The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000138.5(FBN1):c.4409G>A (p.Cys1470Tyr)

Version: 1.0

CA392354488

1325422 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3bb0c419-ebfe-49c4-9329-d99371d562a7
Approved on: 2023/12/29
Published on: 2023/12/29

HGVS expressions

NM_000138.5:c.4409G>A
NM_000138.5(FBN1):c.4409G>A (p.Cys1470Tyr)
NC_000015.10:g.48470684C>T
CM000677.2:g.48470684C>T
NC_000015.9:g.48762881C>T
CM000677.1:g.48762881C>T
NC_000015.8:g.46550173C>T
NG_008805.2:g.180105G>A
ENST00000559133.6:c.4409G>A
ENST00000674301.2:c.4409G>A
ENST00000683268.1:n.376G>A
ENST00000684448.1:n.3083G>A
ENST00000316623.10:c.4409G>A
ENST00000316623.9:c.4409G>A
ENST00000537463.6:c.*172G>A
NM_000138.4:c.4409G>A

Pathogenic

Met criteria codes 6

PM2_Supporting PS4_Moderate PP2 PP3 PP4 PM1_Strong

Not Met criteria codes 20

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

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.4409G>A is a missense variant in FBN1 predicted to cause a substitution of a cysteine by tyrosine at amino acid 1470 (p.Cys1470Tyr). This variant has been identified in at least three individuals with clinical diagnoses of Marfan syndrome (PS4_moderate, PP4; PMIDs: 35058154, 11933199; Bichat, & CHEO internal data). It is absent from gnomAD (PM2_supporting; https://gnomad.broadinstitute.org/ v2.1.1 & v3.1.2). 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 = 0.976). The constraint z-score for missense variants affecting FBN1 is 5.06 (PP2). 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, PP2, PP3, PP4, PM2_supporting.

Met criteria codes

PM2_Supporting	✔	absent from gnomAD
PS4_Moderate	✔	2 probands worth 2.0 PS4 points
PP2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✔	REVEL = 0.976; > 0.750 threshold
PP4	✔	1 internal proband (Bichat) with MFS
PM1_Strong	✔	cysteine-removing variant in cbEGF21

Not Met criteria codes

PVS1	✖	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	✖	PM2_supporting
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
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	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	ℹ	✖	PM2_supporting
PM3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	ℹ	✖	p.Cys1470Arg is LP/P (Bichat internal probands, REVEL, absent from gnomAD, cysteine-removing in cbEGF, etc.); N/A because PM1_strong is applied
PM4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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