

Variant: *NM_000138.5(FBN1):c.6032G>A (p.Cys2011Tyr)*

Version: 1.0

CA10587803 [↗](#)

263898 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: e1d3d3bc-03fb-47ea-bde6-bb6187a53a24

Approved on: 2024/2/22

Published on: 2024/2/22

HGVS expressions

NM_000138.5:c.6032G>A

NM_000138.5(FBN1):c.6032G>A (p.Cys2011Tyr)

NC_000015.10:g.48444546C>T

CM000677.2:g.48444546C>T

NC_000015.9:g.48736743C>T

CM000677.1:g.48736743C>T

NC_000015.8:g.46524035C>T

NG_008805.2:g.206243G>A

ENST00000559133.6:c.6032G>A

ENST00000674301.2:c.6032G>A

ENST00000684448.1:n.4706G>A

ENST00000316623.10:c.6032G>A

ENST00000674301.1:c.1031G>A

ENST00000316623.9:c.6032G>A

ENST00000537463.6:c.*1795G>A

ENST00000559133.5:c.1339G>A

ENST00000560820.1:n.152G>A

NM_000138.4:c.6032G>A

Likely Pathogenic

Met criteria codes 4

PM1_Strong

PP2

PP3

PM2_Supporting

Not Met criteria codes 2

PP4

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.6032G>A is a missense variant in FBN1 predicted to cause a substitution of a cysteine by tyrosine at amino acid 2011 (p.Cys2011Tyr). This variant has been reported four times in ClinVar: once as pathogenic, twice as likely pathogenic, and once as uncertain

significance (Variation ID: 263898). At least two probands with clinical features of Marfan syndrome carry the same variant (internal lab data, PS4_Sup). 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-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). Other missense variants disrupting the Cysteine at this position, (i.e. p.Cys2011Arg and p.Cys2011Ser), have been reported in individuals with features of Marfan syndrome (PMID 29907982, 31163209). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (REVEL: 0.921, 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, PS4_Sup, PM2_Sup, PP2, PP3

Met criteria codes

PM1_Strong			Cys-disrupting variant in cbEGF-like domain
PP2			The constraint z-score for missense variants affecting FBN1 is 5.06
PP3			REVEL: 0.921
PM2_Supporting			Absent in gnomAD

Not Met criteria codes

PP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			PM1_Strong Met

Curation History

▼

▼

Showing 1 to 1 of 1 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

[ClinGen Terms of Use.](#)

[✕ Powered by BCM's Genboree.](#)