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Variant: NM_000138.5(FBN1):c.5518C>T (p.Arg1840Cys)

Version: 1.0

CA055122

519783 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 4e5e2b9c-9621-4b54-b6c4-650cc1dd3827
Approved on: 2024/2/22
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HGVS expressions

NM_000138.5(FBN1):c.5518C>T (p.Arg1840Cys)
NM_000138.5:c.5518C>T
NC_000015.10:g.48452589G>A
CM000677.2:g.48452589G>A
NC_000015.9:g.48744786G>A
CM000677.1:g.48744786G>A
NC_000015.8:g.46532078G>A
NG_008805.2:g.198200C>T
ENST00000559133.6:c.5518C>T
ENST00000674301.2:c.5518C>T
ENST00000684448.1:n.4192C>T
ENST00000316623.10:c.5518C>T
ENST00000674301.1:c.517C>T
ENST00000316623.9:c.5518C>T
ENST00000537463.6:c.*1281C>T
ENST00000559133.5:c.825C>T
NM_000138.4:c.5518C>T

Likely Pathogenic

Met criteria codes 5

PS4_Supporting PP2 PP3 PP4 PM1

Not Met criteria codes 3

PM2 BA1 BS1

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.5518C>T is a missense variant in FBN1 predicted to cause a substitution of an arginine by cysteine at amino acid 1840 (p.Arg1840Cys) within a calcium binding EGF-like domain of the protein. Cysteine residues in these domains are believed to be involved in the formation of disulfide bridges which are essential for the protein structure and this variant may impact disulfide bonding (PM1). This

variant was found in a proband who met revised Ghent criteria, which is a highly specific phenotype for Marfan syndrome (PMID 31149040, PP4). This variant has been reported three times in ClinVar: twice as likely pathogenic and once as uncertain significance (Variation ID: 519783). It has been reported in the literature in individuals with clinical features of Marfan syndrome (PMID 25652356, 29357934, 37042257, Internal data, PS4_Sup). This variant is present in 1/35435 (0.003%) of alleles tested from the Admixed American population gnomAD (https://gnomad.broadinstitute.org/v2.1.1). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (REVEL: 0.78, 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_Sup, PP2, PP3, PP4

Met criteria codes

PS4_Supporting	✔	1.5 Points
PP2	✔	The constraint z-score for missense variants affecting FBN1 is 5.06
PP3	✔	REVEL: 0.78
PP4	✔	PMID 31149040- Italy- 1 Proband with MFS (met revised Ghent criteria)
PM1	✔	Cys-creating residue in calcium binding EGF-like domain

Not Met criteria codes

PM2	✖	V2.1.1: 2/25116 (0.008%) of alleles tested from the Ashkenazi Jewish population –not used V2.1.1: 1/35436 (0.003%) of alleles from the Admixed American population V4.0.0: 2/59998 (0.003%) of alleles from the Admixed American population
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

Curation History

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