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.199T>C (p.Cys67Arg)

Version: 1.0

CA392448448

1380036 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 67aac31f-30fb-4206-b566-b2c546be866c
Approved on: 2023/12/21
Published on: 2023/12/21

HGVS expressions

NM_000138.5:c.199T>C
NM_000138.5(FBN1):c.199T>C (p.Cys67Arg)
NC_000015.10:g.48613058A>G
CM000677.2:g.48613058A>G
NC_000015.9:g.48905255A>G
CM000677.1:g.48905255A>G
NC_000015.8:g.46692547A>G
NG_008805.2:g.37731T>C
ENST00000559133.6:c.199T>C
ENST00000674301.2:c.199T>C
ENST00000316623.10:c.199T>C
ENST00000316623.9:c.199T>C
ENST00000537463.6:c.199T>C
NM_000138.4:c.199T>C

Likely Pathogenic

Met criteria codes 6

PM2_Supporting PP2 PP3 PP4 PM5 PS4_Moderate

Not Met criteria codes 1

PM1

Evidence Links 0

Expert Panel

FBN1 VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

FBN1 VCEP

The NM_00138 c.199T>C is a missense variant in FBN1 predicted to cause a substitution of a cysteine by arginine at amino acid 67 (p.Cys67Arg). This variant was found in a proband with thoracic aortic aneurysm and ectopia lentis which is a highly specific phenotype for Marfan syndrome (Internal data, PP4). This variant has been reported 1 in ClinVar as likely pathogenic and 1 time as uncertain significance (Variantion ID: 1380036). Three other probands with clinical features of Marfan syndrome carry the same variant (PMID 19839986, 33436942, 34281902, PS4_Mod). This variant is not present in gnomAD (PM2_sup; https://gnomad.broadinstitute.org/ v2.1.1). This variant affects a cysteine residue in the fibrillin unique N-terminal (FUN) domain. A different missense variant impacting the same residue,

p.Cys67Ser, has previously been established as likely pathogenic, and reported in individuals with clinical features of Marfan syndrome (PMID 27906200, internal data, PM5). Cysteine residues are believed to be involved in the formation of disulfide bridges which are essential for the protein structure. Computational prediction tools and conservation analysis suggest that this variant may impact the protein (REVEL: 0.883, 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: PS4_Mod, PM5, PM2_Sup, PP2, PP3, PP4

Met criteria codes

PM2_Supporting	✔	Absent in gnomAD
PP2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✔	REVEL score: 0.883 (threshold: >0.75)
PP4	✔	Internal proband with Marfan syndrome with ectopia lentis and thoracic aortic aneurysm
PM5	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4_Moderate	✔	2.5 Points

Not Met criteria codes

PM1	✖	Removal of a Cys in the Fibrillin unique N-terminal (FUN) domain

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.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.