

Variant: *NM_000138.5(FBN1):c.1390C>T (p.Arg464Cys)*

Version: 1.0

CA269559072 [↗](#)

549013 (ClinVar) [↗](#)

Gene: FBN1 ([HGNC:2200](#))

Condition: Marfan syndrome ([MONDO:0007947](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 9177e5b4-a609-4c71-9fd1-aac0638b9f22

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HGVS expressions

NM_000138.5:c.1390C>T

NM_000138.5(FBN1):c.1390C>T (p.Arg464Cys)

NC_000015.10:g.48515465G>A

CM000677.2:g.48515465G>A

NC_000015.9:g.48807662G>A

CM000677.1:g.48807662G>A

NC_000015.8:g.46594954G>A

NG_008805.2:g.135324C>T

ENST00000559133.6:c.1390C>T

ENST00000674301.2:c.1390C>T

ENST00000684448.1:n.64C>T

ENST00000316623.10:c.1390C>T

ENST00000316623.9:c.1390C>T

ENST00000537463.6:c.636+22246C>T

NM_000138.4:c.1390C>T

Likely Pathogenic

Met criteria codes 5

PM1 PS4_Supporting PP1 PP2
PP4

Not Met criteria codes 21

PM3 PM5 PM4 PM6 PM2
BA1 BS1 BS4 BS3 BS2 BP5
BP7 BP4 BP3 BP1 BP2 PS1
PS2 PS3 PVS1 PP3

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(FBN1):c.1390C>T (p.Arg464Cys) NM_00138 c.1390C>T is a missense variant in FBN1 predicted to cause a substitution of an arginine by cysteine at amino acid 464 (p.Arg464Cys). This variant has been found in two probands including one with bilateral ectopia

lentis (EL) and thoracic aortic aneurysm and dissection (TAAD), and one with isolated EL (PP4, PS4_supporting; Invitae & UZG internal data, ClinVar Variation ID: 549013). The variant segregates with features of Marfan syndrome in at least two affected family members (PP1; Invitae internal data). This variant is present in gnomAD v2.1.1 (1/34578 [0.003%] Latino/Admixed American alleles; <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 are unclear about the predicted impact of this variant on 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 likely pathogenic for Marfan syndrome based o the ACMG/AMP criteria applied, as specified by the ClinGen FBN1 VCEP: PM1, PS4_supporting, PP1, PP2, PP4.

Met criteria codes

PM1			Cysteine-creating variant
PS4_Supporting			1 proband worth 1.0 PS4 point
PP1			2 segregations
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			UZG proband with isolated ectopia lentis

Not Met criteria codes

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
PM2			highest MAF: 1/34578 alleles (0.003%) in gnomAD v2.1.1
BA1			highest MAF: 1/34578 alleles (0.003%) in gnomAD v2.1.1
BS1			highest MAF: 1/34578 alleles (0.003%) in gnomAD v2.1.1
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			REVEL= 0.642
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
PP3			REVEL= 0.642

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