

Variant: *NM_000138.5(FBN1):c.1481G>C (p.Cys494Ser)*

Version: 1.0

CA392342805 [↗](#)

502478 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 0fd815a5-f810-4595-8659-2d7a98a4c3f9

Approved on: 2023/11/16

Published on: 2023/11/16

HGVS expressions

NM_000138.5:c.1481G>C

NM_000138.5(FBN1):c.1481G>C (p.Cys494Ser)

NC_000015.10:g.48513656C>G

CM000677.2:g.48513656C>G

NC_000015.9:g.48805853C>G

CM000677.1:g.48805853C>G

NC_000015.8:g.46593145C>G

NG_008805.2:g.137133G>C

ENST00000559133.6:c.1481G>C

ENST00000674301.2:c.1481G>C

ENST00000684448.1:n.155G>C

ENST00000316623.10:c.1481G>C

ENST00000316623.9:c.1481G>C

ENST00000537463.6:c.636+24055G>C

NM_000138.4:c.1481G>C

Likely Pathogenic

Met criteria codes 5

PM1_Strong

PP2

PP3

PS4_Supporting

PM2_Supporting

Not Met criteria codes 21

BP5

BP7

BP4

BP3

BP1

BP2

BS1

BS4

BS3

BS2

PP1

PP4

PS1

PS2

PS3

BA1

PM6

PM3

PM5

PM4

PVS1

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_000138.5(FBN1):c.1481G>C (p.Cys494Ser) NM_00138 c.1481G>C is a missense variant in FBN1 predicted to cause a substitution of a cysteine by serine at amino acid 494 (p.Cys494Ser). This variant was found in two probands, one with isolated thoracic aortic aneurysm

and dissection (TAAD) and one with TAAD and systemic features of Marfan syndrome (PS4_supporting; PMID: 32209317; UZG internal data). This variant has been reported twice in ClinVar as likely pathogenic and once as of uncertain significance (Variation ID: 502478). This variant is not present in gnomAD (PM2_supporting; <https://gnomad.broadinstitute.org/>). This variant affects a cysteine residue in a calcium binding EGF domain; cysteine residues are believed to be involved in the formation of disulfide bridges which are essential for the protein structure (PM1_strong). Other variants affecting this codon have been reported in association with Marfan syndrome (p.Cys494Tyr, p.Cys494Trp, p.Cys494Phe). Computational prediction tools and conservation analysis strongly support that this variant may impact the protein’s 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_strong, PS4_supporting, PP2, PP3, PM2_supporting.

Met criteria codes

PM1_Strong			Cysteine in cbEGF3
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			REVEL = 0.991
PS4_Supporting			2 probands worth 1.0 PS4 point
PM2_Supporting			absent from gnomAD

Not Met criteria codes

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
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
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
BS2			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
PP4			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
BA1			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
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			.Cys494Tyr and p.Cys494Trp, p.Cys494Phe are LP/P; PM1_strong is applied so PM5 is n/a
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
Showing 1 to 1 of 1 rows		

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.