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Variant: NM_000138.5(FBN1):c.2660G>A (p.Cys887Tyr)

Version: 1.0

CA392332017

915814 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: a3ae3431-d3c3-44cf-b1ea-6d1787d7e255
Approved on: 2023/12/29
Published on: 2023/12/29

HGVS expressions

NM_000138.5(FBN1):c.2660G>A (p.Cys887Tyr)
NM_000138.5:c.2660G>A
NC_000015.10:g.48495140C>T
CM000677.2:g.48495140C>T
NC_000015.9:g.48787337C>T
CM000677.1:g.48787337C>T
NC_000015.8:g.46574629C>T
NG_008805.2:g.155649G>A
ENST00000559133.6:c.2660G>A
ENST00000674301.2:c.2660G>A
ENST00000684448.1:n.1334G>A
ENST00000316623.10:c.2660G>A
ENST00000316623.9:c.2660G>A
ENST00000537463.6:c.637-20490G>A
NM_000138.4:c.2660G>A

Likely Pathogenic

Met criteria codes 6

PM1 PM5 PP2 PP3 PP4 PM2_Supporting

Not Met criteria codes 1

PS4

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.2660G>A, is a missense variant in FBN1 predicted to cause a substitution of a cysteine by tyrosine at amino acid 887 (p.Cys887Tyr). This variant was found in a proband with a clinical diagnosis of Marfan syndrome (PMID 23684891) (PP4). This variant has been reported three times in ClinVar: twice as pathogenic and once as uncertain significance (Variation ID: 915814). This variant has been reported in the literature in an individual with a suspected diagnosis of Marfan syndrome (PMID 29907982). This variant is not present in gnomAD (PM2_sup; https://gnomad.broadinstitute.org/ v2.1.1). Other missense variants affecting the same residue, including p.Cys887Tyr

and p.Cys887Arg have been previously reported in individuals with clinical features of Marfan syndrome (PMID 27906200, 34281902, internal data; PM5). 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: 0.926, 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, PP4.

Met criteria codes

PM1	✔	Removes a Cys residue in a hybrid domain
PM5	✔	p.Cys887Ser- Internal data- identified in two families with variable features of Marfan syndrome. Found to segregate with disease in multiple affected relatives. PMID 27906200- (UMD database)- Identified in a proband with features of MFS Invitae ClinVar entry- at least 1 individual with features of MFS Absent in gnomAD, REVEL Score: 0.903
PP2	✔	z-score is 5.06
PP3	✔	REVEL score: 0.926 (0.75 Threshold)
PP4	✔	PMID: 23684891- Proband with clinical diagnosis of MFS
PM2_Supporting	✔	Absent in gnomAD v2.1.1

Not Met criteria codes

PS4	✖	0.5 points

Curation History

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