

Variant: NM_000212.2:c.433G>A

Version: 2.0

CA400021939 [↗](#)

627066 (ClinVar) [↗](#)

Gene: ITGB3 ([HGNC:3690](#))

Condition: Glanzmann thrombasthenia ([MONDO:0100326](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 8b714a8a-f7f4-44a6-8332-c5c1413e5e30

Approved on: 2023/11/2

Published on: 2023/11/3

HGVS expressions

NM_000212.2:c.433G>A

NC_000017.11:g.47284514G>A

CM000679.2:g.47284514G>A

NC_000017.10:g.45361880G>A

CM000679.1:g.45361880G>A

NC_000017.9:g.42716879G>A

NG_008332.2:g.35673G>A

ENST00000696963.1:c.433G>A

ENST00000559488.7:c.433G>A

ENST00000559488.5:c.433G>A

ENST00000560629.1:c.398G>A

ENST00000571680.1:c.433G>A

NM_000212.3:c.433G>A

Likely Pathogenic

Met criteria codes 5

PP4_Moderate

PP3

PM3

PM5

PM2_Supporting

Not Met criteria codes 1

PP1

Evidence Links 1

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_000212.2:c.433G>A variant that results in the Asp145Asn amino acid change is reported in two homozygous individuals in the literature (PMID: 31064749 and Proband NR in PMID: 9215749, Blood abstracts 1997 Suppl., & GT database; PM3). An additional homozygous patient has been identified through clinical testing. One published proband (Ward et al., 1997 Blood Abstracts, Vol 90, Suppl. & GT database, MCW), an Arab female (NR) with frequent bruising, gingival bleeding, epistaxis, menorrhagia, requiring >2 platelet

transfusions, showed absent platelet aggregation with collagen, arachidonic acid, thrombin, ADP and normal aggregation with ristocetin (PP4_moderate). It is absent in population databases, including gnomADv2.1.1 (PM2_supporting) and is predicted damaging by in-silico tools (REVEL score 0.89; PP3). Asp145Tyr is a variant reported at the same residue and classified as likely pathogenic by the Platelet Disorders VCEP (PM5). In summary, based on the available evidence at this time, the Asp145Asn variant is classified as Likely Pathogenic. GT-specific criteria applied: PM2_supporting, PM3, PP3, PP4_moderate and PM5.

Met criteria codes

PP4_Moderate			(1) One unpublished proband data: 5mo Arabic female homozygous for the variant (first-cousin parents, both heterozygous). Umbilical cord bleeding, bruising since birth and anemia reported, requiring transfusion (but unclear bleeding source). Platelet count 340,000, subsequently 19 to 90k in a clinical picture compatible with evolving marrow failure. "Reduced response" to ADP, ASPI, TRAP and ristocetin on platelet aggregation. Platelet receptor flow study showed absent CD41a and CD61. Repeat flow cytometry and platelet glycoprotein analysis showed decreased activated GMP140 (CD62P) and decreased resting and activated GPIIb (CD41A). Variant identified by "platelet function disorder" panel, with no additional variants. This proband does not meet PP4 criteria since response to ristocetin is not normal. Initial flow cytometry shows absent CD61; repeat analysis shows decreased CD41a, but no report on CD61. (2) One published proband (Ward et al., 1997 Blood Abstracts, Vol 90, Suppl. & GT database, MCW): An Arab female (NR) with frequent bruising, gingival bleeding, epistaxis, menorrhagia, requiring >2 platelet transfusions. She showed absent platelet aggregation with collagen, arachidonic acid, thrombin, ADP and normal aggregation with ristocetin. Integrin surface expression was noted to be normal on flow cytometry and western blot. This proband meets PP4_moderate criteria. (3) A homozygous patient is reported in PMID: 31064749 but lacks detailed phenotypic information, only described as having a disease of platelet function. This proband does not meet PP4 criteria. This review article reports the proband (NR) published in the abstract by Ward et al., 1997. PubMed:9215749 
PP3			REVEL score of 0.89 (> 0.7 recommended).
PM3			3 homozygous patients have been identified (PMID: 31064749, PMID: 9215749, and one unpublished patient), meeting criteria for PM3. 1pt
PM5			The Asp145Tyr variant has been reported homozygous in a patient (PMID: 2392682) with variant GT and has been classified as Pathogenic by the ClinGen Platelet Disorders VCEP.
PM2_Supporting			Absent from gnomAD, ExAC, 1000 genomes

Not Met criteria codes

PP1			The unpublished 5mo Arabic female proband's cousin is reported to have GT. However, the genotype information of the cousin is not available.
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