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Variant: NM_000212.3:c.917A>C

Version: 1.1

CA291224999

1330311 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: f08e6a42-0ec0-4b19-b3c0-aa60a34f007f
Approved on: 2024/11/7
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HGVS expressions

NM_000212.3:c.917A>C
NC_000017.11:g.47287209A>C
CM000679.2:g.47287209A>C
NC_000017.10:g.45364575A>C
CM000679.1:g.45364575A>C
NC_000017.9:g.42719574A>C
NG_008332.2:g.38368A>C
ENST00000696963.1:c.917A>C
ENST00000559488.7:c.917A>C
ENST00000559488.5:c.917A>C
ENST00000560629.1:c.882A>C
ENST00000571680.1:c.917A>C
NM_000212.2:c.917A>C

Likely Pathogenic

Met criteria codes 3

PS3_Moderate PP4_Moderate PM3_Strong

Not Met criteria codes 3

PP3 PM2 BS1

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(ITGB3):c.917A>C (p.His306Pro) missense variant has been reported in at least six GT probands, including two homozygotes (Osaka-5 of PMID: 11806996; patient NT of PMID: 9790984) and four compound heterozygotes (PMIDs: 34066320, 15634267, 9790984). Contributing to this classification is patient TK of PMID: 9790984, who is compound heterozygous for the maternal His306Pro variant and the paternal Gly605Ser (classified Likely Pathogenic by the PD-EP) variant. (PM3_Strong). At least three patients (Patients TK,

NT, and HJ in PMID:9790984) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). Additionally, αIIbβ3 surface expression was reduced to 19.9%, 7.5% and15.4% respectively, as measured by flow cytometry. Similarly, surface expression of αIIbβ3 measured by flow cytometry in 293 cells transiently co-transfected with His306Pro variant β3 and wild type αIIb showed decreased expression at 25% indicating that this variant impacts protein function (PMID: 11806996; PS3_moderate). In summary this variant meets criteria to be classified as Likely Pathogenic for autosomal recessive Glanzmann Thrombasthenia based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PS3_moderate, PM3_strong, PP4_moderate.

Met criteria codes

PS3_Moderate	✔	Surface expression of αIIbβ3 measured by flow cytometry in 293 cells transiently co-transfected with His306Pro variant β3 and wild type αIIb showed decreased expression at slightly above 25% indicating that this variant impacts protein function (PMID: 11806996).
PP4_Moderate	✔	At least three patients (Patients TK, NT, and HJ in PMID:9790984) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). Additionally, αIIbβ3 surface expression was reduced to 19.9%, 7.5% and15.4% respectively, as measured by flow cytometry. However, ITGA2B and ITGB3 were not reported to be sequenced across all exons and intron/exon boundaries.
PM3_Strong	✔	At least six GT probands have been reported with this variant, including two homozygotes (Osaka-5 of PMID: 11806996; patient NT of PMID: 9790984) and four compound heterozygotes (PMIDs: 34066320, 15634267, 9790984). Contributing to this classification is patient TK of PMID: 9790984, who is compound heterozygous for the maternal His306Pro variant and the paternal Gly605Ser (classified Likely Pathogenic by the PD-EP) variant. (PM3_Strong) Though this variant does not meet the PM2_supporting threshold, the PD VCEP deemed this number of patients to be significant and found that being below BS1 was sufficient.

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.676, which is below the ClinGen PD VCEP PP3 threshold of >0.7 and does not predict a damaging effect on function. And the computational splicing predictor SpliceAI indicated that the variant has no impact on splicing.
PM2	✖	The highest population minor allele frequency in gnomAD v4.1 is 0.0003564 (16/44888 alleles) in the East Asian population. This intermediate allele frequency is lower than the ClinGen PD VCEP threshold (>0.00158) for BS1 but higher than the threshold (<0.0001) for PM2_Supporting.
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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