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Variant: NM_000212.3:c.1448G>A

Version: 1.0

CA400029324

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9c335287-2703-4a80-9558-4378dd40adb3
Approved on: 2024/6/6
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HGVS expressions

NM_000212.3:c.1448G>A
NC_000017.11:g.47292326G>A
CM000679.2:g.47292326G>A
NC_000017.10:g.45369692G>A
CM000679.1:g.45369692G>A
NC_000017.9:g.42724691G>A
NG_008332.2:g.43485G>A
ENST00000696963.1:c.1448G>A
ENST00000559488.7:c.1448G>A
ENST00000559488.5:c.1448G>A
ENST00000560629.1:c.1413G>A
NM_000212.2:c.1448G>A

Likely Pathogenic

Met criteria codes 5

PM3_Supporting | PP3 | PP4_Moderate | PM2_Supporting | PS3_Moderate

Not Met criteria codes 1

PM5

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 c.1448G>A variant in ITGB3 is a missense variant predicted to cause substitution of Cysteine by Tyrosine at amino acid 483 (p.Cys483Tyr). This variant was identified in a patient (Patient 11, PMID: 2180491) with GT type 1. This patient had a bleeding phenotype, normal platelet count and morphology, absent or severely diminished platelet aggregation by adenosine diphosphate and other agonists but was normal by ristocetin. Another study (PMID 12152649) sequenced ITGB3 in this patient and identified this variant and demonstrated minimal expression on the cell surface using flow cytometry (PP4_Moderate). This same patient is also reported in PMIDs

28395882 and 3535160. This variant was found in the homozygous state in this GT patient in PMID: 12152649 (PM3_Supporting). COS-7 cells were transfected to express this variant and the wild-type alpha-2-beta-3 surface proteins. Both flow cytometry and immunoblot were used to measure the surface expression of proteins and demonstrated a greatly reduced surface expression, estimated from Figure 3 as 6.5% (PMID: 12152649; PS3_Moderate). This variant has a REVEL score of 0.948 which is above the threshold of 0.7 established by the PD EP (PP3). This variant is not present in the gnomAD database v4.1 (PM2_Supporting). In summary, this variant meets the 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: PP4_Moderate, PM3_Supporting, PS3_Moderate, PP3 and PM2_Supporting (VCEP specifications version 2.1.0).

Met criteria codes

PM3_Supporting	✔	This variant was homozygous in a patient with GT type 1 (PMID 12152649) (PM3_Supporting).
PP3	✔	This variant has a REVEL score of 0.948 which is above the threshold of 0.7 established by the PD EP (PP3_Met).
PP4_Moderate	✔	This variant was identified in a patient (Patient 11, PMID: 2180491) with GT type 1. This patient had a bleeding phenotype, normal platelet count and morphology, absent or severely diminished platelet aggregation by adenosine diphosphate and other agonists but was normal by ristocetin. Another study (PMID 12152649) sequenced ITGB3 in this patient and identified this variant and demonstrated minimal expression on the cell surface using flow cytometry (PP4_Moderate). This same patient is also reported in PMIDs 28395882 and 3535160.
PM2_Supporting	✔	This variant is not present in the gnomAD database v4.1 (PM2_Supporting).
PS3_Moderate	✔	COS-7 cells were transfected to express this variant and the wild-type alpha-2-beta-3 surface proteins. Both flow cytometry and immunoblot were used to measure the surface expression of proteins and demonstrated a greatly reduced surface expression, estimated from Figure 3 as 6.5% (PMID: 12152649; PS3_Moderate).

Not Met criteria codes

PM5	✖	Another variant has been reported at the same amino acid residue (NM_000212.3(ITGB3):c.1447T>C (p.Cys483Arg)) but only for autosomal dominant macrothromobocytopenia (PMID: 15819676, PMID: 31064749), no GT cases reported.

Curation History

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