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Variant: NM_000138.5(FBN1):c.1556A>G (p.Tyr519Cys)

Version: 1.0

CA392342185

549024 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 70862165-bdcf-4d1f-ae67-bae146408176
Approved on: 2023/11/16
Published on: 2023/11/16

HGVS expressions

NM_000138.5(FBN1):c.1556A>G (p.Tyr519Cys)
NM_000138.5:c.1556A>G
NC_000015.10:g.48513581T>C
CM000677.2:g.48513581T>C
NC_000015.9:g.48805778T>C
CM000677.1:g.48805778T>C
NC_000015.8:g.46593070T>C
NG_008805.2:g.137208A>G
ENST00000559133.6:c.1556A>G
ENST00000674301.2:c.1556A>G
ENST00000684448.1:n.230A>G
ENST00000316623.10:c.1556A>G
ENST00000316623.9:c.1556A>G
ENST00000537463.6:c.636+24130A>G
NM_000138.4:c.1556A>G

Pathogenic

Met criteria codes 7

PS4 PP1 PP2 PP3 PM1 PM2_Supporting PS2_Supporting

Not Met criteria codes 17

PS1 PS3 PP4 PM3 PM5 PM4 PM6 BA1 BS2 PVS1 BS1 BS3 BP4 BP3 BP2 BP5 BP7

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

The NM_00138 c.1556A>G, is a missense variant in FBN1 predicted to cause a substitution of a tyrosine by cysteine at amino acid 519 (p.Tyr519Cys). This variant was found in at least 7 probands with features consistent with or suggestive of Marfan syndrome including the

following: one proband who met the original Ghent criteria with cardiovascular, skeletal, and skin involvement; one proband with bilateral ectopia lentis (EL) and systemic features; one proband with thoracic aortic aneurysm and dissection (TAAD); one proband with EL and systemic features; one proband with isolated EL; one proband with TAAD and systemic features; and once as de novo with confirmed maternity/paternity with bilateral EL, TAAD, and systemic features, a phenotype highly specific for Marfan syndrome (PS2_supporting, PS4; PMID: 15241795; University of Tokyo, UZG, Invitae, & Ambry internal data; ClinVar Variation ID: 5490254). The variant also segregates with features of Marfan syndrome in at least two affected family members (PP1; Invitae internal data). It is not present in gnomAD (PM2_supporting; https://gnomad.broadinstitute.org/). This variant introduces a novel cysteine residue which may impede the normal formation of critical disulfide bridges (PM1). Computational prediction tools and conservation analysis suggest that this variant may impact the protein's structure or function (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: PS4, PM1, PS2_supporting, PM2_supporting, PP1, PP2, PP3.

Met criteria codes

PS4	✔	5 probands worth 4.5 PS4 points
PP1	✔	at least 2 segregations with features of MFS
PP2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✔	REVEL = 0.933
PM1	✔	Cysteine-creating variant
PM2_Supporting	✔	absent from gnomAD
PS2_Supporting	✔	confirmed de novo (Invitae), phenotype is not considered highly specific to FBN1

Not Met criteria codes

PS1	✖	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
PP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	

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

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	✖	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
PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	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	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3	✖	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

Curation History

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