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Variant: NM_000212.3:c.2356C>T

Version: 2.1

CA400034866

996183 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: a6821494-10c9-4e64-8e3c-7bf1f427f06c
Approved on: 2026/3/17
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HGVS expressions

NM_000212.3:c.2356C>T
NC_000017.11:g.47310193C>T
CM000679.2:g.47310193C>T
NC_000017.10:g.45387559C>T
CM000679.1:g.45387559C>T
NC_000017.9:g.42742558C>T
NG_008332.2:g.61352C>T
ENST00000559488.7:c.2356C>T
ENST00000559488.5:c.2356C>T
ENST00000560629.1:c.2266+2556C>T
NM_000212.2:c.2356C>T
NR_110880.1:n.363-6411G>A
NR_110881.1:n.227-6411G>A

Uncertain Significance

Met criteria codes 1

PP4_Moderate

Not Met criteria codes 5

BP4 PS3 PM3 PM2 PP3

Evidence Links 0

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Platelet Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2.1*
PDF
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The NM_000212.3:c.2356C>T variant in ITGB3 predicts the missense change, Arg786Trp. The variant is reported in a compound heterozygous GT patient who has a GOF variant in trans with this variant (PMID: 29439184). The patient meets GT bleeding and laboratory phenotype criteria (PP4_moderate): Platelet aggregation was impaired in response to ADP and TRAP-6, but normal to ristocetin, with low-normal response to collagen (64 U; nv = 56-144). αIIbβ3 surface expression was reduced (CD41/CD42b 0.1 [nv = 0.43+-0.11], expression

corrected for platelet volume), and PAC-1 binding induced by platelet stimulation impaired (33.6% with ADP [nv = 74.4+-22.3], 20.3% with TRAP-6 [nv = 80.1+-20.05]). Due to the gain of function variant the patient also shows the macrothrombocytopenia phenotype. The REVEL score (0.334) for this variant is low and does not meet PP3 (>0.7) or BP4 (>0.25) criteria. Functional evidence from transfection studies in CHO cells show that the variant does not affect αIIbβ3 expression or PAC-1 binding, but results in reduced CHO cell spreading (PMID: 29439184), not meeting criteria for PS3. The highest population minor allele frequency in gnomAD v4.1 is 0.0002006 (9/44874 alleles) in the East Asian genetic ancestry group, which is lower than the ClinGen PD VCEP threshold (>0.00158) for BS1 but higher than the threshold (<0.0001) for PM2_Supporting. In summary, this variant meets the criteria to be classified as uncertain significance for autosomal recessive Glanzmann Thrombasthenia based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PP4_moderate (PD VCEP specifications version 2.1).

Met criteria codes

PP4_Moderate	✔	Proband from PMID: 29439184 is confirmed compound heterozygous for a GOF (Asn331Ser) and LOF (Arg786Trp) variants. The patient meets GT bleeding and laboratory phenotype criteria (PP4_moderate): Platelet aggregation was impaired in response to ADP and TRAP-6, but normal to ristocetin, with low-normal response to collagen (64 U; nv = 56-144). αIIbβ3 surface expression was reduced (CD41/CD42b 0.1 [nv = 0.43+-0.11], expression corrected for platelet volume), and PAC-1 binding induced by platelet stimulation impaired (33.6% with ADP [nv = 74.4+-22.3], 20.3% with TRAP-6 [nv = 80.1+-20.05]). Due to the gain of function variant the patient also shows the macrothrombocytopenia phenotype.

Not Met criteria codes

BP4	✖	REVEL score of 0.334 does not meet PP3 threshold of <0.25. Splice AI predicts Acceptor Loss score 0.11.
PS3	✖	Experimental evidence in CHO cells from PMID: 29439184 showed normal αIIbβ3 expression and PAC-1 binding, but showed reduced CHO cell spreading indicating impaired outside-in signaling. PS3 critieria not met.
PM3	✖	The patient of PMID: 29439184 is compound heterozygous for maternal Arg786Trp and paternal Asn331Ser variants. Not considered since Asn331Ser is a GOF variant related to macrothrombocytopenia.
PM2	✖	The highest population minor allele frequency in gnomAD v4.1 is 0.0002006 (9/44874 alleles) in the East Asian genetic ancestry group, which is lower than the ClinGen PD VCEP threshold (>0.00158) for BS1 but higher than the threshold (<0.0001) for PM2_Supporting.
PP3	✖	REVEL score of 0.334 does not meet PP3 threshold of >0.7.

Curation History

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