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_000212.2:c.1458C>G

Version: 2.0

CA400029369

953012 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 41465704-1a3b-4e6f-a1c8-46e186157156
Approved on: 2023/11/2
Published on: 2023/11/3

HGVS expressions

NM_000212.2:c.1458C>G
NC_000017.11:g.47292336C>G
CM000679.2:g.47292336C>G
NC_000017.10:g.45369702C>G
CM000679.1:g.45369702C>G
NC_000017.9:g.42724701C>G
NG_008332.2:g.43495C>G
ENST00000696963.1:c.1458C>G
ENST00000559488.7:c.1458C>G
ENST00000559488.5:c.1458C>G
ENST00000560629.1:c.1423C>G
NM_000212.3:c.1458C>G

Likely Pathogenic

Met criteria codes 4

PP4_Strong PM2_Supporting PM3 PP3

Not Met criteria codes 1

PS3

Evidence Links 2

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.1458C>G (p.Cys486Trp) variant has been reported in the literature in at least 1 compound heterozygous proband in trans with pathogenic variant Trp11Arg (PMID: 25373348) and a homozygote in an abstract (Von Bargen et al., 2018; PM3). One proband (PMID: 25373348) meets the criteria for PP4_Strong; including mucocutaneous bleeding, impaired aggregation with all agonists except ristocetin, and reduced surface expression of αIIbβ3 measured by flow cytometry. It is absent from gnomADv2.1.1 (PM2_supporting) and is predicted

to have a deleterious effect (REVEL score of 0.909; PP3). In summary, this variant meets criteria to be classified as Likely Pathogenic for GT. GT-specific criteria applied: PM2_supporting, PM3, PP3, and PP4_strong.

Met criteria codes

PP4_Strong ✔

The Cys486Trp variant has been described in one proband (PMID: 25373348) who meets the criteria for PP4_Strong; including mucocutaneous bleeding, impaired aggregation with all agonists except ristocetin, and reduced surface expression of αIIbβ3 measured by flow cytometry. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries.

Patient GT2 heterozygous for Cys486Trp has severe bleeding symptoms and severely reduced platelet aggregation after stimulation with agonists such as collagen, adenosine diphosphate, arachidonic acid, adrenaline, and epinephrine. Ristocetin aggregation was almost normal. Decreased, <5% alphaIIb-beta3 expression was determined by flow cytometry. Platelet count and size were not mentioned. PubMed:25373348

PM2_Supporting ✔

Absent from ExAC and gnomAD.

PM3 ✔

The Cys486Trp variant has been reported in the literature (PMID: 25373348) to be in trans with pathogenic variant Trp11Arg (1pt) An additional homozygous case was reported in an abstract by Von Bargen et al., 2018. 0.5pt

Patient GT2 has the Trp11Arg variant (VUS) in trans with Cys486Trp. Phase is confirmed to be in trans. PubMed:25373348

PP3 ✔

SIFT (Damaging), Polyphen2-HDIV (probably Damaging), and Mutation Taster (disease causing) agree that this variant has a deleterious effect and the REVEL score is 0.909 (>0.7 threshold).

Not Met criteria codes

PS3 ✖

From PMID: 32770549: The mutant β3 construct was transfected together with wild-type αIIb or wild-type αv into HEK293 cells, and the expression of αIIbβ3 and αvβ3 on the surface of stable transfected cells was analyzed by flow cytometry using mAbs that reacted against β3 (mAb AP3), αIIbβ3 (mAb Gi5), and αvβ3 (mAb 23C6) complex. Similar to wild-type, both mutant-transfected cells expressed a comparable amount of αIIbβ3 and αvβ3 heterodimers on the cell surface, confirming that Cys460Trp mutation did not significantly impair the surface expression of αIIbβ3 and αvβ3 integrin. Immunoblotting analysis showed that the mutant β3 migrated slightly slower in comparison with wild-type β3 isoform, indicating that the disruption of one disulfide bond due to Cys460Trp mutation alters the secondary structure of integrin αIIbβ3. Further flow cytometry found the Cys460Trp mutation affects the binding of type II mAbs against HPA-1a(such as 26.4 and B2G1)

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Curation History

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