

Variant: NM_000138.5(FBN1):c.7775G>T (p.Cys2592Phe)

Version: 1.0

CA16619939 [↗](#)

423498 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: ce4dbad8-1bb8-4127-83c0-e1d61fd66e08

Approved on: 2024/8/22

Published on: 2024/8/22

HGVS expressions

NM_000138.5:c.7775G>T

NM_000138.5(FBN1):c.7775G>T (p.Cys2592Phe)

NC_000015.10:g.48420731C>A

CM000677.2:g.48420731C>A

NC_000015.9:g.48712928C>A

CM000677.1:g.48712928C>A

NC_000015.8:g.46500220C>A

NG_008805.2:g.230058G>T

ENST00000559133.6:c.*583G>T

ENST00000674301.2:c.*1288G>T

ENST00000682170.1:n.1956G>T

ENST00000682767.1:n.1072G>T

ENST00000316623.10:c.7775G>T

ENST00000674301.1:c.2941G>T

ENST00000316623.9:c.7775G>T

ENST00000559133.5:c.3144G>T

NM_000138.4:c.7775G>T

Pathogenic

Met criteria codes **6**

PM6_Supporting

PM1_Strong

PP2

PP3

PS4_Moderate

PM2_Supporting

Not Met criteria codes **2**

PP1

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.7775G>T, is a missense variant in FBN1 predicted to cause a substitution of a cysteine by phenylalanine at amino acid 2592 (p.Cys2592Phe). This variant has been reported three times in ClinVar: once as pathogenic, once as likely pathogenic, and once as

uncertain significance (Variation ID: 423498). This variant is not present in gnomAD (PM2_sup; <https://gnomad.broadinstitute.org/ v2.1.1>). This variant has been identified in an individual with ectopia lentis and a systemic score >7 and was reported to be de novo without confirmation of parental relationships (internal lab data, PM6_Sup). At least two additional individuals with clinical features of Marfan syndrome carry this variant (internal lab data, Invitae ClinVar, PS4_Mod). In one individual with thoracic aortic aneurysm and skeletal features, the variant was found to segregate in an affected sister (Internal lab data). This variant affects a cysteine residue in a calcium binding EGF-like domain. Cysteine residues in these domains are believed to be involved in the formation of disulfide bridges which are essential for the protein structure (PM1_strong). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (REVEL: 0.839, PP3). The constraint z-score for missense variants affecting FBN1 is 8.18 (PP2; <https://gnomad.broadinstitute.org/ v4.0.0>). In summary, this variant meets criteria to be classified as pathogenic for Marfan syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen FBN1 VCEP: PM1_Strong, PS4_Moderate, PM2_Sup, PM6_Sup, PP2, PP3.

Met criteria codes

PM6_Supporting			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1_Strong			Cys-disrupting variant in cbEGF-like domain
PP2			Missense variant
PP3			REVEL score: 0.839
PS4_Moderate			2 points
PM2_Supporting			Absent in gnomAD

Not Met criteria codes

PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			N/A- PM1_Strong met Other variants at this residue resported in patients with MFS/ MFS-related features: p.Cys2592Ser- PMID 16222657, 31227806 Absent in GnomAD p.Cys2592Tyr- P/LP by multiple labs Absent in gnomAD

Curation History 

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Showing 1 to 1 of 1 rows

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