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Variant: NM_000138.5(FBN1):c.4330T>A (p.Cys1444Ser)

Version: 1.0

CA353655

222604 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3ae64fc8-99d1-4681-b0cf-6ece56643d71
Approved on: 2023/12/29
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HGVS expressions

NM_000138.5(FBN1):c.4330T>A (p.Cys1444Ser)
NM_000138.5:c.4330T>A
NC_000015.10:g.48472557A>T
CM000677.2:g.48472557A>T
NC_000015.9:g.48764754A>T
CM000677.1:g.48764754A>T
NC_000015.8:g.46552046A>T
NG_008805.2:g.178232T>A
ENST00000559133.6:c.4330T>A
ENST00000674301.2:c.4330T>A
ENST00000683268.1:n.297T>A
ENST00000684448.1:n.3004T>A
ENST00000316623.10:c.4330T>A
ENST00000316623.9:c.4330T>A
ENST00000537463.6:c.*93T>A
NM_000138.4:c.4330T>A

Pathogenic

Met criteria codes 6

PM2_Supporting PS4_Moderate PP2 PP3 PP4 PM1_Strong

Not Met criteria codes 20

PVS1 BS2 BS1 BS4 BS3 BP4 BP3 BP1 BP2 BP5 BP7 PS1 PS2 PS3 BA1 PM3 PM5 PM4 PM6 PP1

Evidence Links 0

Expert Panel

FBN1 VCEP

Criteria Specification Information

Criteria Specification: *ClinGen FBN1 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1*
PDF
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

FBN1 VCEP

NM_000138.5 c.4330T>A is a missense variant in FBN1 predicted to cause a substitution of a cysteine by serine at amino acid 1444 (p.Cys1444Ser). This variant has been identified in an adult patient with Marfan syndrome with bilateral ectopia lentis (EL), borderline thoracic aortic aneurysm and dissection (TAAD), and systemic features (PP4; Invitae internal data). A different nucleotide substitution (c.4331G>C) resulting in the same amino acid change has been identified in three individuals with clinical diagnoses of Marfan syndrome, all of whom were noted to have have EL in addition to other features of Marfan syndrome (PS4_moderate; University of Tokyo, Bichat, & Invitae internal data); in one family, c.4331G>C was found to segregate with annuloaortic ectasia and arachnodactyly in an infant child (University of Tokyo internal data). Of note, there is no predicted difference in splicing patterns between the two nucleotide substitutions. The c.4330T>A variant is absent from gnomAD (PM2_supporting; https://gnomad.broadinstitute.org, v2.1.1 & v3.1.2). It affects a cysteine residue in a calcium-binding EGF-like domain; cysteine residues are involved in the formation of disulfide bridges which are essential for the protein structure (PM1_strong). Computational prediction tools and conservation analysis further support that this variant is likely to impact the protein (PP3; REVEL = 0.949). The constraint z-score for missense variants affecting FBN1 is 5.06 (PP2). In summary, c.4330T>A (p.Cys1444Ser) 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, PP2, PP3, PP4, PM2_supporting.

Met criteria codes

PM2_Supporting	✔	absent from gnomAD
PS4_Moderate	✔	2 (University of Tokyo and Invitae) probands worth 2.0 PS4 points
PP2	✔	no benign criteria
PP3	✔	REVEL = 0.949; > 0.750 threshold
PP4	✔	Invitae proband with MFS
PM1_Strong	✔	Cysteine-removing variant in cbEGF20

Not Met criteria codes

PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	PM2_supporting met
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP4		✖	PP3 met
BP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1		✖	VCEP decided to include c.4331G>C (p.Cys1444Ser) as equivalent for purposes of curation; no predicted differences in splicing between the two nucleotide substitutions
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1		✖	PM2_supporting met
PM3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5		✖	p.Cys1444Phe, p.Cys1444Trp, p.Cys1444Tyr all P/LP; PM5 N/A because PM1_strong is applied
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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