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.6254G>A (p.Cys2085Tyr)

Version: 1.0

CA392337017

547338 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: b718fa92-e734-41e4-a076-e12d27ce2739
Approved on: 2024/8/22
Published on: 2024/8/22

HGVS expressions

NM_000138.5(FBN1):c.6254G>A (p.Cys2085Tyr)
NM_000138.5:c.6254G>A
NC_000015.10:g.48437827C>T
CM000677.2:g.48437827C>T
NC_000015.9:g.48730024C>T
CM000677.1:g.48730024C>T
NC_000015.8:g.46517316C>T
NG_008805.2:g.212962G>A
ENST00000559133.6:c.6254G>A
ENST00000674301.2:c.6254G>A
ENST00000316623.10:c.6254G>A
ENST00000674301.1:c.1253G>A
ENST00000316623.9:c.6254G>A
ENST00000537463.6:c.*2017G>A
ENST00000559133.5:c.1561G>A
ENST00000560820.1:n.374G>A
NM_000138.4:c.6254G>A

Likely Pathogenic

Met criteria codes 7

PS4_Moderate PP2 PP3 PP4 PM1 PM5 PM2_Supporting

Not Met criteria codes 19

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

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.6254G>A is a missense variant in FBN1 predicted to cause a substitution of a cysteine by tyrosine at amino acid 2085 (p.Cys2085Tyr). This variant was found in a proband with a phenotype that satisfies the revised Ghent criteria for a clinical diagnosis of Marfan syndrome (MFS) (PP4; PMID: 25907466). It has been identified in another individual who meets clinical diagnostic criteria for MFS and one who does not meet diagnostic criteria but has thoracic aortic aneurysm (TAA) and a systemic score of 4 (PS4_moderate; PMID: 29768367; Bichat internal data). It has been reported 2 times in ClinVar as likely pathogenic (1) and of uncertain significance (1) (Variation ID: 547338). It is not present in gnomAD (PM2_supporting; https://gnomad.broadinstitute.org/). This variant alters a cysteine in a TGFβ binding-protein-like (TB) domain, in which cysteine residues are believed to form disulfide bridges important for proper protein folding (PM1). Computational prediction tools and conservation analysis suggest that this variant may impact the protein structure (PP3; REVEL = 0.886). A different variant at the same amino acid position (c.6253T>G:p.Cys2085Gly) has been identified in at least two individuals with TAA and ectopia lentis and is classified as pathogenic or likely pathogenic; this further supports the functional importance of this amino acid position (PM5; Invitae internal data). The constraint z-score for missense variants affecting FBN1 is 8.2 (PP2; gnomAD v4.1.0). In summary, this variant meets criteria to be classified as likely pathogenic for Marfan syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen FBN1 VCEP: PM1, PM5, PP2, PP3, PP4, PM2_supporting, PS4_supporting.

Met criteria codes

PS4_Moderate	✔	2 probands (excluding that used for PP4) worth 2.0 PS4 points
PP2	✔	no benign evidence
PP3	✔	REVEL = 0.886, > 0.750
PP4	✔	patient meets revised Ghent criteria
PM1	✔	cysteine-removing variant in TB6 domain
PM5	✔	c.6253T>G (p.Cys2085Gly): likely pathogenic at minimum - PM1 - PM2_supporting (absent all versions) - PP2 - PP3 (REVEL = 0.802) - PP4 (Invitae patient: MFS clinical dx with EL and TAA) - PS4_supporting (Invitae patient: tall stature, mild TAA, and EL)
PM2_Supporting	✔	absent from all versions of gnomAD

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
PS3	✖	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
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
BA1	ℹ	✖	PM2_supporting met
BS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	ℹ	✖	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
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
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

Curation History

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