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Variant: NM_000138.5(FBN1):c.2287T>C (p.Cys763Arg)

Version: 1.0

CA392335589

519758 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 0616f4a3-3be9-41aa-b430-8334a56e100c
Approved on: 2023/12/29
Published on: 2023/12/29

HGVS expressions

NM_000138.5(FBN1):c.2287T>C (p.Cys763Arg)
NM_000138.5:c.2287T>C
NC_000015.10:g.48497272A>G
CM000677.2:g.48497272A>G
NC_000015.9:g.48789469A>G
CM000677.1:g.48789469A>G
NC_000015.8:g.46576761A>G
NG_008805.2:g.153517T>C
ENST00000559133.6:c.2287T>C
ENST00000674301.2:c.2287T>C
ENST00000684448.1:n.961T>C
ENST00000316623.10:c.2287T>C
ENST00000316623.9:c.2287T>C
ENST00000537463.6:c.637-22622T>C
NM_000138.4:c.2287T>C

Likely Pathogenic

Met criteria codes 4

PM1_Strong PP2 PP3 PM2_Supporting

Not Met criteria codes 2

PM5 PS4

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.2287T>C is a missense variant in FBN1 predicted to cause a substitution of a cysteine by arginine at amino acid 763 (p.Cys763Arg). This variant has been reported 3 times in ClinVar, twice as likely pathogenic and once as uncertain significance (Variation ID: 519758). To our knowledge, this variant has not previously been reported in individuals affected with Marfan syndrome in the literature. This variant is not present in gnomAD (PM2_sup; https://gnomad.broadinstitute.org/ version 2.1.1). 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). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (REVEL: 0.979) (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_Strong, PM2_Sup, PP2, PP3

Met criteria codes

PM1_Strong	✔	Affects a cysteine residue in a calcium binding EGF domain
PP2	✔	z-score is 5.06
PP3	✔	REVEL=0.979 (>0.75 Threshold)
PM2_Supporting	✔	Absent in gnomAD v2.1.1.

Not Met criteria codes

PM5	✖	
PS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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