

Variant: *NM_000138.5(FBN1):c.2669G>A (p.Cys890Tyr)*

Version: 1.0

CA392331935 [↗](#)

431935 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 797259f6-a65f-4f86-b079-056f10bb550d

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HGVS expressions

NM_000138.5(FBN1):c.2669G>A (p.Cys890Tyr)

NM_000138.5:c.2669G>A

NC_000015.10:g.48495131C>T

CM000677.2:g.48495131C>T

NC_000015.9:g.48787328C>T

CM000677.1:g.48787328C>T

NC_000015.8:g.46574620C>T

NG_008805.2:g.155658G>A

ENST00000559133.6:c.2669G>A

ENST00000674301.2:c.2669G>A

ENST00000684448.1:n.1343G>A

ENST00000316623.10:c.2669G>A

ENST00000316623.9:c.2669G>A

ENST00000537463.6:c.637-20481G>A

NM_000138.4:c.2669G>A

Likely Pathogenic

Met criteria codes 7

PP2 PP3 PP4 PM1 PM5 PM6
PM2_Supporting

Not Met criteria codes 19

BP5 BP7 BP4 BP3 BP1 BP2
PS1 PS2 PS3 PS4 PP1 PM3
PM4 BA1 PVS1 BS1 BS4
BS3 BS2

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_000138 c.2669G>A variant is a missense variant in FBN1 predicted to cause a substitution of cysteine by tyrosine at amino acid position 890. This variant has not been reported in the literature but was identified at one institution as de novo in proband with ectopia

lentis and a systemic score of 2 (PP4, PM6; UZG). This variant has also been reported four times in ClinVar, with two classifications of likely pathogenic and two classifications of pathogenic (Variation ID: 431935). It is not present in gnomAD v2.1.1 or 3.1.2 (PM2_supporting; <https://gnomad.broadinstitute.org/>). This variant affects a cysteine residue in the hybrid 2 domain; cysteine residues in the hybrid domains are believed to be important for proper protein folding (PM1). Computational prediction tools and conservation analysis support that this variant may impact the protein (PP3; REVEL = 0.926). The constraint z-score for missense variants affecting FBN1 is 5.06 (PP2). Three other missense variants at the same amino acid position (p.Cys890Arg, p.Cys890Gly, p.Cys890Trp) have been identified and are classified as likely pathogenic (PM5; PMIDs: 12938084, 16222657, 20564469). In summary, this variant meets criteria to be classified as likely pathogenic for Marfan syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen FBN1 VCEP: PM1, PM5, PM6, PM2_supporting, PP2, PP3, PP4.

Met criteria codes

PP2			missense variant, no benign criteria asserted
PP3			REVEL = 0.926
PP4			6yo proband with EL + SS =2 (facial features, pectus excavatum), no TAAD; VCEP determined that based on the specificity of ectopia lentis to FBN1 and the proband's young age, PP4 would be applied
PM1			Cys in Hyb2 domain
PM5			p.Cys890Arg, p.Cys890Gly, and p.Cys890Trp all likely pathogenic per VCEP specifications
PM6			6yo proband with EL + SS =2 (facial features, pectus excavatum), no TAAD; VCEP determined that based on the specificity of ectopia lentis to FBN1, in addition to some systemic features, and the proband's young age, PM6 would be applied
PM2_Supporting			absent from gnomAD v2.1.1 and v3.1.2

Not Met criteria codes

BP5			no evidence
BP7			n/a
BP4			PP3 met
BP3			n/a for FBN1
BP1			n/a for FBN1
BP2			n/a for FBN1

PS1			no evidence
PS2			no evidence
PS3			no evidence
PS4			no evidence
PP1			no evidence
PM3			n/a for FBN1
PM4			n/a
BA1			PM2_supporting met
PVS1			n/a
BS1			PM2_supporting met
BS4			no evidence
BS3			no evidence
BS2			no evidence

Curation History 		
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