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.6446A>G (p.Tyr2149Cys)

Version: 1.0

CA016465

42402 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 4af545ca-cc58-4dda-a435-17262478443f
Approved on: 2024/8/22
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HGVS expressions

NM_000138.5(FBN1):c.6446A>G (p.Tyr2149Cys)
NM_000138.5:c.6446A>G
NC_000015.10:g.48437011T>C
CM000677.2:g.48437011T>C
NC_000015.9:g.48729208T>C
CM000677.1:g.48729208T>C
NC_000015.8:g.46516500T>C
NG_008805.2:g.213778A>G
ENST00000559133.6:c.6446A>G
ENST00000674301.2:c.6446A>G
ENST00000682170.1:n.55A>G
ENST00000316623.10:c.6446A>G
ENST00000674301.1:c.1445A>G
ENST00000316623.9:c.6446A>G
ENST00000537463.6:c.*2209A>G
ENST00000559133.5:c.1753A>G
NM_000138.4:c.6446A>G

Pathogenic

Met criteria codes 7

PM2_Supporting PS2 PS4 PP2 PP3 PP4 PM1

Not Met criteria codes 19

PVS1 BS1 BS4 BS3 BS2 BP5 BP7 BP4 BP3 BP1 BP2 PS1 PS3 BA1 PP1 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.6446A>G is a missense variant in FBN1 predicted to cause a substitution of a tyrosine by cysteine amino acid 2149 (p.Tyr2149Cys). This variant has been identified in at least 13 individuals with features suggestive of, or consistent with, Marfan syndrome (MFS), including four patients meeting clinical diagnostic criteria for MFS, seven with thoracic aortic aneurysm or dissection (TAAD) with or without additional features of MFS, and two with unspecified clinical suspicion of MFS (PS4, PP4; Johns Hopkins, University of Texas-Houston, LMM, & Invitae internal data; PMIDs: 24793577, 27611364, 37684520, 31098894). The variant was found to be de novo in five of these patients, including three (maternity/paternity assumed) with phenotypes consistent with, but not highly specific to, FBN1, one (maternity/paternity assumed) with TAAD and borderline systemic involvement, and one (maternity/paternity confirmed) with a non-specific and genetically heterogeneous phenotype of TAAD and mitral valve prolapse (PS2; Johns Hopkins & Invitae internal data; PMIDs: 31098894, 37684520). It is absent from gnomAD (PM2_supporting; https://gnomad.broadinstitute.org/, v2.1.1, 3.1.2, 4.0.0). This variant introduces a novel cysteine residue which may impede the normal formation of essential disulfide bridges and occurs at a conserved residue in a critical calcium-binding site within a calcium-binding EGF-like domain (PM1). Computational prediction tools and conservation analysis support that this variant is likely to impact the protein (PP3; REVEL = 0.900). 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: PS2, PS4, PM1, PP2, PP3, PP4, PM2_supporting.

Met criteria codes

PM2_Supporting	✔	absent from all versions of gnomAD
PS2	✔	1 de novo with confirmed mat/pat, phenotype non-specific/high genetic heterogeneity (0.5 ClinGen de novo points) + 3 de novo with assumed mat/pat, phenotype consistent but not highly specific (1.5 ClinGen de novo points) + 1 de novo with assumed mat/pat, phenotype non-specific/high genetic heterogeneity (0.25 ClinGen de novo points) = 2.25 total de novo points = PM6_strong or PS2
PS4	✔	12+ probands worth >4.0 PS4 points
PP2	✔	no benign evidence
PP3	✔	REVEL > 0.750
PP4	✔	Johns Hopkins internal proband meets revised Ghent criteria
PM1	✔	cysteine-creating variant in cbEGF32; also at a tyrosine in the consensus calcium-binding sequence

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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
PS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1		✖	PM2_supporting met
PP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6		✖	see PS2
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

Curation History

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