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Variant: NM_000138.5(FBN1):c.5966G>T (p.Cys1989Phe)

Version: 1.0

CA392339801

638559 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 04d959ce-14d0-4ae4-b998-caa24dcb60f5
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HGVS expressions

NM_000138.5(FBN1):c.5966G>T (p.Cys1989Phe)
NM_000138.5:c.5966G>T
NC_000015.10:g.48444612C>A
CM000677.2:g.48444612C>A
NC_000015.9:g.48736809C>A
CM000677.1:g.48736809C>A
NC_000015.8:g.46524101C>A
NG_008805.2:g.206177G>T
ENST00000559133.6:c.5966G>T
ENST00000674301.2:c.5966G>T
ENST00000684448.1:n.4640G>T
ENST00000316623.10:c.5966G>T
ENST00000674301.1:c.965G>T
ENST00000316623.9:c.5966G>T
ENST00000537463.6:c.*1729G>T
ENST00000559133.5:c.1273G>T
ENST00000560820.1:n.86G>T
NM_000138.4:c.5966G>T

Pathogenic

Met criteria codes 7

PP2 PP3 PP4 PM6 PM1_Strong PM2_Supporting PS4_Moderate

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.5966G>T, is a missense variant in FBN1 predicted to cause a substitution of a cysteine by phenylalanine at amino acid 1989 (p.Cys1989Phe). This variant was found in a proband diagnosed with typical Marfan syndrome (internal lab data, PP4); in this family,

the variant was found to be de novo in the proband's symptomatic mother (internal lab data, PM6). This variant has been reported three times in ClinVar: once as pathogenic, once as likely pathogenic, and once as uncertain significance (Variation ID: 638559). At least three other probands with Marfan syndrome and/or clinical features of Marfan syndrome carry the same variant (PMID 29848614, Petrovsky National Research Centre of Surgery ClinVar entry, Cologne University ClinVar entry, PS4_Mod). 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). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (REVEL: 0.947, PP3). The constraint z-score for missense variants affecting FBN1 is 5.06 (PP2). In summary, this variant meets criteria to be classified as pathogenic for Marfan syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen FBN1 VCEP: PM1_Strong, PS4_Mod, PM2_Sup, PP2, PP3, PP4.

Met criteria codes

PP2	✔	The constraint z-score for missense variants affecting FBN1 is 5.06
PP3	✔	REVEL score: 0.947
PP4	✔	1 proband with typical MFS
PM6	✔	Bichat Internal Lab data- - typical MFS-symptomatic carriers; occurred de novo in the mom, no confirmation of maternity/paternity
PM1_Strong	✔	Cys-disrupting residue in cbEGF-like domain
PM2_Supporting	✔	Absent in gnomAD
PS4_Moderate	✔	2 Points

Not Met criteria codes

PM5	✖	Bichat Internal Lab data- Cys1989Tyr found in 1 proband with MFS; Not met as PM1_Strong is applied

Curation History

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