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.7409G>T (p.Cys2470Phe)

Version: 1.0

CA392327764

1098776 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: dd443373-9fa6-4d1e-86c4-b882988ecab5
Approved on: 2024/8/22
Published on: 2024/8/22

HGVS expressions

NM_000138.5(FBN1):c.7409G>T (p.Cys2470Phe)
NM_000138.5:c.7409G>T
NC_000015.10:g.48425413C>A
CM000677.2:g.48425413C>A
NC_000015.9:g.48717610C>A
CM000677.1:g.48717610C>A
NC_000015.8:g.46504902C>A
NG_008805.2:g.225376G>T
ENST00000559133.6:c.*217G>T
ENST00000674301.2:c.*922G>T
ENST00000682170.1:n.1590G>T
ENST00000682767.1:n.706G>T
ENST00000316623.10:c.7409G>T
ENST00000674301.1:c.2575G>T
ENST00000316623.9:c.7409G>T
ENST00000559133.5:c.2778G>T
NM_000138.4:c.7409G>T

Likely Pathogenic

Met criteria codes 5

PP2 PP3 PP4 PM1_Strong PM2_Supporting

Not Met criteria codes 21

PP1 PM6 BA1 PM3 PM5 PM4 BS1 BS4 BS3 BS2 PS1 PS2 PS3 PS4 PVS1 BP5 BP7 BP4 BP3 BP1 BP2

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.7409G>T is a missense variant in FBN1 predicted to cause a substitution of a cysteine by phenylalanine at amino acid 2470 (p.Cys2470Phe). This variant was found in a proband with thoracic aortic aneurysm (TAA) and a systemic score ≥7 which is a specific phenotype that satisfies the revised Ghent criteria for a clinical diagnosis of Marfan syndrome (MFS) (PP4; PMID: 38374194). This variant has been reported 3 times in ClinVar as pathogenic (1) likely pathogenic (1), and of uncertain significance (1) (Variation ID: 1098776). It has been identified in a proband who does not meet diagnostic criteria for MFS but has TAA and several systemic features of MFS (Invitae internal data). This variant is not present in gnomAD (PM2_supporting; https://gnomad.broadinstitute.org/). 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 suggest that this variant may impact the protein (PP3; REVEL = 0.989). 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_strong, PP2, PP3, PP4, PM2_supporting.

Met criteria codes

PP2	✔	no benign evidence
PP3	✔	REVEL = 0.989, > 0.750 threshold
PP4	✔	patient in Abolhassani et al. meets revised Ghent criteria
PM1_Strong	✔	cysteine-removing variant in cbEGF38
PM2_Supporting	✔	absent from all versions of gnomAD

Not Met criteria codes

PP1	✖	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	✖	PM2_supporting met
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 met; several other P/LP variants at this position
PM4	✖	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
PS1		✖	n/a
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
PS4		✖	1 proband (excluding that used for PP4) worth 0.5 PS4 points
PVS1		✖	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

Curation History

Showing 1 to 1 of 1 rows

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