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Variant: NM_000419.4(ITGA2B):c.2333A>C (p.Gln778Pro)

Version: 1.0

CA290947544

225393 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann's thrombasthenia (MONDO:0010119)
Inheritance Mode: Autosomal recessive inheritance
UUID: c277c257-17ca-43c5-bfb7-913ae9e84528
Approved on: 2020/9/8
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HGVS expressions

NM_000419.4:c.2333A>C
NM_000419.4(ITGA2B):c.2333A>C (p.Gln778Pro)
NC_000017.11:g.44376323T>G
CM000679.2:g.44376323T>G
NC_000017.10:g.42453691T>G
CM000679.1:g.42453691T>G
NC_000017.9:g.39809217T>G
NG_008331.1:g.18183A>C
ENST00000262407.6:c.2333A>C
ENST00000648408.1:c.1764A>C
ENST00000262407.5:c.2333A>C
ENST00000592462.5:n.1128A>C
NM_000419.3:c.2333A>C
NM_000419.5:c.2333A>C

Pathogenic

Met criteria codes 3

PM3_Strong PP4_Strong PM2_Supporting

Not Met criteria codes 2

PS3 PP3

Evidence Links 7

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The NM_000419.4:c.2333A>C variant that results in the p.Gln778Pro amino acid change is reported in at least 5 homozygous and 6 compound heterozygous probands in the literature (PMID: 9722314, 22190468, 9763559, 29675921, 32237906). At least 5 variants in trans with Gln778Pro have been curated and evaluated for PM3 scoring. The variant is reported at frequency <0.0001 in the combined gnomAD v3 and v2.1.1 datasets. In summary, based on the available evidence at this time, the Gln778Pro variant is classified as pathogenic. GT-specific criteria applied: PM2_Supporting, PM3_Strong, PP4_Strong.

Met criteria codes

PM3_Strong ✔

A total of 2.5 points are applied based on the the SVI recommendation, meeting criteria for PM3_Strong. Two homozygous patients and two compound heterozygous probands (with additional variants Pathogenic Gln891Ter and Likely Pathogenic c.2975del) from PMIDs: 29675921 and 22190468 were included. Several additional compound heterozygous probands have been identified but were not included here to avoid circularity.

Patient 3 is compound heterozygous, with phase confirmation, for this variant and c.2975del, which is classified as likely pathogenic by the Platelet Disorders VCEP. A score of 1 point is applied toward PM3 scoring, according to the SVI recommendation. PubMed:22190468
PubMed:12181054
PubMed:9763559
PubMed:29675921
PubMed:32237906

PP4_Strong ✔

5 homozygous and 4 compound heterozygous probands from PMIDs: 9722314, 22190468, 9763559, 29675921 meet criteria for PP4. With those of PMID: 29675921 meeting 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.

Case 3: 32y/F with bleeding diathesis since early childhood, normal platelet counts, absent platelet aggregation with ADP, collagen, epinephrine, but normal response to ristocetin, normal clot retraction. Flow cytometry revealed 16% and 14% surface expression of αIIbβ3 complex detected by AP-2 and LJ-P9, respectively. No history of consanguinity known. Case 4: 35y/F with bleeding diathesis since early childhood, normal platelet counts, absent platelet aggregation with ADP, collagen, epinephrine, but normal response to ristocetin, normal clot retraction. Flow cytometry revealed 24% and 21% surface expression of αIIbβ3 complex detected by AP-2 and LJ-P9, respectively. No history of consanguinity known. Both homozygous probands meet criteria for PP4. PubMed:9722314
Patient 3: 10y/M with cerebral hemorrhage, disease onset at birth, normal CBC and platelet morphology, PFA-100 299s/>300s, absent or markedly reduced aggregation responses to ADP, collagen, and epinephrine with a relatively normal aggregation response to ristocetin on LTA. 7.2%/5% expression of CD41/CD61 on flow cytometry. Other variant in patient: c.2975delA (p.E992Gfs*30). Patient 4: 4y/M with easy bruising and petechia, disease onset at 2m, normal CBC and platelet morphology, PFA-100 291s/242s, absent or markedly reduced aggregation responses to ADP, collagen, and epinephrine with a relatively normal aggregation response to ristocetin on LTA. 7.5% expression of CD41/CD61 on flow cytometry. Other variant in patient: c.1750C>T (p.R584X). PubMed:22190468
Patient MT (homozygous): 40/F, Japanese, with a life-long history of moderate mucocutaneous bleeding, nonconsanguineous parents, absence of platelet aggregation in response to ADP, epinephrine, and collagen, but a normal response to ristocetin, normal clot retraction, immunoblot showed 15% and 22% of αIIb and β3 Patient MS (compound het with c.1753-1G>A; confirmed in trans): 44/F, Japanese, diagnosed with GT, slightly impaired clot retraction, immunoblot showed 4% and 8% of αIIb and β3. No report of LTA in patient MS. Patient MT meets criteria for PP4. PubMed:9763559
21y/F with history of purpura and epistaxis. The authors note that flow cytometry and western blotting revealed markedly reduced expression of integring αIIbβ3, but data is not shown. No information on CBC, platelet

morphology, LTA analysis. Patient was compound heterozygote with other variant, c.257T>C p.Leu86Pro.
PubMed:12181054
Patient CabGT-13: homozygous individual diagnosed Type I GT with <5% GPIIb and GP IIIa. No other phenotypic information available. PubMed:20020534

PM2_Supporting ✔

The variant is absent from the gnomAD v3 population (3134 East Asian alleles) and reported at a frequency of 0.0001087 (2/18394 East Asian alleles). The combined frequency of this variant is 0.00009 (2/21520 alleles) and meets criteria for PM2

Not Met criteria codes

PS3 ✖

The evidence does not meet PS3_Moderate as alphaIIb-betaIII expression was only moderately reduced and fibrinogen/PAC-1 binding of the complex was unaffected.

Mutant αIIb cDNA construct with Gln778Pro variant was transfected into CHO-K1 cells with wild-type β3 cDNA by electroporation. 61% of CHO cells expressed the αIIb(Q778P)β3 complex on flow cytometry, but fibrinogen binding of the mutant receptor complex seemed unaffected. PubMed:9722314
Wild-type or mutant (Gln778Pro) αIIb constructs were cotransfected into 293 cells with wild-type β3 constructs. Flow cytometry and immunoprecipitation showed that mutant Pro778αIIbβ3 expression was moderately reduced compared with wild-type. Western blot with polyclonal antisera showed reduced amount of mature Pro747αIIb and β3. Immunoprecipitation and densitometric analysis showed that the association of the mutant Pro778αIIb with β3 was the same as that of wild-type, and pulse-chase analysis showed moderately impaired cleavage of the mutant complex into heavy and light chains. However, PAC-1 ligand binding of the mutant complex was normal.
PubMed:9763559

PP3 ✖

The Gln778Pro variant is predicted benign by SIFT and PolyPhen and has a REVEL score of 0.268. This does not meet the >0.7 threshold for PP3 or <0.25 threshold for BP4.

Curation History

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