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.3557A>G (p.Tyr1186Cys)

Version: 1.0

CA392324980

495594 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 40d44fc6-1e1f-408a-8694-a304f4acafde
Approved on: 2023/12/29
Published on: 2023/12/29

HGVS expressions

NM_000138.5:c.3557A>G
NM_000138.5(FBN1):c.3557A>G (p.Tyr1186Cys)
NC_000015.10:g.48487107T>C
CM000677.2:g.48487107T>C
NC_000015.9:g.48779304T>C
CM000677.1:g.48779304T>C
NC_000015.8:g.46566596T>C
NG_008805.2:g.163682A>G
ENST00000559133.6:c.3557A>G
ENST00000674301.2:c.3557A>G
ENST00000684448.1:n.2231A>G
ENST00000316623.10:c.3557A>G
ENST00000316623.9:c.3557A>G
ENST00000537463.6:c.637-12457A>G
NM_000138.4:c.3557A>G

Pathogenic

Met criteria codes 6

PM1 PS4 PP1 PP2 PP3 PM2_Supporting

Not Met criteria codes 20

PVS1 PM6 PM3 PM5 PM4 BA1 BS2 BS1 BS4 BS3 BP5 BP7 BP4 BP3 BP1 BP2 PS1 PS2 PS3 PP4

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.3557A>G is a missense variant in FBN1 predicted to cause a substitution of a tyrosine by a cysteine at amino acid 1186 (p.Tyr1186Cys). It has been identified in at least five individuals with diagnoses or suspicion of Marfan syndrome including the following: a

pediatric patient with bilateral ectopia lentis (EL), severe thoracic aortic aneurysm and dissection (TAAD), and a systemic score of 9; an adult patient with EL and a systemic score of 6; a patient with bilateral EL, TAAD, and systemic features; an individual reported to have Marfan syndrome without specific details provided; and an individual with bilateral EL, TAAD, retinal detachment, and systemic features (PS4; PMIDs: 31061752, 11933199; UZG, Bichat, & Invitae internal data). It was also found to segregate with Marfan syndrome in two other members of an aforementioned family (PP1; Bichat internal data). It is absent from gnomAD (PM2_supporting; https://gnomad.broadinstitute.org/, v2.1.1 & v3.1.2). This variant introduces a novel cysteine residue which may impede the normal formation of critical disulfide bridges (PM1). Computational prediction tools and conservation analysis support that this variant is likely to impact the protein (PP3; REVEL = 0.974). 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: PS4, PM1, PP1, PP2, PP3, PM2_supporting.

Met criteria codes

PM1	✔	Cysteine-creating variant in cbEGF14
PS4	✔	5 probands worth 4.5 PS4 points (proband with MFS from Stheneur et al./Bichat internal data currently counting for PP4, and is not included in PS4 application)
PP1	✔	2 segregations with Marfan syndrome (Bichat)
PP2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✔	REVEL = 0.974; > 0.750
PM2_Supporting	✔	absent from gnomAD

Not Met criteria codes

PVS1	✖	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	✖	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

BA1	ℹ	✖	PM2_supporting met
BS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	PM2_supporting met
BS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	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
BP4	ℹ	✖	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
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
PP4	ℹ	✖	internal proband meeting revised Ghent criteria (Bichat); VCEP decision is to include this proband in the PS4 argument rather than PP4

Curation History

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