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Variant: NM_000138.5(FBN1):c.3290G>A (p.Cys1097Tyr)

Version: 1.0

CA392327231

549150 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 84fff3f2-562a-42df-95a6-8a4ba7e43b29
Approved on: 2023/12/29
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HGVS expressions

NM_000138.5(FBN1):c.3290G>A (p.Cys1097Tyr)
NM_000138.5:c.3290G>A
NC_000015.10:g.48488160C>T
CM000677.2:g.48488160C>T
NC_000015.9:g.48780357C>T
CM000677.1:g.48780357C>T
NC_000015.8:g.46567649C>T
NG_008805.2:g.162629G>A
ENST00000559133.6:c.3290G>A
ENST00000674301.2:c.3290G>A
ENST00000684448.1:n.1964G>A
ENST00000316623.10:c.3290G>A
ENST00000316623.9:c.3290G>A
ENST00000537463.6:c.637-13510G>A
NM_000138.4:c.3290G>A

Pathogenic

Met criteria codes 7

PM1_Strong | PS4_Moderate | PP2 | PP3 | PP4 | PM6 | PM2_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.3290G>A, is a missense variant in FBN1 predicted to cause a substitution of a cysteine by tyrosine at amino acid 1097 (p.Cys1097Tyr). This variant was found in a proband with a neonatal onset of Marfan syndrome (internal data, PP4). This variant has been reported four times in ClinVar: once as pathogenic, twice as likely pathogenic, and once as uncertain significance (Variation ID: 549150). This variant has been reported in the literature in individuals with clinical diagnosis of Marfan syndrome and/or features of Marfan syndrome (PMID 37684520, 29357934, Invitae ClinVar entry, internal data; PS4_Mod), and was observed de novo without parental confirmation in one individual with a highly specific phenotype (PMID 37684520; PM6). This variant is not present in gnomAD (PM2_sup; https://gnomad.broadinstitute.org/ v2.1.1). 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 pathogenic for Marfan syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen FBN1 VCEP: PM1_Strong, PS4_moderate, PM6, PM2_Sup, PP2, PP3, PP4.

Met criteria codes

PM1_Strong	✔	Removal of a Cys residue in calcium binding EGF-like domain
PS4_Moderate	✔	Total points: 3
PP2	✔	z-score is 5.06
PP3	✔	REVEL: 0.979
PP4	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✔	Identified in 1 deceased indv with neonate onset of MFS; de novo (no parental confirmation mentioned). Features include: aortic dilation, severe MVP, long extremities, thin stature, arachnodactyly, and other typical skeletal features. EL, early myopia, pulmonary bullae, and spontaneous pneumothorax. Phenotype highly specifc for gene, unconfirmed parental relationships: 1 pt
PM2_Supporting	✔	Absent in gnomAD

Curation History

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