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_000138.4(FBN1):c.4459G>A (p.Asp1487Asn)

Version: 1.0

CA269554323

549232 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: bcb32b50-f400-4bba-8030-d8f1e31ee6ac
Approved on: 2022/12/1
Published on: 2022/12/1

HGVS expressions

NM_000138.4(FBN1):c.4459G>A (p.Asp1487Asn)
NM_000138.4:c.4459G>A
NC_000015.10:g.48470634C>T
CM000677.2:g.48470634C>T
NC_000015.9:g.48762831C>T
CM000677.1:g.48762831C>T
NC_000015.8:g.46550123C>T
NG_008805.2:g.180155G>A
ENST00000559133.6:c.4459G>A
ENST00000674301.2:c.4459G>A
ENST00000683268.1:n.426G>A
ENST00000684448.1:n.3133G>A
ENST00000316623.10:c.4459G>A
ENST00000316623.9:c.4459G>A
ENST00000537463.6:c.*222G>A
NM_000138.5:c.4459G>A

Pathogenic

Met criteria codes 7

PP1_Strong PM2_Supporting PS4 PM1 PP2 PP3 PP4

Not Met criteria codes 19

PVS1 BS2 BS1 BS4 BS3 BP4 BP3 BP1 BP2 BP5 BP7 PS1 PS2 PS3 BA1 PM3 PM5 PM4 PM6

Evidence Links 0

Expert Panel

FBN1 VCEP

Criteria Specification Information

Criteria Specification: *ClinGen FBN1 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1*
PDF
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

FBN1 VCEP

The NM_000138 c.4459G>A, is a missense variant in FBN1 predicted to cause a substitution of an Aspartic acid by Asparagine at amino acid 1487 p.(Asp1487Asn). This variant was found in four probands meeting the Ghent criteria (PP4, PS4_strong). The variant segregates with the disease in six affected family members of one proband and three affected family members of another proband (PP1_strong). This variant has been reported three times in ClinVar as likely pathogenic (Variation ID: 549232). It has been reported one time in the literature in a proband with classical Marfan syndrome (PMID: 19293843). This variant is not present in gnomAD v2.1.1 (PM2_sup; https://gnomad.broadinstitute.org/). This variant lies in a critical calcium binding site within a calcium binding EGF domain (PM1). Computational prediction tools and conservation analysis suggest that this variant may impact the protein structure (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: PS4, PP1_strong, PM1, PP2, PP3, PP4, PM2_supporting

Met criteria codes

PP1_Strong	✔	Co-segregation with disease in 6 affected family members in one center and 2 family members in another center
PM2_Supporting	✔	Not present in gnomad v2.1.1
PS4	✔	This variant was identified in four probands meeting the Ghent criteria. An additional proband was described in the literature.
PM1	✔	Affects cb-sequence in cb-EGF domain: cbEGF22
PP2	✔	The constraint z-score for missense variants affecting FBN1 is 5.06
PP3	✔	REVEL Score of 0.818, MetaLR and CADD predict this variant as pathogenic
PP4	✔	Patient has TAD and EL

Not Met criteria codes

PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5		✖	Cannot apply PM5.
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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