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# *Variant: NM_000419.5(ITGA2B):c.1346G>A (p.Gly449Asp)*

Version: 2.0

*CA399803552*

*691627 (ClinVar)*

**Gene**: ITGA2B (HGNC:3674)
**Condition**: Glanzmann thrombasthenia (MONDO:0100326)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 1d8ef499-3ee3-4757-97d7-620a09c5b1c4
**Approved on**: 2023/9/7
**Published on**: 2023/9/21

## *HGVS expressions*

**NM_000419.5:c.1346G>A**
**NM_000419.5(ITGA2B):c.1346G>A (p.Gly449Asp)**
NC_000017.11:g.44380926C>T
CM000679.2:g.44380926C>T
NC_000017.10:g.42458294C>T
CM000679.1:g.42458294C>T
NC_000017.9:g.39813820C>T
NG_008331.1:g.13580G>A
ENST00000262407.6:c.1346G>A
ENST00000648408.1:c.777G>A
ENST00000262407.5:c.1346G>A
ENST00000592226.5:n.586G>A
ENST00000592462.5:n.141G>A
NM_000419.3:c.1346G>A
NM_000419.4:c.1346G>A

**Likely Pathogenic**

**Met criteria codes** 5

PM3_Supporting PP3 PS3_Moderate PP4_Moderate PM2_Supporting

**Not Met criteria codes** 1

PM5

### 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_000419.5 (ITGA2B):c.1346G>A variant that results in the Gly449Asp amino acid change is reported in one homozygous Glanzmann thrombasthenia patient in the literature (PMID: 7508443; PM3_supporting). The patient had a severe bleeding phenotype, abnormal**

**aggregometry and absent surface expression of GPIIb (PP4_moderate). It is absent in population databases, including gnomADv2.1.1 (PM2_supporting), and is predicted damaging by in-silico tools (REVEL score 0.895; PP3). Experimental evidence shows the variant results in lack of surface expression of the alphaIIb-beta3 complex (PMID: 7508443; PS3_moderate). In summary, based on the available evidence at this time, the Gly449Asp variant is classified as likely pathogenic for autosomal recessive Glanzmann thrombasthenia. GT-specific criteria applied: PM2_Supporting, PP3, PP4_Moderate, PS3_Moderate and PM3_Supporting.**

**Met criteria codes**

| | | |
|---|---|---|
| **PM3_Supporting** | ✔ | 1 homozygous patient (LM) reported in PMID: 7508443 (and PMID: 9215749) meets criteria for PM3_Supporting |
| **PP3** | ✔ | Gly449Asp has a REVEL score of 0.895 (Recommended threshold >/= 0.7) |
| **PS3_Moderate** | ✔ | The experimental evidence in PMID: 7508443 shows lack of surface expression of the alphaIIb-beta3 complex by immunoprecipitation and immunofluorescence analyses. Based on expert review of this piece of evidence, PS3_Moderate is applied.<br><br>Wild-type (Gly449) and mutant (Asp449) constructs of GPIIa were cotransfected with wild-type GPIIIa in COS-7 cells. Immunoprecipitation with antibodies to GPIIb, GPIIIa, or GPIIb-IIIa complex and indirect immunoflorescence analysis showed lack of surface expression of the complex in mutant cells. Pulse-chase analysis revealed synthesis of stable pro-GPIIb that coimmunoprecipitated with GPIIIa, but lacking the mature GPIIa heavy chain, and subsequent intracellular degradation of the complex. The complex was retained in the ER, evidenced by endoH sensitivity post immunoprecipitation. PubMed:7508443 |
| **PP4_Moderate** | ✔ | Only one patient with the Gly449Asp variant is reported in the literature: patient LM from PMID: 7508443. The proband meets criteria for PP4_moderate based on severe bleeding phenotype, abnormal aggregometry and absent surface expression of GPIIb.<br><br>Patient LM had a severe bleeding phenotype with bleeding time > 20 minutes and had abnormal platelet aggregation on aggregometry analysis (ascertained by personal communication from authors). Western blot on platelet lysates and flow cytometry on platelet surface reveal undetectable GPIIb and low levels of GPIIIa. PubMed:7508443 |
| **PM2_Supporting** | ✔ | The variant is absent from gnomAD and meets criteria for PM2. |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PM5** | ✖ | Gly449Ser is another missense change seen at a very low frequency in gnomAD. This variant has not been reported in patients with GT, to the best of our knowledge, and has not been evaluated by the Platelet Disorders VCEP. However, the information is noted here for future reference. |

Curation History

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