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Variant: NM_000419.4:c.1882C>T

Version: 1.0

CA399801310

953033 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann's thrombasthenia (MONDO:0010119)
Inheritance Mode: Autosomal recessive inheritance
UUID: 582fd2c4-5386-45d3-9a32-d57334d08142
Approved on: 2020/9/6
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HGVS expressions

NM_000419.4:c.1882C>T
NC_000017.11:g.44378707G>A
CM000679.2:g.44378707G>A
NC_000017.10:g.42456075G>A
CM000679.1:g.42456075G>A
NC_000017.9:g.39811601G>A
NG_008331.1:g.15799C>T
ENST00000262407.6:c.1882C>T
ENST00000648408.1:c.1313C>T
ENST00000262407.5:c.1882C>T
ENST00000592462.5:n.677C>T
NM_000419.3:c.1882C>T
NM_000419.5:c.1882C>T

Pathogenic

Met criteria codes 5

PVS1 PP4_Strong PM2_Supporting PM3 PP1

Not Met criteria codes 1

PS3

Evidence Links 3

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The NM_000419.3:c.1882C>T (p.Arg628Ter) nonsense variant generates a premature stop codon in exon 19 of 30, and is predicted to result in NMD. It has been seen in at least two probands with a phenotype highly specific to GT, including cosegregation in two affected siblings (PMID: 25728920). It occurs at an extremely low frequency of 0.00003983 in the gnomAD Latino population. In summary, based on the evidence available at this time, the variant is classified as pathogenic. GT-specific criteria applied: PVS1, PM2_supporting, PM3, PP1, PP4_strong.

Met criteria codes

PVS1	✔	This nonsense variant, Arg628Ter generates a premature stop codon in exon 19 of 30, and is predicted to result in NMD.
PP4_Strong	✔	Both probands of PMID: 25728920 meet the 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.
PM2_Supporting	✔	This variant is at an extremely low frequency (below the <1/10,000 threshold) with an overall allele frequency from gnomAD of 0.000006169 and MAF of 0.00003983 (1/25,106 alleles) in the Latino population.
PM3	✔	At least two homozygous probands has been reported in PMID: 12008952 and PMID: 25728920. As well as two compound heterozygous probands with Tyr471Ter and Ile185Met, not included in this assessment. PubMed:25728920 PubMed:12008952 PubMed:25373348
PP1	✔	Affected siblings 39a and 39b are both homozygous for Arg628Ter (PMID: 25728920).

Not Met criteria codes

PS3	✖	In-vitro studies in PMID: 12008952 show absent GPIIb-IIIA complex expression on the cell surface in CHO cells however only immunoprecipitation was used for analysis not Western blot or flow cytometry. Coexpression of normal GPIIIa and variant GPIIb in CHO cells failed to show surface expression of GPIIb(variant)-IIIa complexes. PubMed:12008952

Curation History

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