The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000419.5(ITGA2B):c.818G>A (p.Gly273Asp)

Version: 2.0

CA115837

2894 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 315ee6aa-c6dd-4c98-97b1-5c49fedfb665
Approved on: 2024/5/2
Published on: 2024/5/3

HGVS expressions

NM_000419.5(ITGA2B):c.818G>A (p.Gly273Asp)
NM_000419.5:c.818G>A
NC_000017.11:g.44384567C>T
CM000679.2:g.44384567C>T
NC_000017.10:g.42461935C>T
CM000679.1:g.42461935C>T
NC_000017.9:g.39817461C>T
NG_008331.1:g.9939G>A
ENST00000262407.6:c.818G>A
ENST00000648408.1:c.249G>A
ENST00000262407.5:c.818G>A
ENST00000589645.5:n.269G>A
ENST00000591990.5:n.180G>A
ENST00000592075.5:n.187G>A
ENST00000592226.5:n.58G>A
ENST00000592253.5:n.326G>A
ENST00000592944.1:n.500G>A
NM_000419.3:c.818G>A
NM_000419.4:c.818G>A

Likely Pathogenic

Met criteria codes 5

PM3_Supporting | PS3_Moderate | PP3 | PM2_Supporting | PP4_Moderate

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.818G>A (p.Gly273Asp) variant has been reported, in the homozygous state (PM3_supporting), in at least one proband (PMID: 8282784) with a GT-specific phenotype. The patient in PMID: 8282784 meets the criteria for PP4_moderate; including mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin. Additionally, the patient had <5% expression by flow cytometry. The variant is absent from gnomADv4.0 (PM2_supporting) and is predicted deleterious (REVEL score 0.845; PP3). Heterologous expression followed by the preferred assays, of either Western blot or flow cytometry, has not been reported for this variant. However in PMID: 8282784, to test for mutant complexes on the cell surface, COS-1 cells were cotransfected with WT ITGB3 and Gly273Asp ITGA2B, cells were surface labeled with 125I and immunoprecipitated, then labeled heterodimers were detected on the surface of cotransfected cells containing wildtype ITGA2B but not on the surface of cells containing Gly273Asp. PMID: 8916916 reports similar immunoprecipitation results. These results were considered sufficient evidence of impaired surface expression for application of the PS3_moderate criteria. In summary, this variant meets criteria to be classified as likely pathogenic for GT. GT-specific criteria applied: PS3_moderate, PM2_supporting, PM3_supporting, PP3, and PP4_moderate.

Met criteria codes

PM3_Supporting	✔	The patient from PMID: 8282784 is homozygous for Gly273Asp.
PS3_Moderate	✔	Heterologous expression followed by the preferred assays, of either Western blot or flow cytometry, has not been reported for this variant. However in PMID: 8282784, to test for mutant complexes on the cell surface, COS-1 cells were cotransfected with WT ITGB3 and Gly273Asp ITGA2B, cells were surface labeled with 125I and immunoprecipitated, then labeled heterodimers were detected on the surface of cotransfected cells containing wildtype ITGA2B but not on the surface of cells containing Gly273Asp. PMID: 8916916 reports similar immunoprecipitation results. These results were considered sufficient evidence of impaired surface expression for application of the PS3_moderate criteria. Gly273Asp was expressed with wildtype ITGB3 in COS-1 cells. Immunoprecipitation from cell extracts did not result in any heterodimers using the heterodimer-specific mAb A2A9 (in contrast to the COS-1 cells with both wildtype proteins). Using the anti-ß3 mAb SSA6 heterodimers from cell extracts were observed, however the heterodimers had not been cleaved into heavy and light chains. To test for mutant complexes on the cell surface, cotransfected cells were surface labeled with 125I and immunoprecipitated, labeled heterodimers were detected on the surface of cotransfected cells containing wildtype ITGA2B, but not on the surface of cells containing Gly273Asp. Neither Western blot nor flow cytometry was used to determine surface expression. PubMed:8282784
PP3	✔	The REVEL score for this variant is 0.845, exceeding the VCEP-established threshold of >0.7 to support a deleterious effect.
PM2_Supporting	✔	This variant is absent from gnomADv4.0
PP4_Moderate	✔	The patient in PMID: 8282784 meets the criteria for PP4_moderate; including mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin. Additionally, the patient had <5% expression by flow cytometry. The same individual was reported as GTP2 in PMID: 24335497, with no additional phenotypic information.

Curation History

Showing 1 to 2 of 2 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.