

Variant: *NM_000138.5(FBN1):c.6541T>C (p.Cys2181Arg)*

Version: 1.0

CA392335055 [↗](#)

429425 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 8a79b62f-2272-45f5-852c-32bba97da645

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HGVS expressions

NM_000138.5(FBN1):c.6541T>C (p.Cys2181Arg)

NM_000138.5:c.6541T>C

NC_000015.10:g.48434669A>G

CM000677.2:g.48434669A>G

NC_000015.9:g.48726866A>G

CM000677.1:g.48726866A>G

NC_000015.8:g.46514158A>G

NG_008805.2:g.216120T>C

ENST00000559133.6:c.6541T>C

ENST00000674301.2:c.6541T>C

ENST00000682170.1:n.150T>C

ENST00000316623.10:c.6541T>C

ENST00000674301.1:c.1540T>C

ENST00000316623.9:c.6541T>C

ENST00000537463.6:c.*2304T>C

ENST00000559133.5:c.1848T>C

NM_000138.4:c.6541T>C

Likely Pathogenic

Met criteria codes 6

PS4_Supporting PP2 PP3 PP4
PM1_Strong PM2_Supporting

Not Met criteria codes 20

PP1 PM6 BA1 PM3 PM5
PM4 BS1 BS4 BS3 BS2
PS1 PS2 PS3 PVS1 BP5
BP7 BP4 BP3 BP1 BP2

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 c.6541T>C is a missense variant in FBN1 predicted to cause a substitution of cysteine by an arginine at amino acid 2181 (p.Cys2182Arg). It has been identified in one patient meeting clinical diagnostic criteria for Marfan syndrome, including thoracic aortic aneurysm and dissection (TAAD) and systemic involvement, and was found to segregate with TAAD and systemic features in the patient’s sibling (PP4; University of Tokyo). This variant has also been reported in two patients with TAAD, without additional phenotypes noted (PS4_supporting; PMID: 37042257, GeneDx internal data). It is absent from gnomAD (PM2_supporting; <https://gnomad.broadinstitute.org/>, v2.1.1, 3.1.2, 4.0.0). This variant affects a cysteine residue in a calcium-binding EGF-like domain; cysteine residues are involved in the formation of disulfide bridges which are essential for the protein structure (PM1_strong). Computational prediction tools and conservation analysis support that this variant is likely to impact the protein (PP3; REVEL = 0.993). The constraint z-score for missense variants affecting FBN1 is 8.18 (PP2; gnomAD v4.0.0). 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, PP2, PP3, PP4, PS4_supporting, PM2_supporting.

Met criteria codes			
PS4_Supporting			2 probands worth 1.0 PS4 point
PP2			no benign evidence
PP3			REVEL > 0.750
PP4			University of Tokyo proband meets revised Ghent criteria, with suspected family history of MFS
PM1_Strong			cysteine in cbEGF33
PM2_Supporting			absent from all versions of gnomAD

Not Met criteria codes			
PP1			1 segregation (University of Tokyo)
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			PM2_supporting met
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			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

BS1			PM2_supporting met
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
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
PVS1			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
BP4			PP3 met
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

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