

Variant: *NM_000138.5(FBN1):c.1147G>A (p.Glu383Lys)*

Version: 1.0

CA011960 [↗](#)

200177 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: d0b6949d-1d14-4ad1-a119-d219fef5a5be

Approved on: 2024/5/23

Published on: 2024/10/31

HGVS expressions

NM_000138.5(FBN1):c.1147G>A (p.Glu383Lys)

NM_000138.5:c.1147G>A

NC_000015.10:g.48520659C>T

CM000677.2:g.48520659C>T

NC_000015.9:g.48812856C>T

CM000677.1:g.48812856C>T

NC_000015.8:g.46600148C>T

NG_008805.2:g.130130G>A

ENST00000559133.6:c.1147G>A

ENST00000674301.2:c.1147G>A

ENST00000316623.10:c.1147G>A

ENST00000316623.9:c.1147G>A

ENST00000537463.6:c.636+17052G>A

NM_000138.4:c.1147G>A

Likely Pathogenic

Met criteria codes 5

PS4_Moderate

PP2

PP3

PP4

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.1147G>A is a missense variant in FBN1 predicted to cause a substitution of a glutamic acid by lysine at amino acid 383 (p.Glu383Lys). This variant was found in a proband with a systemic score >7 and thoracic aortic aneurysm and/or dissection, which is a highly specific phenotype for Marfan syndrome (MFS) (PMID 11700157, internal lab data, PP4). This variant has been reported four times in ClinVar: once as pathogenic, once as likely pathogenic, and twice as uncertain significance (Variation ID: 200177). This variant is not present in gnomAD (PM2_sup; <https://gnomad.broadinstitute.org/> v2.1.1). This variant has been reported in the literature in at least three individuals with clinical features of MFS and/or thoracic aortic aneurysm and dissection (PS4_Mod; PMID 19159394, Invitae ClinVar entry,

internal lab data) and in an individual with left iliac aneurysm (GeneDx internal lab data). Computational prediction tools and conservation analysis are inconclusive with regards to a possible impact on this variant’s protein function and structure (REVEL: 0.702). This variant is located in the last nucleotide of exon 9. In silico prediction programs predict that this variant may disrupt RNA splicing (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: PS4_Mod, PM2_Sup, PP2, PP3, PP4

Met criteria codes

PS4_Moderate			2 Points
PP2			Missense variant
PP3			REVEL score: 0.702 (<0.75 cut-off); Weakening of canonical donor site: MaxEnt: -41.6%, NNSPLICE: -10.6%, GeneSplixer: -39.5% (Splice AI Donor loss: 0.44)
PP4			1 indiv with SS>7 and TAAD
PM2_Supporting			Absent in gnomAD

Not Met criteria codes

PM1			Glu in TB1 domain
-----	---	---	-------------------

Curation History

▼

▼

Showing 1 to 1 of 1 rows

--

