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Variant: NM_000419.4(ITGA2B):c.2944G>A (p.Val982Met)

Version: 1.0

CA16608466

381747 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann's thrombasthenia (MONDO:0010119)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7cd349a6-46e9-4a53-84cf-0c3313a6f570
Approved on: 2020/9/6
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HGVS expressions

NM_000419.4(ITGA2B):c.2944G>A (p.Val982Met)
NM_000419.4:c.2944G>A
NC_000017.11:g.44374470C>T
CM000679.2:g.44374470C>T
NC_000017.10:g.42451838C>T
CM000679.1:g.42451838C>T
NC_000017.9:g.39807364C>T
NG_008331.1:g.20036G>A
ENST00000262407.6:c.2944G>A
ENST00000648408.1:c.2374+189G>A
ENST00000262407.5:c.2944G>A
ENST00000587295.5:c.253+1363G>A
ENST00000588098.1:c.37+189G>A
ENST00000592462.5:n.2643G>A
NM_000419.3:c.2944G>A
NM_000419.5:c.2944G>A

Pathogenic

Met criteria codes 6

PP3 PM3 PS3_Moderate PS2 PP4_Moderate PM2_Supporting

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Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The c.2944G>A (p.Val982Met) missense variant has been reported in at least three compound heterozygous probands with a phenotype highly specific to GT (PMID: 28983057, 25539746,15099289); one of which was a de novo occurrence (PMID: 25539746). It is found at an extremely low frequency (MAF of 0.00006486 in the non-Finnish European population from gnomAD). This variant is predicted by HSF and MaxEntScan to result in a broken splice donor site. Flow cytometry found that this variant had a marked deleterious effect on αIIbβ3 expression (~25% of control levels) in COS-7 cells (PMID: 15099289). In summary, this variant meets criteria to be classified as Pathogenic for GT. GT-specific criteria applied: PS2, PM3, PM2_supporting, PS3_Moderate, PP3, and PP4_moderate.

Met criteria codes

PP3 ✔

There is not consensus among pathogenicity predictors; SIFT predicts this variant to be Tolerated, Polyphen probably damaging, and MutationTaster Disease Causing Automatic. The CADD score is only 4.298917 and the REVEL score of 0.333 is below the >0.7 threshold. However, this variant occurs adjacent to an intron/exon boundary and both HSF (-30.45% variation) and MaxEntScan (-128.86% variation) agree that this variant results in a broken donor site.

PM3 ✔

This variant has been observed in compound heterozygotes; once with the splice variant c.1946+1G>A (classified as Pathogenic by the ClinGen Platelet Disorders VCEP), as well as with Glu538Ter (classified as Pathogenic by the ClinGen Platelet Disorders VCEP).

The proband was described to have triple heterozygosity with a maternally inherited pathogenic splice variant, c.1946+1G>A, in trans with both Val982Met and Ala958Thr, inherited paternally. However it was asserted that Ala989Thr was a polymorphism and Val982Met is the second variant of interest in this patient. 1pt PubMed:15099289

Case 37 is a compound heterozygote for this Val982Met variant and a c.2965del frameshift variant. No confirmation was reported that the variants are in trans phase. However, to avoid circularity the proband was counted only towards the classification of c.2965del not Val982Met. PubMed:28983057

GT-6 was described to have triple heterozygosity with a paternally inherited nonsense, Glu538Ter, pathogenic variant and both Val982Met and Ala958Thr occurring as de novo variants. However it was asserted that Ala989Thr was a polymorphism and Val982Met is the second variant of interest in this patient. No confirmation was reported that the variants are in trans phase. 0.5pt PubMed:25539746

PS3_Moderate ✔

The Val982Met substitution had a marked deleterious effect on αIIbβ3 expression (~25% of control levels) in COS-7 cells (PMID: 15099289).

COS-7 cells were transiently cotransfected with wild-type β3 cDNA and mutated or wild-type αIIb cDNA. The Val982Met (reported as V951M) substitution had a marked deleterious effect on αIIbβ3 expression (~25% of control levels). PubMed:15099289

PS2 ✔

This variant was found to occur de novo in one proband (PMID: 25539746). The individual is compound heterozygous with a pathogenic nonsense, Glu538Ter, variant provisionally classified as Pathogenic by the ClinGen Platelet Disorders VCEP.

This Val982Met variant was found to occur de novo in patient GT-6. It was not present in the father, mother, or brother of the patient. Paternity and maternity were confirmed. The individual is compound heterozygous with Glu538Ter (classified as Pathogenic by the ClinGen Platelet Disorders VCEP). 2pt PubMed:25539746

PP4_Moderate ✔

All three compound heterozygous probands reported in the literature meet the criteria for PP4_moderate; including mucocutaneous bleeding, impaired aggregation with all agonists except ristocetin, and reduced surface expression of αIIbβ3.

Patient J.V. has history of severe bruising and epistaxis with a normal to mildly elevated platelet count of (430–660×10^9 L−1). There is no aggregation in response to ADP, epinephrine or arachidonic acid, but a small residual response to collagen on two occasions. Ristocetin-induced agglutination was low-normal. Flow cytometry found an approximate 4% residual αIIbβ3 surface expression and Western blot analysis confirmed the presence of small amounts of residual αIIb heavy chain (αIIbH) and β3 in the patient's platelets. The patient was also diagnosed with type 1 VWD. PubMed:15099289

Case 37 had a ISTH-BAT score of 5 with a normal platelet count of 238x10^9/L. There was severely impaired platelet aggregation with TRAP, ADP, epinephrine, arachidonic acid, and collagen. Platelet aggregation with ristocetin was low-normal. There was undetectable GPIIb/IIIa platelet expression by flow cytometry and <20% agonist induced fibrinogen binding. PubMed:28983057

All GT patients from this study had a history of bleeding with normal platelet number and size. There was impaired aggregation to ADP and arachidonic acid but normal or only mildly reduced agglutination with ristocetin. On flow cytometry GT-6 was classified as type II GT (αIIbβ3 expression between 5% and 20%) and exhibited no binding of PAC-1 activation-specific anti- αIIbβ3 antibody upon stimulation with ADP or TRAP. PubMed:25539746

PM2_Supporting ✔

This variant occurs at an extremely low frequency (below the <1/10,000 threshold) with an overall allele frequency in gnomAD of 0.00003187 and a MAF of 0.00006486 (1/15418 alleles) in the non-Finnish European population.

Curation History

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