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Variant: NM_000138.5(FBN1):c.3650G>A (p.Gly1217Asp)

Version: 1.0

CA392324483

549180 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 4a8d3506-3393-401b-b56e-a28a50410118
Approved on: 2024/5/23
Published on: 2024/10/31

HGVS expressions

NM_000138.5:c.3650G>A
NM_000138.5(FBN1):c.3650G>A (p.Gly1217Asp)
NC_000015.10:g.48485436C>T
CM000677.2:g.48485436C>T
NC_000015.9:g.48777633C>T
CM000677.1:g.48777633C>T
NC_000015.8:g.46564925C>T
NG_008805.2:g.165353G>A
ENST00000559133.6:c.3650G>A
ENST00000674301.2:c.3650G>A
ENST00000684448.1:n.2324G>A
ENST00000316623.10:c.3650G>A
ENST00000316623.9:c.3650G>A
ENST00000537463.6:c.637-10786G>A
NM_000138.4:c.3650G>A

Likely Pathogenic

Met criteria codes 6

PM1 PS4_Moderate PM2_Supporting PP2 PP3 PP4

Not Met criteria codes 16

PM3 PM5 PM6 BA1 BS1 BS4 BS3 BS2 BP5 BP4 BP1 BP2 PS1 PS2 PS3 PP1

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.3650G>A is a missense variant in FBN1 predicted to cause a substitution of a glycine by aspartic acid at amino acid 1217 (p.Gly1217Asp). This cysteine-creating variant impacts a critical glycine between Cys3 and Cys4 within a calcium binding EGF-like domain, important for interdomain packaging (PM1, PMID 31227806). This variant was found in a pediatric proband with a systemic score >7 and

thoracic aortic dissection, which is a highly specific phenotype for Marfan syndrome (MFS) (internal lab data, PP4). In this family, the variant was found to be inherited from the probands affected father (internal lab data). This variant has been reported three times in ClinVar: once as likely pathogenic, and twice as uncertain significance (Variation ID: 549180). This variant has also been reported in at least 4 individuals with a clinical diagnosis of MFS or clinical features of MFS (PS4_Mod; PMID 27112580, Petrovsky National Research Centre of Surgery ClinVar entry, Internal lab data). This variant is not present in gnomAD (PM2_sup; https://gnomad.broadinstitute.org/v2.1.1). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (REVEL: 0.987, 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, PS4_Mod, PM2_Sup, PP2, PP3, PP4.

Met criteria codes

PM1	✔	Gly between Cys3-Cys4 if there is an upstream cbEGF domain
PS4_Moderate	✔	3 points
PM2_Supporting	✔	Absent in gnomAD
PP2	✔	Missense variant
PP3	✔	REVEL score: 0.869
PP4	✔	1 pediatric individual with Systemic score >7 and thoracic aortic disease

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Not Met criteria codes

PM3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	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
BA1	✖	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
BS2		✖	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
BP4		✖	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
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
PP1		✖	Internal lab data: 1 pediatric individual with SS>7 and TAD; inherited from affected father

Curation History

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