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Variant: NM_000138.5(FBN1):c.6820T>C (p.Cys2274Arg)

Version: 1.0

CA353663

222610 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 67a42422-1e18-4754-b1ba-f80eabdff6a2
Approved on: 2024/8/22
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HGVS expressions

NM_000138.5:c.6820T>C
NM_000138.5(FBN1):c.6820T>C (p.Cys2274Arg)
NC_000015.10:g.48430722A>G
CM000677.2:g.48430722A>G
NC_000015.9:g.48722919A>G
CM000677.1:g.48722919A>G
NC_000015.8:g.46510211A>G
NG_008805.2:g.220067T>C
ENST00000559133.6:c.6820T>C
ENST00000674301.2:c.*271T>C
ENST00000682170.1:n.429T>C
ENST00000316623.10:c.6820T>C
ENST00000674301.1:c.1924T>C
ENST00000316623.9:c.6820T>C
ENST00000559133.5:c.2127T>C
ENST00000560720.1:n.107T>C
NM_000138.4:c.6820T>C

Likely Pathogenic

Met criteria codes 4

PM1_Strong PP2 PP3 PM2_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.6820T>C is a missense variant in FBN1 predicted to cause a substitution of cysteine by arginine at amino acid 2274 (p.Cys2274Arg). This variant is not reported in the literature. This variant has been reported twice in ClinVar as Likely pathogenic and once as uncertain significance (Variation ID: 222610). This variant is not present in gnomAD (PM2_Sup; https://gnomad.broadinstitute.org/ v4.0.0). This variant affects a cysteine residue in a calcium binding EGF domain. Cysteine residues are believed to be involved in the formation of disulfide bridges which are essential for the protein structure (PM1_strong). 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_Strong, PM2_Sup,PP2, PP3

Met criteria codes

PM1_Strong	✔	Cys- disrupting residue in cbEGF-like domain
PP2	✔	The constraint z-score for missense variants affecting FBN1 is 5.06.
PP3	✔	REVEL score: 0.992
PM2_Supporting	✔	Absent in gnomAD.

Curation History

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