

Variant: *NM_000138.5(FBN1):c.6410G>A (p.Cys2137Tyr)*

Version: 1.0

CA392336648 [↗](#)

633211 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: e09bca8b-b5bd-4e00-9b72-769cd05c78d9

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HGVS expressions

NM_000138.5(FBN1):c.6410G>A (p.Cys2137Tyr)

NM_000138.5:c.6410G>A

NC_000015.10:g.48437047C>T

CM000677.2:g.48437047C>T

NC_000015.9:g.48729244C>T

CM000677.1:g.48729244C>T

NC_000015.8:g.46516536C>T

NG_008805.2:g.213742G>A

ENST00000559133.6:c.6410G>A

ENST00000674301.2:c.6410G>A

ENST00000682170.1:n.19G>A

ENST00000316623.10:c.6410G>A

ENST00000674301.1:c.1409G>A

ENST00000316623.9:c.6410G>A

ENST00000537463.6:c.*2173G>A

ENST00000559133.5:c.1717G>A

NM_000138.4:c.6410G>A

Pathogenic

Met criteria codes **7**

PS4_Moderate PM1_Strong
PM2_Supporting PP1 PP2 PP3
PP4

Not Met criteria codes **19**

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

FBN1 VCEP

NM_000138.5 c.6410G>A is a missense variant in FBN1 predicted to cause a substitution of cysteine by a tyrosine at amino acid 2137 (p.Cys2137Tyr). This variant has been identified in at least five patients with thoracic aortic aneurysm and dissection (TAAD), including two meeting clinical diagnostic criteria for Marfan syndrome (MFS), and in a patient with an unspecified clinical suspicion of Marfan syndrome (PS4_moderate, PP4; University of Texas-Houston & Invitae internal data). The variant was also found to segregate with aortic dilation in two individuals across two families (PP1; University of Texas-Houston & Invitae 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 = 0.916). 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 pathogenic for Marfan syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen FBN1 VCEP: PM1_strong, PS4_moderate, PP1, PP2, PP3, PP4, PM2_supporting.

Met criteria codes

PS4_Moderate			5 probands worth 3.0 PS4 points (1 other Invitae proband accounted for by PP4)
PM1_Strong			cysteine in cbEGF32
PM2_Supporting			absent from all versions of gnomAD
PP1			2 segregations
PP2			no benign evidence
PP3			REVEL > 0.750
PP4			proband at Invitae meeting revised Ghent criteria

Not Met criteria codes

PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			other variants at this position LP/P; PM5 n/a due to PM1_strong
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
BA1			PM2_supporting met

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
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
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

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