

Variant: *NM_000138.5(FBN1):c.5747G>A (p.Cys1916Tyr)*

Version: 1.0

CA016026 [↗](#)

42391 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: c5663969-cd67-40de-80f4-b96e8399345c

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HGVS expressions

NM_000138.5:c.5747G>A

NM_000138.5(FBN1):c.5747G>A (p.Cys1916Tyr)

NC_000015.10:g.48446747C>T

CM000677.2:g.48446747C>T

NC_000015.9:g.48738944C>T

CM000677.1:g.48738944C>T

NC_000015.8:g.46526236C>T

NG_008805.2:g.204042G>A

ENST00000559133.6:c.5747G>A

ENST00000674301.2:c.5747G>A

ENST00000684448.1:n.4421G>A

ENST00000316623.10:c.5747G>A

ENST00000674301.1:c.746G>A

ENST00000316623.9:c.5747G>A

ENST00000537463.6:c.*1510G>A

ENST00000559133.5:c.1054G>A

NM_000138.4:c.5747G>A

Likely Pathogenic

Met criteria codes 4

PM1_Strong

PM2_Supporting

PP2

PP3

Not Met criteria codes 1

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.5747G>A, is a missense variant in FBN1 predicted to cause a substitution of a cysteine by tyrosine at amino acid 1916 (p.Cys1916Tyr). This variant was found in a proband diagnosed with Marfan syndrome (PMID 24793577, PP4). This variant has been reported three times in ClinVar: once as pathogenic, once as likely pathogenic, and once as uncertain significance (Variation ID: 42391).

This variant is not present in gnomAD(PM2_sup; <https://gnomad.broadinstitute.org/ v2.1.1>). This variant affects a cysteine residue in a calcium binding EGF domain. Cysteine residues 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: 0.967, 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_Strong, PM2_Sup, PP2, PP3, PP4.

Met criteria codes

PM1_Strong			Cys-disrupting residue in cbEGF-like domain
PM2_Supporting			Absent in gnomAD
PP2			The constraint z-score for missense variants affecting FBN1 is 5.06
PP3			REVEL: 0.967

Not Met criteria codes

PM5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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Curation History

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