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Variant: NM_000138.5(FBN1):c.7726C>T (p.Arg2576Cys)

Version: 1.0

CA017349

36118 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 9bf16f2a-2ab2-4784-af0d-61499009e04f
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HGVS expressions

NM_000138.5(FBN1):c.7726C>T (p.Arg2576Cys)
NM_000138.5:c.7726C>T
NC_000015.10:g.48420780G>A
CM000677.2:g.48420780G>A
NC_000015.9:g.48712977G>A
CM000677.1:g.48712977G>A
NC_000015.8:g.46500269G>A
NG_008805.2:g.230009C>T
ENST00000559133.6:c.*534C>T
ENST00000674301.2:c.*1239C>T
ENST00000682170.1:n.1907C>T
ENST00000682767.1:n.1023C>T
ENST00000316623.10:c.7726C>T
ENST00000674301.1:c.2892C>T
ENST00000316623.9:c.7726C>T
ENST00000559133.5:c.3095C>T
NM_000138.4:c.7726C>T

Pathogenic

Met criteria codes 6

PM6 PM1 PP1_Strong PS4 PP2 PM2_Supporting

Not Met criteria codes 1

PP3

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.7726C>T is a missense variant in FBN1 predicted to cause a substitution of an arginine by cysteine at amino acid 2576 (p.Arg2576Cys) within a calcium binding EGF-like domain of the protein (PM1). This variant was found in a proband with aortic aneurysm and dissection and ectopia lentis, which is a highly specific phenotype for Marfan syndrome (MFS) (Internal lab data; PP4). This variant has

been reported nine times in ClinVar: five times as pathogenic, three times as likely pathogenic, and once as uncertain significance (Variation ID: 36118). This variant has also been identified in at least 9 individuals with clinical diagnosis of MFS as well as in individuals with clinical features of MFS (PMID 24161884, 31830381, 33711475, 23278365, 33824467, 37042257, internal lab data; PS4). In three individuals with MFS, this variant was reported to be de novo, without confirmation of parental relationships (internal lab data, Prevention Genetics ClinVar, PM6). In at least 5 families with MFS, the variant was found to segregate with MFS and/or clinical features of MFS in several affected relatives (Internal lab data, Laboratory Corporation of America ClinVar, PP1_Strong). This variant is present in in 1/250782 (0.0004%) of alleles tested in gnomAD but did not pass the quality control criteria in the exome subset (PM2_Sup; https://gnomad.broadinstitute.org/ v2.1.1). Computational prediction tools and conservation analysis are inconclusive with regards to a possible impact on this variant's protein function and structure (REVEL: 0.686). 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: PS4, PP1_Strong, PM1, PM6, PM2_Sup, PP2, PP4

Met criteria codes

PM6	✔	Points towards PM6: 1.25
PM1	✔	Cys-creating variant in a cbEGF-like domain
PP1_Strong	✔	>5 segregations
PS4	✔	>4 points
PP2	✔	Missense variant
PM2_Supporting	✔	V2.1.1: Present in 1/250782 (0.0004%); including in 1/10050 (0.01%) of alleles tested from the Ashkenazi Jewish population (not used towards PM2_Sup) Failed QC: Random forest filters in Exomes subset V4.0.0: 2/1111950 (0.0002%) of European non-Finnish individuals

Not Met criteria codes

PP3	✖	REVEL score: 0.686

Curation History

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