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.6491G>A (p.Cys2164Tyr)

Version: 1.0

CA392336264

547340 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 56b0fed5-cc14-4984-881d-92f7643f0f5b
Approved on: 2024/8/22
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HGVS expressions

NM_000138.5(FBN1):c.6491G>A (p.Cys2164Tyr)
NM_000138.5:c.6491G>A
NC_000015.10:g.48436966C>T
CM000677.2:g.48436966C>T
NC_000015.9:g.48729163C>T
CM000677.1:g.48729163C>T
NC_000015.8:g.46516455C>T
NG_008805.2:g.213823G>A
ENST00000559133.6:c.6491G>A
ENST00000674301.2:c.6491G>A
ENST00000682170.1:n.100G>A
ENST00000316623.10:c.6491G>A
ENST00000674301.1:c.1490G>A
ENST00000316623.9:c.6491G>A
ENST00000537463.6:c.*2254G>A
ENST00000559133.5:c.1798G>A
NM_000138.4:c.6491G>A

Pathogenic

Met criteria codes 7

PM2_Supporting PS4 PM1_Strong PP1 PP2 PP3 PP4

Not Met criteria codes 19

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

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.6419G>A is a missense variant in FBN1 predicted to cause a substitution of a cysteine by tyrosine at amino acid 2164 (p.Cys2164Tyr). This variant has been identified in at least four individuals meeting clinical diagnostic criteria for Marfan syndrome (MFS) and two individuals with non-specific features suggestive of a connective tissue disorder (PS4, PP4; Bichat & UZG internal data; PMIDs: 31730815, 37558401, 29095814). In one of these individuals, it was found to be de novo; however, phenotype details were not provided and therefore the specificity and consistency of the phenotype with FBN1 cannot be assessed (PMID: 29095814). In another of these families, the variant was found to segregate with disease in two affected family members (PP1; Bichat 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 = 0.863). 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, PP1, PP2, PP3, PP4, PM2_supporting.

Met criteria codes

PM2_Supporting	✔	absent from all versions of gnomAD
PS4	✔	5 probands worth 4.0 PS4 points
PM1_Strong	✔	cysteine in cbEGF32
PP1	✔	2 segregations with disease (Bichat)
PP2	✔	no benign evidence
PP3	✔	REVEL > 0.750
PP4	✔	Mannucci et al. patient meets revised Ghent criteria

Not Met criteria codes

PVS1	✖	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

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
BA1		✖	PM2_supporting met
PM6		✖	no phenotype data provided for Hu et al. proband, so cannot assess consistency and specificity of their phenotype
PM3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5		✖	n/a because PM1_strong is applied
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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