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.7016G>A (p.Cys2339Tyr)

Version: 1.0

CA392330332

495644 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: ecfd14b5-e2a8-4834-968a-2c45a7922949
Approved on: 2024/8/22
Published on: 2024/8/22

HGVS expressions

NM_000138.5(FBN1):c.7016G>A (p.Cys2339Tyr)
NM_000138.5:c.7016G>A
NC_000015.10:g.48427755C>T
CM000677.2:g.48427755C>T
NC_000015.9:g.48719952C>T
CM000677.1:g.48719952C>T
NC_000015.8:g.46507244C>T
NG_008805.2:g.223034G>A
ENST00000559133.6:c.7078G>A
ENST00000674301.2:c.*529G>A
ENST00000682170.1:n.1197G>A
ENST00000682767.1:n.313G>A
ENST00000316623.10:c.7016G>A
ENST00000674301.1:c.2182G>A
ENST00000316623.9:c.7016G>A
ENST00000559133.5:c.2385G>A
NM_000138.4:c.7016G>A

Likely Pathogenic

Met criteria codes 6

PM1 PM5 PP2 PP3 PM2_Supporting PS4_Supporting

Evidence Links 0

Expert Panel

FBN1 VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

FBN1 VCEP

NM_00138 c. 7016G>A is a missense variant in FBN1 predicted to cause a substitution of cysteine by tyrosine at amino acid 2339 (p.Cys2339Tyr). This variant has been identified in one individual with clinical features of Marfan syndrome (PS4_Sup). This variant has been reported 1 time in ClinVar as Likely pathogenic and 1 time as uncertain significance (VariationID:495644).This variant is not present in gnomAD (PM2_Sup; https://gnomad.broadinstitute.org/ v4.0.0). This variant affects a cysteine residue in a TB domain. Cysteine residues are believed to be involved in the formation of disulfide bridges which are essential for the protein structure (PM1). The constraint z-score

for missense variants affecting FBN1 is 8.18 (PP2; https://gnomad.broadinstitute.org/ v4.0.0). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (REVEL: 0.992, PP3). 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_Sup, PM2_Sup, PP2, PP3.

Met criteria codes

PM1	✔	Cys disrupting residue in a TB7 like domain
PM5	✔	Alternate variants : p.Cys2339Arg, p.Cys2339Gly, p.Cys2339Ser. p.Cys2339Ser: This variant is a likely pathogenic variant (PP3, PS4_Supp (https://doi.org/10.1093/ehjcr/ytac063), PP2, PM2_Supp, PM1_Moderate).
PP2	✔	No benign criteria. The constraint z-score for missense variants affecting FBN1 is 5.06.
PP3	✔	REVEL score: 0.973
PM2_Supporting	✔	Absent in gnomAD
PS4_Supporting	✔	One patient is reported with ocular features such as ectopia lentis, flat corneas and arachnodactyly (PMID 12203992)

Curation History

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