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Variant: NM_000138.5(FBN1):c.3707G>A (p.Cys1236Tyr)

Version: 1.0

CA392324303

495599 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 5ec31f85-0600-444a-80bc-517d8d4448fa
Approved on: 2023/12/29
Published on: 2023/12/29

HGVS expressions

NM_000138.5(FBN1):c.3707G>A (p.Cys1236Tyr)
NM_000138.5:c.3707G>A
NC_000015.10:g.48485379C>T
CM000677.2:g.48485379C>T
NC_000015.9:g.48777576C>T
CM000677.1:g.48777576C>T
NC_000015.8:g.46564868C>T
NG_008805.2:g.165410G>A
ENST00000559133.6:c.3707G>A
ENST00000674301.2:c.3707G>A
ENST00000684448.1:n.2381G>A
ENST00000316623.10:c.3707G>A
ENST00000316623.9:c.3707G>A
ENST00000537463.6:c.637-10729G>A
NM_000138.4:c.3707G>A

Pathogenic

Met criteria codes 6

PS4_Moderate PM1_Strong PM2_Supporting PP2 PP3 PP4

Not Met criteria codes 20

PM3 PM5 PM4 PM6 BA1 BS1 BS4 BS3 BS2 BP5 BP7 BP4 BP3 BP1 BP2 PS1 PS2 PS3 PVS1 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.3707G>A is a missense variant in FBN1 predicted to cause a substitution of a cysteine by tyrosine at amino acid 1236 (p.Cys1236Tyr). This variant has been identified in at least three individuals including two probands with clinical diagnoses of Marfan

syndrome, with neonatal onset in one case, and one proband with a highly specific Marfan syndrome phenotype including thoracic aortic aneurysm and dissection (TAAD), ectopia lentis, and systemic features of Marfan syndrome (PS4_moderate, PP4; UZG, Mayo, & Bichat internal data). It is not present in gnomAD (PM2_supporting; https://gnomad.broadinstitute.org/ v2.1.1 & v3.1.2). This variant 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 support that this variant is likely to impact the protein (PP3; REVEL = 0.960). 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, PP2, PP3, PP4, PM2_supporting.

Met criteria codes

PS4_Moderate	✔	2 probands worth 2.0 PS4 points
PM1_Strong	✔	Cysteine-removing variant in cbEGF15
PM2_Supporting	✔	absent from gnomAD
PP2	✔	no benign criteria
PP3	✔	REVEL = 0.960; > 0.750
PP4	✔	Internal proband (Bichat) meeting revised Ghent criteria

Not Met criteria codes

PM3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	p.Cys1236Arg is LP/P; 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
BA1	✖	PM2_supporting met
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
BS2		✖	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
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
PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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
PVS1		✖	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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