

Variant: *NM_000138.5(FBN1):c.2624G>A (p.Cys875Tyr)*

Version: 1.0

CA10587846 [↗](#)

264089 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 818ffe7b-d6f4-4191-a8e8-0061ef38117c

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HGVS expressions

NM_000138.5:c.2624G>A

NM_000138.5(FBN1):c.2624G>A (p.Cys875Tyr)

NC_000015.10:g.48495176C>T

CM000677.2:g.48495176C>T

NC_000015.9:g.48787373C>T

CM000677.1:g.48787373C>T

NC_000015.8:g.46574665C>T

NG_008805.2:g.155613G>A

ENST00000559133.6:c.2624G>A

ENST00000674301.2:c.2624G>A

ENST00000684448.1:n.1298G>A

ENST00000316623.10:c.2624G>A

ENST00000316623.9:c.2624G>A

ENST00000537463.6:c.637-20526G>A

NM_000138.4:c.2624G>A

Likely Pathogenic

Met criteria codes **5**

PM2_Supporting

PP2

PP3

PM1

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.2624G>A is a missense variant in FBN1 predicted to cause a substitution of a cysteine by tyrosine at amino acid 875 (p.Cys875Tyr). This variant has been reported three times in ClinVar: twice as likely pathogenic and once as uncertain significance (Variation ID: 264089). A different missense variant impacting the same residue, p.Cys875Arg has been previously reported in individuals with clinical features of Marfan syndrome and found to segregate with disease in multiple affected relatives from one family (PMID 19293843, 28973303, internal data; PM5). This variant is not present in gnomAD (PM2_sup; <https://gnomad.broadinstitute.org/> v2.1.1). This variant affects a cysteine residue in a hybrid domain. Cysteine residues are believed to be involved in the formation of disulfide bridges which are essential for the protein structure (PM1). Computational prediction tools and conservation analysis suggest that this

variant may impact the protein (REVEL: 0.986, 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, PM5, PM2_Sup, PP2, PP3.

Met criteria codes

PM2_Supporting			Absent in gnomAD v2.1.1
PP2			z-score is 5.06
PP3			REVEL 0.986
PM1			Impacting a Cys residue in a hybrid domain
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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