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Variant: NM_000138.5(FBN1):c.5826C>A (p.Cys1942Ter)

Version: 1.0

CA269532860

547334 (ClinVar)

Gene: FBN1 (HGNC:2200)
Condition: Marfan syndrome (MONDO:0007947)
Inheritance Mode: Autosomal dominant inheritance
UUID: 76fe5b55-7709-49dc-b27d-dfa97cef8168
Approved on: 2024/2/22
Published on: 2024/2/22

HGVS expressions

NM_000138.5(FBN1):c.5826C>A (p.Cys1942Ter)
NM_000138.5:c.5826C>A
NC_000015.10:g.48445467G>T
CM000677.2:g.48445467G>T
NC_000015.9:g.48737664G>T
CM000677.1:g.48737664G>T
NC_000015.8:g.46524956G>T
NG_008805.2:g.205322C>A
ENST00000559133.6:c.5826C>A
ENST00000674301.2:c.5826C>A
ENST00000684448.1:n.4500C>A
ENST00000316623.10:c.5826C>A
ENST00000674301.1:c.825C>A
ENST00000316623.9:c.5826C>A
ENST00000537463.6:c.*1589C>A
ENST00000559133.5:c.1133C>A
NM_000138.4:c.5826C>A

Pathogenic

Met criteria codes 6

PP1 PP4 PVS1 PM2_Supporting PS4_Supporting PM6_Supporting

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.5826C>A, is a nonsense variant in FBN1 expected to cause a premature stop codon and likely results in an absent or disrupted protein product (PVS1). This variant was found in a proband with infantile Marfan syndrome (MFS) and was found to be de novo without confirmation of parental relationships (internal data, PP4, PM6_Supporting). This variant has been reported 7 times in ClinVar, twice as pathogenic and five times as uncertain significance (Variantion ID: 547334). At least three other probands with clinical features of MFS carry the same variant (PMID 12068374, 22772377, Centre for Human Genetics ClinVar entry, PS4_Sup). In one family with features of

MFS, including mitral valve prolapse, striae, pectus carinatum, scoliosis, striae, joint hypermobility, and wrist and thumb sign, this variant was found to segregate with disease in four affected family members (PMID 12068374, PP1). This variant is not present in gnomAD (PM2_sup; https://gnomad.broadinstitute.org/ v2.1.1). 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: PVS1, PS4_Sup, PM2_Sup, PM6_Sup, PP1, PP4

Met criteria codes

PP1	✔	3 segregations in 1 family with high systemic score
PP4	✔	one proband with infantile MFS, de novo without confirmation of maternity/paternity
PVS1	✔	PTC at 1942, predicted to undergo NMD
PM2_Supporting	✔	Absent in gnomAD
PS4_Supporting	✔	1.5 Pts
PM6_Supporting	✔	1 de novo with phenotype consistent with gene without confirmation of parental relationships

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000138.5(FBN1):c.5826C>A (p.Cys...	Pathogenic	Marfan Syndrome	2024-02-22	1.0	-	FBN1

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