

Variant: *NM_000138.5(FBN1):c.3554G>A (p.Gly1185Asp)*

Version: 1.0

CA392324992 [↗](#)

549173 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: a105dcc4-2e3f-4c8c-9afc-9b908c27ed46

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HGVS expressions

NM_000138.5:c.3554G>A

NM_000138.5(FBN1):c.3554G>A (p.Gly1185Asp)

NC_000015.10:g.48487110C>T

CM000677.2:g.48487110C>T

NC_000015.9:g.48779307C>T

CM000677.1:g.48779307C>T

NC_000015.8:g.46566599C>T

NG_008805.2:g.163679G>A

ENST00000559133.6:c.3554G>A

ENST00000674301.2:c.3554G>A

ENST00000684448.1:n.2228G>A

ENST00000316623.10:c.3554G>A

ENST00000316623.9:c.3554G>A

ENST00000537463.6:c.637-12460G>A

NM_000138.4:c.3554G>A

Likely Pathogenic

Met criteria codes **6**

PP2

PP3

PP4

PM6

PS4_Supporting

PM2_Supporting

Not Met criteria codes **1**

PM1

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.3554G>A is a missense variant in FBN1 predicted to cause a substitution of a glycine by aspartic acid at amino acid 1185 (p.Gly1185Asp), in a cbEGF-like domain of the protein. This variant was found in a proband who met revised Ghent criteria with a clinical diagnosis of Marfan syndrome (MFS) (PMID 35058154, internal lab data, PP4). This variant has been reported three times in ClinVar: once as pathogenic, once as likely pathogenic, and once as uncertain significance (Variation ID: 549173). This variant was also found to be de novo in a proband with infantile MFS without confirmation of paternity and maternity (PM6, PS4_Sup; internal lab data). This variant is not

present in gnomAD (PM2_sup; <https://gnomad.broadinstitute.org/v2.1.1>). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (REVEL: 0.942, 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: PM6, PS4_Sup, PM2_Sup, PP2, PP3, PP4.

Met criteria codes

PP2			Missense variant
PP3			REVEL score: 0.942
PP4			Internal patient- met revised Ghent criteria
PM6			1yo proband with infantile form of MFS, de novo without confirmation of paternity/maternity
PS4_Supporting			1 point- Internal Bichat proband- 1yo proband with infantile form of MFS
PM2_Supporting			Absent in gnomAD

Not Met criteria codes

PM1			Non-critical Gly in cbEGF-like domain
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Curation History

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