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Variant: NM_000419.4:c.1186G>A

Version: 2.0

CA399804315

627218 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: bcbc61f3-c795-4980-b64a-37af73ad477b
Approved on: 2021/12/2
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HGVS expressions

NM_000419.4:c.1186G>A
NC_000017.11:g.44383517C>T
CM000679.2:g.44383517C>T
NC_000017.10:g.42460885C>T
CM000679.1:g.42460885C>T
NC_000017.9:g.39816411C>T
NG_008331.1:g.10989G>A
ENST00000262407.6:c.1186G>A
ENST00000648408.1:c.617G>A
ENST00000262407.5:c.1186G>A
ENST00000592226.5:n.426G>A
NM_000419.3:c.1186G>A
NM_000419.5:c.1186G>A

Pathogenic

Met criteria codes 4

PP3 PP4_Strong PM3_Strong PM2_Supporting

Evidence Links 0

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The NM_000419.4:c.1186G>A variant that results in the missense change, Asp396Asn, is reported at a low frequency of 0.000066 in gnomAD (PM2_supporting). It is reported in three compound heterozygous (PMID: 25373348, 34267460, and 31064749) and one apparently homozygous (PMID: 19172520) probands (PM3_strong). Probands from PMID: 25373348 and 34267460 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. It is predicted damaging by in-silico tools, with a REVEL score of 0.871. In summary, there is evidence to classify the Asp396Asn variant as Pathogenic for GT. GT-specific criteria applied: PM3_strong, PM2_Supporting, PP3, PP4_Strong.

Met criteria codes

PP3		✔	The variant has a REVEL score of 0.871 (threshold: >0.7) and meets PP3
PP4_Strong		✔	1 proband from PMID: 25373348 meets 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.
PM3_Strong		✔	1 assumed homozygous proband from PMID: 19172520 (not clear if truly homozygous) and 2 compound heterozygous probands from PMID: 25373348 (c.3060+2T>C, classified Pathogenic by Platelet Disorders VCEP, confirmed in trans, 1pt) and PMID: 34267460 (c.3092del, classified Likely Pathogenic by the PD-EP; 1pt) are reported.
PM2_Supporting		✔	The variant is reported at a frequency of 0.00006622 (2/30202 alleles in the South Asian population) in gnomAD and meets criteria (<1/10000 alleles) for PM2.

Curation History

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