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Variant: NM_000419.5:c.188G>A

Version: 2.1

CA8603528

1691490 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 01249594-0a67-4c5d-a972-5fc975cc3564
Approved on: 2024/12/17
Published on: 2024/12/17

HGVS expressions

NM_000419.5:c.188G>A
NC_000017.11:g.44389286C>T
CM000679.2:g.44389286C>T
NC_000017.10:g.42466654C>T
CM000679.1:g.42466654C>T
NC_000017.9:g.39822180C>T
NG_008331.1:g.5220G>A
ENST00000262407.6:c.188G>A
ENST00000262407.5:c.188G>A
NM_000419.3:c.188G>A
NM_000419.4:c.188G>A

Likely Pathogenic

Met criteria codes 3

PM3_Supporting PP4_Strong PM2_Supporting

Not Met criteria codes 2

PP3 BP4

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 NM_000419.5:c.188G>A variant in ITGA2B is a missense variant predicted to cause substitution of Arginine by Lysine at amino acid 63 (Arg63Lys). At least one patient (1yo female proband from Morocco in PMID:12871379) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia. Additionally, αIIbβ3 surface expression was reduced to <10% (threshold: <25%), as measured by flow cytometry and Western blot. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries (PP4_Strong, PMID: 12871379). This variant has been detected in homozygosity in at least 1 proband with Glanzmann thrombasthenia. Parents were heterozygous. (0.5pts, PMID: 12871379). Total points:

0.5 (PM3_Supporting). The highest population minor allele frequency in gnomAD v4.1 is 0.000002542 (3/1180026alleles) in the non-Finnish European population, which is lower than the ClinGen PD VCEP threshold (<0.0001; 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_Strong, PM2_Supporting, PM3_Supporting. (VCEP specifications version 2)

Met criteria codes

PM3_Supporting	✔	This variant has been detected in homozygosity in at least 1 proband with Glanzmann thrombasthenia. Parents were heterozygous. (0.5pts, PMID: 12871379). Total points: 0.5 (PM3_Supporting).
PP4_Strong	✔	At least one patient (1yo female proband from Morocco in PMID:12871379) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia. Additionally, αIIbβ3 surface expression was reduced to <10% (threshold: <25%), as measured by flow cytometry and Western blot. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries.
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1 is 0.000002542 (3/1180026alleles) in the non-Finnish European population, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting)

Not Met criteria codes

PP3	✖	
BP4	✖	The Arg63Lys variant has a REVEL score of 0.089, and would meet the threshold for BP4. However, there is evidence to suggest that this variant results in a splicing defect, and therefore BP4 is not applied. The computational splicing predictor SpliceAI gives a score of 0.17 for donor site loss and 0.6 for a donor gain at -17bp, predicting that the variant disrupts the splice site of intron 1 of ITGA2B (PP3). In PMID: 12871379, authors transiently transfected GPIIb constructs incorporating chimeric intronic sequence into CHO cells stably expressing human GPIIIa. The construct containing the splice site mutation yielded minute amounts of transcript of the expected normal spliced form of 561bp along with two additional splicing forms. In one of them, the use of a nearby cryptic donor splicing site led to the incorporation of 7bp, yielding a 568-bp transcript. Another, most abundant, form of 804bp in size was the result of non-splicing of the chimeric intronic sequence.

Curation History

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