The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000138.5(FBN1):c.3677G>T (p.Gly1226Val)

Version: 1.0

CA392324369

495598 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: afc149f1-d8ba-4738-aee1-4df04897a09f
Approved on: 2024-05-23
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HGVS expressions

NM_000138.5:c.3677G>T
NM_000138.5(FBN1):c.3677G>T (p.Gly1226Val)
NC_000015.10:g.48485409C>A
CM000677.2:g.48485409C>A
NC_000015.9:g.48777606C>A
CM000677.1:g.48777606C>A
NC_000015.8:g.46564898C>A
NG_008805.2:g.165380G>T
ENST00000559133.6:c.3677G>T
ENST00000674301.2:c.3677G>T
ENST00000684448.1:n.2351G>T
ENST00000316623.10:c.3677G>T
ENST00000316623.9:c.3677G>T
ENST00000537463.6:c.637-10759G>T
NM_000138.4:c.3677G>T

Uncertain Significance

Met criteria codes 3

PP2 PP3 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.3677G>T is a missense variant in FBN1 predicted to cause a substitution of a glycine by valine at amino acid 1226 (p.Gly1226Val), in a cbEGF-like domain of the protein. This variant was found in a pediatric proband with ectopia lentis and severe annuloaortic ectasia, which is a highly specific phenotype for Marfan syndrome (MFS) (PMID 26796135; PP4). This variant has been reported twice in ClinVar: once as likely pathogenic and once as uncertain significance (Variation ID: 495598). 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: 0.912). The constraint z-score for missense variants affecting FBN1 is 5.06 (PP2). Due to

insufficient evidence, this variant is classified as uncertain significance for Marfan syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen FBN1 VCEP: PM2_Sup, PP2, PP3, PP4.

Met criteria codes

PP2	✔	Missense variant
PP3	✔	REVEL score: 0.912
PM2_Supporting	✔	Absent in gnomAD

Not Met criteria codes

PM1	✖	Non-critical Gly in cbEGF-like domain

Curation History

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