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Variant: NM_000138.5(FBN1):c.2287T>G (p.Cys763Gly)

Version: 1.0

CA392335588

549070 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: c6e31e31-fd57-4bb1-af09-e057b9a6ccda
Approved on: 2023/12/29
Published on: 2023/12/29

HGVS expressions

NM_000138.5:c.2287T>G
NM_000138.5(FBN1):c.2287T>G (p.Cys763Gly)
NC_000015.10:g.48497272A>C
CM000677.2:g.48497272A>C
NC_000015.9:g.48789469A>C
CM000677.1:g.48789469A>C
NC_000015.8:g.46576761A>C
NG_008805.2:g.153517T>G
ENST00000559133.6:c.2287T>G
ENST00000674301.2:c.2287T>G
ENST00000684448.1:n.961T>G
ENST00000316623.10:c.2287T>G
ENST00000316623.9:c.2287T>G
ENST00000537463.6:c.637-22622T>G
NM_000138.4:c.2287T>G

Pathogenic

Met criteria codes 7

PM6 PM1_Strong PP2 PP3 PP4 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

The NM_00138 c.2287T>G is a missense variant in FBN1 predicted to cause a substitution of a cysteine by glycine at amino acid 763 (p.Cys763Gly). This variant was found in two probands with a clinical diagnosis of Marfan syndrome (internal data, PP4, PS4_Supporting). In one of these probands the variant was found de novo with assumed paternity and maternity (PM6). This variant has been reported 3 times in ClinVar, once as pathogenic, once as likely pathogenic and once as uncertain significance (Variation ID: 549070). 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: 0.98) (PP3). The constraint z-score for missense variants affecting FBN1 is 5.06 (PP2). In summary, this variant meets criteria to be classified as pathogenic for Marfan syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen FBN1 VCEP: PM1_Strong, PM6, PS4_Supporting, PM2_Sup, PP2, PP3, PP4.

Met criteria codes

PM6	✔	1 individual with highly specific phenotype, without parental confirmation
PM1_Strong	✔	Affects a cysteine residue in a calcium binding EGF domain
PP2	✔	z-score is 5.06
PP3	✔	REVEL=0.98 (>0.75 Threshold)
PP4	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2_Supporting	✔	Absent in gnomAD
PS4_Supporting	✔	1 individual with ectopia lentis and thoracic aortic aneurysm

Curation History

Showing 1 to 1 of 1 rows

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