138.5(FBN1):c.1468G>T (p.Asp490Tyr)

NC_000015.10:g.48515387C>A

CM000677.2:g.48515387C>A

NC_000015.9:g.48807584C>A

CM000677.1:g.48807584C>A

NC_000015.8:g.46594876C>A

NG_008805.2:g.135402G>T

ENST00000559133.6:c.1468G>T

ENST00000674301.2:c.1468G>T

ENST00000684448.1:n.142G>T

ENST00000316623.10:c.1468G>T

ENST00000316623.9:c.1468G>T

ENST00000537463.6:c.636+22324G>T

NM_000138.4:c.1468G>T

Likely Pathogenic

Met criteria codes **7**

PS4_Moderate

PP2

PP3

PP4

PM1

PM5

PM2_Supporting

Evidence Links **0**

Expert Panel

FBN1 VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

FBN1 VCEP

The NM_00138 c.1468G>T is a missense variant in FBN1 predicted to cause a substitution of a aspartic acid by tyrosine at amino acid 490 (p.Asp490Tyr). This variant impacts an aspartic acid within a calcium-binding (cb) (D/N)-X-(D/N)-(E/Q)-Xm-(D/N)-Xn-(Y/F) consensus sequence of a cbEGF-like domain (PM1). This variant was found in a proband with a clinical diagnosis of Marfan syndrome (MFS) (PMID 35058154, internal lab data, PP4). This variant has been reported three times in ClinVar: twice as pathogenic and once as uncertain significance (Variation ID: 549019). This variant has also been identified in at least 2 individuals with a clinical diagnosis of MFS as well as in an individual with clinical features of MFS (PMID 11826022, 20886638, Invitae ClinVar entry; PS4_Mod). A different missense variant at this position, c.1468G>C (p.Asp490His), has previously been previously established as (likely) pathogenic and has been found in at least 3

individuals with clinical features of MFS and was found to segregate with disease (PMID 25652356, internal data; PM5), Computational prediction tools and conservation analysis suggest that this variant may impact the protein (REVEL: 0.965, PP3). This variant is located in the last nucleotide of the exon. In silico prediction programs predict that this variant may disrupt RNA splicing (PP3). The constraint z-score for missense variants affecting FBN1 is 5.06 (PP2). In summary, this variant meets criteria to be classified as likely pathogenic for Marfan syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen FBN1 VCEP: PM1, PM5, PS4_Moderate, PM2_Sup, PP2, PP3, PP4.

Met criteria codes

PS4_Moderate			2.5 points
PP2			Missense variant
PP3			REVEL score: 0.965; Predicted to weaken/ disrupt canonical donor site: MaxENT: -59.5%, NNSplice: 0.98=> --, GeneSplicer: -67.1%
PP4			Internal lab data- Lorsartan proband- Met revised Ghent criteria
PM1			Asp in (D/N)-X-(D/N)-(E/Q)-Xm-(D/N)-Xn-(Y/F) cb consensus sequence
PM5			c.1468G>C (p.Asp490His)- at least LP: Absent in gnomAD, REVEL: 0.976, Splice: weaken donor site (MaxEnt: -20.6%, NNSPLICE: -40.8%, GeneSplicer: -45.7%) Internal UZG- 2 probands with MFS, classified as LP, applying PP4 and +PP1
PM2_Supporting			Absent in gnomAD

Curation History

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