

Variant: *NM_000138.5(FBN1):c.338C>G (p.Ser113Cys)*

Version: 1.0

CA353680 [↗](#)

222600 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 42715a92-75d4-4f3b-8f17-e17ee816b367

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HGVS expressions

NM_000138.5(FBN1):c.338C>G (p.Ser113Cys)

NM_000138.5:c.338C>G

NC_000015.10:g.48610736G>C

CM000677.2:g.48610736G>C

NC_000015.9:g.48902933G>C

CM000677.1:g.48902933G>C

NC_000015.8:g.46690225G>C

NG_008805.2:g.40053C>G

ENST00000559133.6:c.338C>G

ENST00000674301.2:c.338C>G

ENST00000316623.10:c.338C>G

ENST00000316623.9:c.338C>G

ENST00000537463.6:c.338C>G

NM_000138.4:c.338C>G

Likely Pathogenic

Met criteria codes 5

PP2

PP4

PM1

PS4_Moderate

PM2_Supporting

Not Met criteria codes 1

PP3

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.338C>G is a missense variant in FBN1 predicted to cause a substitution of a tyrosine by cysteine at amino acid 113 (p.Ser113Cys) within an EGF-like domain of the protein. Cysteine residues are believed to be involved in the formation of disulfide bridges which are essential for the protein structure and this variant may impact disulfide bonding (PM1). This variant was found in a proband with thoracic aortic aneurysm and ectopia lentis, which is a highly specific phenotype for Marfan syndrome (Internal data, PP4). This variant has been reported twice in ClinVar: once as likely pathogenic and once as uncertain significance (Variation ID: 222600). It has been reported in the literature in individuals with a clinical diagnosis or clinical features of Marfan syndrome (PMID 34281902, Invitae Clinvar

entry, Blueprint Genetics ClinVar entry, internal data, PS4_Mod). This variant is not present in gnomAD (PM2_sup; <https://gnomad.broadinstitute.org/> v2.1.1). Computational prediction tools and conservation analysis are inconclusive with regards to a possible impact on this variant protein function and structure (REVEL: 0.384). 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: PS4_Mod, PM1, PM2_Sup, PP2, PP4

Met criteria codes

PP2			z-score is 5.06
PP4			Internal Lab- 1 proband with ectopia lentis and thoracic aortic aneurysm
PM1			Creating a Cys residue in an EGF-like domain
PS4_Moderate			2 points total
PM2_Supporting			Absent in gnomAD

Not Met criteria codes

PP3			REVEL: 0.384
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Curation History



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