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.1708T>C (p.Cys570Arg)

Version: 1.0

CA269554328

956400 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 38d36d10-5c7c-455c-9338-0706c4a6f7f9
Approved on: 2023/11/16
Published on: 2023/11/16

HGVS expressions

NM_000138.5:c.1708T>C
NM_000138.5(FBN1):c.1708T>C (p.Cys570Arg)
NC_000015.10:g.48510050A>G
CM000677.2:g.48510050A>G
NC_000015.9:g.48802247A>G
CM000677.1:g.48802247A>G
NC_000015.8:g.46589539A>G
NG_008805.2:g.140739T>C
ENST00000559133.6:c.1708T>C
ENST00000674301.2:c.1708T>C
ENST00000684448.1:n.382T>C
ENST00000316623.10:c.1708T>C
ENST00000316623.9:c.1708T>C
ENST00000537463.6:c.636+27661T>C
NM_000138.4:c.1708T>C

Pathogenic

Met criteria codes 7

PM1_Strong PS4_Moderate PP2 PP3 PP4 PM2_Supporting PS3_Supporting

Not Met criteria codes 17

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

Evidence Links 1

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.1708T>C is a missense variant in FBN1 predicted to cause a substitution of a cysteine by arginine at amino acid 570 (p.Cys570Arg). This variant has been found in two probands with ectopia lentis (EL), one of whom was also reported to have numerous systemic features of Marfan syndrome without thoracic aortic aneurysm and dissection (TAAD), as well as a proband with isolated TAAD (PS4_moderate; PMID: 10486319; 3billion & Invitae internal data, ClinVar Variation ID: 956400). An additional proband with a severe Marfan syndrome phenotype including EL, TAAD, and major skeletal involvement (PP4; Bichat internal data). Functional studies performed on patient fibroblasts with this variant demonstrated reduced fibrillin synthesis and secretion (50% and 28% of controls, respectively) (PS3_supporting; PMID: 10486319). 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). Several other variants affecting this codon have been reported in association with Marfan syndrome (p.Cys570Gly, p.Cys570SerSer, p.Cys570Trp, p.Cys570Tyr). Computational prediction tools and conservation analysis 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 pathogenic for Marfan syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen FBN1 VCEP: PM1_strong, PS4_moderate, PS3_supporting, PM2_supporting, PP2, PP3, PP4.

Met criteria codes

PM1_Strong	✔	Cysteine in cbEGF4
PS4_Moderate	✔	3 probands worth 2.5 PS4 points
PP2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✔	REVEL = 0.983
PP4	✔	1 internal proband meeting revised Ghent criteria (Bichat)
PM2_Supporting	✔	Absent from gnomAD
PS3_Supporting	✔	acceptable functional assay per FBN1 VCEP; per ClinGen SVI the study was lacking sufficient replicates to use at full strength Study of fibroblasts from patient with p.Cys570Arg (patient cited in PS4 evidence); studies demonstrated reduced fibrillin synthesis (50% of wild type/control) and reduced fibrillin secretion (28% of wild type/control) PubMed:10486319

Not Met criteria codes

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

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
PM5		✖	p.Cys570Ser, p.Cys570Tyr both LP/P per FBN1 VCEP specifications; PM1_strong applied so PM5 n/a
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		✖	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
PVS1		✖	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
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
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

Curation History

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