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Variant: NM_000138.5(FBN1):c.8002G>T (p.Gly2668Cys)

Version: 1.0

CA16606683

381609 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8b15930c-0ef1-4857-bbe2-7c68730b5c9f
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HGVS expressions

NM_000138.5:c.8002G>T
NM_000138.5(FBN1):c.8002G>T (p.Gly2668Cys)
NC_000015.10:g.48415585C>A
CM000677.2:g.48415585C>A
NC_000015.9:g.48707782C>A
CM000677.1:g.48707782C>A
NC_000015.8:g.46495074C>A
NG_008805.2:g.235204G>T
ENST00000559133.6:c.*810G>T
ENST00000674301.2:c.*1515G>T
ENST00000682158.1:n.1383G>T
ENST00000682170.1:n.2183G>T
ENST00000682767.1:n.1299G>T
ENST00000316623.10:c.8002G>T
ENST00000674301.1:c.3168G>T
ENST00000316623.9:c.8002G>T
ENST00000559133.5:c.3371G>T
ENST00000561429.1:n.257G>T
NM_000138.4:c.8002G>T

Likely Pathogenic

Met criteria codes 5

PM1 PP2 PP3 PP4 PM2_Supporting

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.8002G>T is a missense variant in FBN1 predicted to cause a substitution of a glycine by cysteine at amino acid 2668 (p.Gly2668Cys). This cysteine-creating variant impacts a critical glycine between Cys3 and Cys4 within a calcium binding EGF-like domain, important for interdomain packaging (PM1, PMID 31227806). This variant has been reported twice in ClinVar: once as likely pathogenic, and once as uncertain significance (Variation ID: 381609). This variant has been reported in three individuals from the same study who met revised Ghent criteria; however, the relatedness of these individuals was not provided (PMID 26787436, PP4). This variant was also found in an individual with thoracic aortic dissection and striae (Internal lab data, PMID 11700157). This variant is not present in gnomAD (PM2_sup; https://gnomad.broadinstitute.org/ v2.1.1). A different missense variant at this position, c.8003G>A p.Gly2668Asp, has previously been reported in individuals with a clinical diagnosis of Marfan syndrome (MFS) or MFS-related features (PMID 26787436, internal lab data), however the p.Gly2668Asp variant has not yet been reviewed the FBN1 Variant Curation Expert Panel. Computational prediction tools and conservation analysis suggest that this variant may impact the protein (REVEL: 0.987, PP3). The constraint z-score for missense variants affecting FBN1 is 8.18 (PP2; https://gnomad.broadinstitute.org/ v4.0.0). 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, PM2_Sup, PP2, PP3, PP4.

Met criteria codes

PM1	✔	Cys-creating variant in cbEGF-like domain; Also impacting a critical Gly between Cys3 and Cys4
PP2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✔	REVEL score: 0.987
PP4	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2_Supporting	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Not Met criteria codes

PM5	✖	c.80003G>A p.Gly2668Asp – Not yet interpreted by ClinGen VCEP Bichat: found in one proband with aortic dissection+SK (+0.5) PMID 26787436- Netherlands- 1 proband met revised Ghent criteria (PP4) PMID 19293843- likely overlap with internal Bichat case REVEL: 0.939, Absent in gnomAD (PM1, PM5, PM2_Sup, PP2, PP3, PP4)- Meets Likely Path

Curation History

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