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Variant: NM_000138.5(FBN1):c.3712G>A (p.Asp1238Asn)

Version: 1.0

CA014476

200022 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 5c845737-bde4-45b2-8c08-0024c841edce
Approved on: 2024/5/23
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HGVS expressions

NM_000138.5:c.3712G>A
NM_000138.5(FBN1):c.3712G>A (p.Asp1238Asn)
NC_000015.10:g.48485374C>T
CM000677.2:g.48485374C>T
NC_000015.9:g.48777571C>T
CM000677.1:g.48777571C>T
NC_000015.8:g.46564863C>T
NG_008805.2:g.165415G>A
ENST00000559133.6:c.3712G>A
ENST00000674301.2:c.3712G>A
ENST00000684448.1:n.2386G>A
ENST00000316623.10:c.3712G>A
ENST00000316623.9:c.3712G>A
ENST00000537463.6:c.637-10724G>A
NM_000138.4:c.3712G>A

Pathogenic

Met criteria codes 8

PM1 PM5 PP1_Moderate PS4 PM2_Supporting PP2 PP3 PP4

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.3712G>A is a missense variant in FBN1 predicted to cause a substitution of an aspartic acid by asparagine at amino acid 1238 (p.Asp1238Asn). This variant impacts the first aspartic acid within a calcium-binding (cb) (D/N)-X-(D/N)-(E/Q)-Xm-(D/N)-Xn-(Y/F) consensus sequence of a cbEGF-like domain (PM1). This variant was found in a proband with a clinical diagnosis of Marfan syndrome (MFS) (Internal lab data, PP4). This variant has been reported 12 times in ClinVar: three times as pathogenic, eight times as likely pathogenic, and once as uncertain significance (Variation ID: 200022). This variant has also been reported in multiple individuals with a clinical diagnosis of MFS, ectopia lentis and/or clinical features of MFS (PS4_Strong; PMID 32730690, 10533071, 30675029, internal lab data). This variant was found to segregate with disease in at least four affected relatives with MFS from four families (PMID 32730690, internal lab

data; PP1_Mod). This variant is not present in gnomAD (PM2_sup; https://gnomad.broadinstitute.org/ v2.1.1). A different missense variant at this position, c.3713A>G (p.Asp1238Gly), has previously been previously established as (likely) pathogenic and was reported an individual with a clinical diagnosis of MFS (PM5; PMID 11175294). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (REVEL: 0.895). This variant is located in the last nucleotide of the exon. In silico prediction programs suggest a possibly impact on splicing, however RNA analysis using patient blood showed no impact for this variant on RNA splicing (PMID 32123317). 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_Strong, PM1, PM5, PP1_Mod, PM2_Sup, PP2, PP3, PP4.

Met criteria codes

PM1	✔	Asp to Asn in the first Asp in the (D/N)-X-(D/N)-(E/Q)-Xm-(D/N)-Xn-(Y/F) cb consensus sequence
PM5	✔	c.3713A>G (p.Asp1238Gly): Absent in gnomAD, REVEL: 0.952; No pred impact on splicing PMID 11175294- D1238G Germany, Denmark- 1 met revised Ghent criteria (PP4)
PP1_Moderate	✔	4 segregations in patients with Marfan syndrome
PS4	✔	> 4 unrelated individuals with a clinical diagnosis of Marfan syndrome
PM2_Supporting	✔	Absent in gnomAD
PP2	✔	Missense variant
PP3	✔	REVEL score: 0.895 Predicted to weaken donor splice site by: MaxEEnt: -24.0%, NNSplice: -3.7%, GeneSplicer: -42.5%-Splice AI donor gain: 0.54
PP4	✔	Internal lab data- 1 with clinical diagnosis of Marfan syndrome

Curation History

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