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.1379G>A (p.Cys460Tyr)

Version: 1.0

CA392343867

636640 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: ab15a40d-fa25-4505-b348-609d46c698a0
Approved on: 2023/11/16
Published on: 2023/11/16

HGVS expressions

NM_000138.5(FBN1):c.1379G>A (p.Cys460Tyr)
NM_000138.5:c.1379G>A
NC_000015.10:g.48515476C>T
CM000677.2:g.48515476C>T
NC_000015.9:g.48807673C>T
CM000677.1:g.48807673C>T
NC_000015.8:g.46594965C>T
NG_008805.2:g.135313G>A
ENST00000559133.6:c.1379G>A
ENST00000674301.2:c.1379G>A
ENST00000684448.1:n.53G>A
ENST00000316623.10:c.1379G>A
ENST00000316623.9:c.1379G>A
ENST00000537463.6:c.636+22235G>A
NM_000138.4:c.1379G>A

Likely Pathogenic

Met criteria codes 6

PM2_Supporting PS4_Supporting PM1 PM5 PP2 PP3

Not Met criteria codes 20

PVS1 BS2 BS1 BS4 BS3 BP4 BP3 BP1 BP2 BP5 BP7 PS1 PS2 PS3 BA1 PM3 PM4 PM6 PP1 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_00138 c.1379G>A is a missense variant in FBN1 predicted to cause a substitution of a cysteine by tyrosine at amino acid 460 (p.Cys460Tyr). This variant was found in a proband with bilateral ectopia lentis and mitral valve prolapse (PS4_supporting; PMID:

21932315). This variant has been reported twice in ClinVar as likely pathogenic and once as of uncertain significance (Variation ID: 636640). This variant is not present in gnomAD (PM2_supporting; https://gnomad.broadinstitute.org/). This variant affects a cysteine residue in a EGF domain; cysteine residues are believed to be involved in the formation of disulfide bridges which are essential for the protein structure (PM1). Other variants altering this codon are pathogenic or likely pathogenic (p.Cys460Ser, p.Cys460Trp), supporting the functional importance of this amino acid position (PM5). Computational prediction tools and conservation analysis suggest that this variant may impact the protein's structure or function (PP3). The constraint z-score for missense variants affecting FBN1 is 5.06 (PP2). 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, PS4_supporting, PM2_supporting, PP2, PP3.

Met criteria codes

PM2_Supporting	✔	absent from gnomAD
PS4_Supporting	✔	1 proband with 1.0 PS4 point
PM1	✔	Cysteine in EGF2 domain
PM5	✔	p.Cys460Ser and p.Cys460Trp are LP/P with FBN1 VCEP specifications
PP2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✔	REVEL = 0.928

Not Met criteria codes

PVS1	✖	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
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

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
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
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		✖	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		✖	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
PP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4		✖	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

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.