Variant: NM_000138.5(FBN1):c.3422C>T (p.Pro1141Leu)

Version: 1.0

CA014098

42334 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 33b1c05d-fe29-4995-a9e2-14529a6a0c8f
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HGVS expressions

NM_000138.5:c.3422C>T
NM_000138.5(FBN1):c.3422C>T (p.Pro1141Leu)
NC_000015.10:g.48487353G>A
CM000677.2:g.48487353G>A
NC_000015.9:g.48779550G>A
CM000677.1:g.48779550G>A
NC_000015.8:g.46566842G>A
NG_008805.2:g.163436C>T
ENST00000559133.6:c.3422C>T
ENST00000674301.2:c.3422C>T
ENST00000684448.1:n.2096C>T
ENST00000316623.10:c.3422C>T
ENST00000316623.9:c.3422C>T
ENST00000537463.6:c.637-12703C>T
NM_000138.4:c.3422C>T

Benign

Met criteria codes 2

BS1 BS4

Not Met criteria codes 20

PM1 PM3 PM5 PM6 PM2
BA1 BS2 BS3 BP4 BP1 BP2
BP5 PS1 PS2 PS3 PS4 PP1
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

NM_00138 c.3422C>T is a missense variant in FBN1 predicted to cause a substitution of a Proline by Leucine at amino acid 1141 (p.Pro1141Leu). This variant has been reported in the literature in at least 3 individuals in association with thoracic aortic aneurysm and dissection (TAAD), MASS syndrome, and features possibly consistent with Marfan syndrome (PMID: 10533071; PMID: 24740214; PMID:

26188975). This variant was also identified in an internal proband with isolated TAAD with a family history highly specific for Marfan syndrome, however it does not segregate with disease in an affected family member (BS4) and therefore PP4 cannot be used. This variant has been previously reported in ClinVar as benign, likely benign, and uncertain significance (Variation ID: 42334). This variant has been identified in 0.026% of individuals of European origin (BS1; https://gnomad.broadinstitute.org/ version 2.1.1). Computational prediction tools and conservation analysis are unclear on the predicted impact on the protein. The constraint z-score for missense variants affecting FBN1 is 5.06, however due to the presence of two benign arguments PP2 cannot be used. In summary, this variant meets criteria to be classified as benign for Marfan syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen FBN1 VCEP: BS1, BS4

Met criteria codes

BS1	✔	MAF 0.026% (34/129194 alleles) in European sub-population (gnomAD v2.1.1)
BS4	✔	Variant not present in internal individual's affected son (ectopia lentis, systemic score ≥7, TAD)

Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3	✖	N/A for FBN1
PM5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✖	no evidence for this
PM2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	✖	MAF 0.026% (34/129194 alleles) in European sub-population (gnomAD v2.1.1)
BS2	✖	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	✖	REVEL = 0.694 (>0.326)
BP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	✖	no evidence for this

BP5	✖	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 evidence for this
PS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	BS1 is met; cannot apply PS4 at any strength (despite multiple probands in the literature without well-described phenotypes which otherwise would meet PS4_supporting)
PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2	✖	Due to the use of BS1
PP3	✖	REVEL = 0.694 (<0.75)
PP4	✖	Internal proband meets the Ghent criteria, but this variant does not segregate with the disease in the family, therefore PP4 should not apply

Curation History

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