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Variant: NM_000419.4:c.91del

Version: 1.0

CA913203486

953035 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann's thrombasthenia (MONDO:0010119)
Inheritance Mode: Autosomal recessive inheritance
UUID: b6180e8f-f45f-4279-8681-e3f31d75c9d0
Approved on: 2020/9/6
Published on: 2021/1/22

HGVS expressions

NM_000419.4:c.91del
NC_000017.11:g.44389385del
CM000679.2:g.44389385del
NC_000017.10:g.42466753del
CM000679.1:g.42466753del
NC_000017.9:g.39822279del
NG_008331.1:g.5123del
ENST00000262407.6:c.91del
ENST00000262407.5:c.91del
NM_000419.3:c.91del
NM_000419.5:c.91del

Pathogenic

Met criteria codes 4

PM2_Supporting PP1 PVS1 PP4_Strong

Not Met criteria codes 1

PM3

Evidence Links 1

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The 1-bp deletion vairant, NM_000419.4:c.91del, causes a frameshift, Ala31ProfsTer2 and a premature termination codon at position 33. The resulting transcript is predicted to undergo NMD. The variant is absent from gnomAD. The variant is reported in two siblings in the compound heterozygous state with another frameshift variant, Leu973AlafsTer63 (PMID: 25728920). In summary, based on the evidence available at this time, the variant is classified as pathogenic. GT-specific criteria applied: PVS1, PM2_Supporting, PP1, PP4_Strong.

Met criteria codes

PM2_Supporting ✔ Ala31ProfsTer2 is absent from population databases, including gnomAD, and meets criteria for PM2.

PP1	✔	PP1 is met as the 2 affected siblings in PMID: 25728920 are compound heterozygous for this variant and Leu973AlafsTer63. GT41a and GT41b are siblings compound heterozygous for this variant and Leu973AlafsTer63. The variants have been confirmed to be in trans (Supp Fig 2) and therefore PP1 is applied. PubMed:25728920
PVS1	✔	Ala31ProfsTer2 is a frameshift variant resulting from the 1-bp (G) deletion at nucleotide position 91, which causes premature termination at amino acid position 32 in exon 1 of 30. NMD is predicted.
PP4_Strong	✔	Both compound heterozygous siblings (GT41a & GT41b) reported in PMID: 25728920 meet criteria for PP4_strong, including mucocutaneous bleeding, impaired aggregation with all agonists except ristocetin, and reduced surface expression of αIIbβ3 measured by flow cytometry. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries. 2 siblings, GT41a & GT41b, are compound heterozygous for this variant and Leu973AlafsTer63. GT41a is a 15yo female patient of Canadian and Chinese origins with frequent and severe epistaxis requiring hospital treatment (platelet and rFVIIa transfusion, nasal support, anti-fibrinolytic treatment) and easy bruising, with a WHO bleeding score of 4. Platelet aggregation was absent with 3 agonists, but normal with ristocetin. αIIbβ3 expression assessed by flow cytometry was <5%. She was compound heterozygous for Leu973Alafster63 & Ala31ProfsTer2, phase not confirmed. GT41b is a 13yo male patient of Canadian and Chinese origins with epistaxis, ecchymoses, easy bruising and a WHO bleeding score of 2. Treatment included administration of rFVIIa and anti-fibrinolytics. Platelet aggregation was absent with 3 agonists, but normal with ristocetin. αIIbβ3 expression assessed by flow cytometry was <5%. He was compound heterozygous for Leu973Alafster63 & Ala31ProfsTer2, phase not confirmed. PubMed:25728920

Not Met criteria codes

PM3	✖	Variant found in trans with Leu973Alafs, with phase confirmation. PM3 is not considered here to avoid circularity. PubMed:25728920

Curation History

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