

Variant: *NM_000138.5(FBN1):c.1073G>A (p.Cys358Tyr)*

Version: 1.0

CA392347578 [↗](#)

549001 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: d8789da1-0fca-41c7-b3af-75a3d4f73d73

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HGVS expressions

NM_000138.5(FBN1):c.1073G>A (p.Cys358Tyr)

NM_000138.5:c.1073G>A

NC_000015.10:g.48520733C>T

CM000677.2:g.48520733C>T

NC_000015.9:g.48812930C>T

CM000677.1:g.48812930C>T

NC_000015.8:g.46600222C>T

NG_008805.2:g.130056G>A

ENST00000559133.6:c.1073G>A

ENST00000674301.2:c.1073G>A

ENST00000316623.10:c.1073G>A

ENST00000316623.9:c.1073G>A

ENST00000537463.6:c.636+16978G>A

NM_000138.4:c.1073G>A

Likely Pathogenic

Met criteria codes **7**

PS4_Supporting PP2 PP3 PP4
PM1 PM5 PM2

Not Met criteria codes **19**

PVS1 BA1 BP4 BP3 BP1
BP2 BP5 BP7 BS2 BS1 BS4
BS3 PP1 PM3 PM4 PM6
PS1 PS2 PS3

Evidence Links **0**

Expert Panel

[FBN1 VCEP](#) [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** *ClinGen FBN1 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1*

[↗](#) **PDF**

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

FBN1 VCEP

NM_00138 c.1073G>A is a missense variant in **FBN1** predicted to cause a substitution of a cysteine by tyrosine at amino acid 358(p.Cys358Tyr). This variant has been found in two probands, one with the clinical diagnosis of Marfan syndrome but without a specified phenotype and one with ectopia lentis, thoracic aortic aneurysm and dissection, and a systemic score of 9 (PP4, PS4_supporting; PMID:

35058154; UZG internal data). This variant has been reported two times in ClinVar, once as likely pathogenic and once as of uncertain significance (Variation ID: 549001). This variant is not present in gnomAD (PM2_supporting; <https://gnomad.broadinstitute.org/>). This variant affects a cysteine residue in a TGFβ binding-protein-like (TB) domain; cysteine residues are believed to be involved in the formation of disulfide bridges which are essential for the protein structure (PM1). Other variants altering this codon are pathogenic or likely pathogenic (p.Cys358Trp, p.Cys358Arg), supporting the functional importance of this amino acid position (PM5). Computational prediction tools and conservation analysis suggest that this variant may impact protein structure or function (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_supporting, PM2_supporting, PP2, PP3, PP4.

Met criteria codes

PS4_Supporting			1 proband worth 1.0 PS4 point
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			REVEL = 0.939
PP4			proband meets revised Ghent criteria
PM1			Cysteine in TB1 domain
PM5			p.Cys358Trp, p.Cys358Arg are LP/P with FBN1 specifications
PM2			absent from gnomAD

Not Met criteria codes

PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

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