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Variant: NM_000138.5(FBN1):c.3589G>A (p.Asp1197Asn)

Version: 1.0

CA014319

42339 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8e2ba4cd-d082-444b-abd6-750aeb8f76e7
Approved on: 2024/5/23
Published on: 2024/10/31

HGVS expressions

NM_000138.5:c.3589G>A
NM_000138.5(FBN1):c.3589G>A (p.Asp1197Asn)
NC_000015.10:g.48487075C>T
CM000677.2:g.48487075C>T
NC_000015.9:g.48779272C>T
CM000677.1:g.48779272C>T
NC_000015.8:g.46566564C>T
NG_008805.2:g.163714G>A
ENST00000559133.6:c.3589G>A
ENST00000674301.2:c.3589G>A
ENST00000684448.1:n.2263G>A
ENST00000316623.10:c.3589G>A
ENST00000316623.9:c.3589G>A
ENST00000537463.6:c.637-12425G>A
NM_000138.4:c.3589G>A

Likely Pathogenic

Met criteria codes 7

PS4_Supporting PP2 PP3 PP4 PM6 PM1 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.3589G>A is a missense variant in FBN1 predicted to cause a substitution of an aspartic acid by asparagine at amino acid 1197 (p.Asp1197Asn). 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 identified in two unrelated pediatric probands with a clinical diagnosis of Marfan syndrome (MFS), and was found to be de novo without confirmation of paternity and maternity (internal lab data, PM6, PP4, PS4_Sup). This variant has been reported three times in ClinVar: once as likely pathogenic, and twice as uncertain significance (Variation ID: 42339). This variant was found in an individual with thoracic aortic aneurysm and/or dissection (Internal lab data). This variant is not present in gnomAD (PM2_sup; https://gnomad.broadinstitute.org/ v2.1.1). A different missense variant at this position, c.3589G>C

p.Asp1197His, has previously been previously established as (likely) pathogenic and was reported as de novo in an individual with Marfan syndrome (PMID 19293843, PM5). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (REVEL: 0.772, PP3). This variant is located in the last nucleotide of the exon. In silico prediction programs predict that this variant may disrupt RNA splicing (PP3). The constraint z-score for missense variants affecting FBN1 is 5.06 (PP2). 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, PM5, PM6, PS4_Sup, PM2_Sup, PP2, PP3, PP4.

Met criteria codes

PS4_Supporting	✔	1.5 pts
PP2	✔	Missense variant
PP3	✔	REVEL score: 0.772; Weakening/ disrupt canonical donor site by MaxEnt (-25.6%), NNSplice (-18.4%), and GeneSplicer (1.91=>--) (SpliceAI Donor gain: 0.76 4bp downstream)
PP4	✔	Internal lab data- 1 pediatric proband with MFS
PM6	✔	Internal lab data- 1 pediatric proband with EL, TAA, and SK features, de novo without parentage confirmation
PM1	✔	Asp to Asn in (D/N)-X-(D/N)-(E/Q)-Xm-(D/N)-Xn-(Y/F) cb consensus sequence
PM5	✔	c.3589G>C p.Asp1197His Absent in gnomAD, REVEL: 0.922, Splc pred (MaxEnt (-15.2%), (-6.7%), (-5.8%), GeneSplicer (1.91=>--); SpliceAI Donor gain: 0.52 4bp downstream PMID 19293843- France- De novo in proband with Classical MFS (PS4_Supp) (PM6_Supp- 0.5 pts, consistent phentype unconfirmed parents) Likely Path: PM1, PS4_Sup, PM2_Sup, PM6_Sup, PP2, PP3

Curation History

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