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Variant: NM_000212.3:c.989T>A

Version: 3.0

CA400025722

1691459 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 982aceca-eaa9-4feb-a56c-15396353f2a2
Approved on: 2024/11/7
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HGVS expressions

NM_000212.3:c.989T>A
NC_000017.11:g.47289730T>A
CM000679.2:g.47289730T>A
NC_000017.10:g.45367096T>A
CM000679.1:g.45367096T>A
NC_000017.9:g.42722095T>A
NG_008332.2:g.40889T>A
ENST00000696963.1:c.989T>A
ENST00000559488.7:c.989T>A
ENST00000559488.5:c.989T>A
ENST00000560629.1:c.954T>A
ENST00000571680.1:c.989T>A
NM_000212.2:c.989T>A

Likely Pathogenic

Met criteria codes 5

PM3 PS3_Supporting PM2_Supporting PP4_Moderate PP3

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_000212.3(ITGB3):c.989T>A (p.Ile330Asn) missense variant has been reported in at least one patient (in PMID: 15634267) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). Additionally, αIIbβ3 surface expression was remarkably reduced, as measured by flow cytometry. Similarly, when mutant β3 cDNA/pSG5 were cotransfected into COS7 cells with WT αIIb/pSG5 and the percentage of positive

transfected cells was determined by flow cytometry only 4% of COS7 cells were positive (15% of the WT level, 27%; PS3_supporting). The patient in PMID: 15634267 is compound heterozygous for the maternal Ile330Asn and paternal His306Pro (classified Likely Pathogenic by the PD-VCEP) variants (PM3). The computational predictor REVEL gives a score of 0.97 for Ile330Asn, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3). This variant is absent from gnomAD v4.1 (PM2_Supporting). In summary this variant meets 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: PS3_supporting, PM2_supporting, PM3, PP3, PP4_moderate.

Met criteria codes

PM3	✔	The patient in PMID: 15634267 is compound heterozygous for the maternal Ile330Asn and paternal His306Pro (classified Likely Pathogenic by the PD-VCEP) variants.
PS3_Supporting	✔	Mutant β3 cDNA possessing A at position 1009 that leads to Asn304, was constructed using a site-directed mutagenesis kit, and cloned into expression vector pSG5. WT β3/pSG5 or the mutant β3 cDNA/pSG5 were cotransfected into COS7 cells with WT αIIb/pSG5. Forty-eight hours after transfection, harvested COS7 cells were incubated with PE-CD41a, which recognizes the αIIbβ3 complex, and the percentage of positive transfected cells was determined by flow cytometry. The mean values of 27% of COS7 cells transfected with WT αIIb/pSG5 and WT β3/pSG5 were positive for the PE-conjugated monoclonal antibody against αIIbβ3. On the other hand, only 4% of COS7 cells transfected with WT αIIb/pSG5 and Ile304Asn β3/pSG5 possessing A at position 1009 were positive (15% of the WT level). In addition, immunoprecipitation analysis indicated the absence of αIIbβ3 inside COS7 cells transfected with mutant β3 cDNA. This evidence was downgraded to PS3_Supporting because the level of αIIb, β3, and αIIbβ3 cell surface expression was not reported, only whether cells were positive or negative for surface αIIb, β3, and αIIbβ3. Mutant β3 cDNA possessing A at position 1009 that leads to Asn304, was constructed using a site-directed mutagenesis kit, and cloned into expression vector pSG5. WT β3/pSG5 or the mutant β3 cDNA/pSG5 were cotransfected into COS7 cells with WT αIIb/pSG5. Forty-eight hours after transfection, harvested COS7 cells were incubated with PE-CD41a, which recognizes the αIIbβ3 complex, and the percentage of positive transfected cells was determined by flow cytometry. The mean values of 27% of COS7 cells transfected with WT αIIb/pSG5 and WT β3/pSG5 were positive for the PE-conjugated monoclonal antibody against αIIbβ3. On the other hand, only 4% of COS7 cells transfected with WT αIIb/pSG5 and Ile304Asn β3/pSG5 possessing A at position 1009 were positive (15% of the WT level). In addition, immunoprecipitation analysis indicated the absence of αIIbβ3 inside COS7 cells transfected with mutant β3 cDNA. This evidence was downgraded to PS3_Supporting because the level of αIIb, β3, and αIIbβ3 cell surface expression was not reported, only whether cells were positive or negative for surface αIIb, β3, and αIIbβ3. PubMed:15634267
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).
PP4_Moderate	✔	At least one patient (in PMID: 15634267) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia (PP4_moderate). Additionally, αIIbβ3 surface expression was remarkably reduced, as measured by flow cytometry. However, ITGA2B and ITGB3 were not reported to be sequenced across all exons and intron/exon boundaries.
PP3	✔	The computational predictor REVEL gives a score of 0.97, which is above the ClinGen PD VCEP threshold of >0.7 and predicts a damaging effect on function (PP3).

Curation History

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