

Variant: *NM_000138.4(FBN1):c.629G>A (p.Cys210Tyr)*

Version: 1.0

CA392446003 [↗](#)

426140 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 77b48e1f-cb71-4c80-a685-6379cde2503d

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HGVS expressions

NM_000138.4(FBN1):c.629G>A (p.Cys210Tyr)

NM_000138.4:c.629G>A

NC_000015.10:g.48537718C>T

CM000677.2:g.48537718C>T

NC_000015.9:g.48829915C>T

CM000677.1:g.48829915C>T

NC_000015.8:g.46617207C>T

NG_008805.2:g.113071G>A

ENST00000559133.6:c.629G>A

ENST00000674301.2:c.629G>A

ENST00000316623.10:c.629G>A

ENST00000316623.9:c.629G>A

ENST00000537463.6:c.629G>A

NM_000138.5:c.629G>A

Likely Pathogenic

Met criteria codes 5

PS4_Moderate PP2 PP3 PM2
PM1

Not Met criteria codes 13

BS1 BS4 BS3 BP5 BP4 BP2
PS2 PS3 BA1 PP1 PP4
PM6 PM5

Evidence Links 0

Expert Panel

FBN1 VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

FBN1 VCEP

The NM_00138 c.629G>A, is a missense variant in FBN1 predicted to cause a substitution of a cysteine by tyrosine at amino acid 210 (p.Cys210Tyr). This variant was reported in an individual diagnosed with Marfan syndrome (PMID 33711475), and in an individual with ectopia lentis, pectus carinatum, foot deformity, dural ectasia, and protrusio acetabuli (PMID 31825148) (PS4_Mod). This variant was also found in a 7-year-old male proband with lens luxation, big stature, but a normal cardiac ultrasound, and was inherited from his healthy

father, however ophthalmology exams are pending (Internal data). This variant is not present in gnomAD (PM2_sup; <https://gnomad.broadinstitute.org/>). The variant in FBN1 has been reported twice in ClinVar as likely pathogenic (Variation ID: 426140). This variant affects a cysteine residue is in the 1st Hybrid domain of protein (PM1). Computational prediction tools and conservation analysis suggest that this variant may impact the protein structure (REVEL: 0.94) (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 on the ACMG/AMP criteria applied, as specified by the ClinGen FBN1 VCEP: PM1, PS4_Moderate, PM2_Supportive, PP2, PP3

Met criteria codes

PS4_Moderate			Reported in 2 individuals with MFS, and in one individual with features of MFS= 2.5 pts
PP2			Based on the SVI WG recommendation concerning constraint scores: if missense constraint z scores are > 3.09 in ExAC, this criterion may be used. For FBN1, the constraint score is higher than 5. Hence, PP2 is applicable as described.
PP3			REVEL score 0.94; >0.75 threshold
PM2			Absent in the Genome Aggregation Database (gnomAD).
PM1			Located in a mutational hot spot and/or critical and well-established functional domain (e.g. active site of an enzyme) without benign variation: Cys in the 1st Hybid domain.

Not Met criteria codes

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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
BP5			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
BP2			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
BA1			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
PP4			No clinical information available.
PM6			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

Curation History 		
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