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Variant: NM_000419.4:c.526C>G

Version: 1.0

CA399805793

953000 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann's thrombasthenia (MONDO:0010119)
Inheritance Mode: Autosomal recessive inheritance
UUID: 81ad1388-e2c1-4808-a45b-a3a6439d1026
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HGVS expressions

NM_000419.4:c.526C>G
NC_000017.11:g.44385599G>C
CM000679.2:g.44385599G>C
NC_000017.10:g.42462967G>C
CM000679.1:g.42462967G>C
NC_000017.9:g.39818493G>C
NG_008331.1:g.8907C>G
ENST00000262407.6:c.526C>G
ENST00000262407.5:c.526C>G
ENST00000592944.1:n.211C>G
NM_000419.3:c.526C>G
NM_000419.5:c.526C>G

Pathogenic

Met criteria codes 6

PM3_Supporting PS3 PP1 PP3 PP4_Strong PM2_Supporting

Not Met criteria codes 1

PM5

Evidence Links 2

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The c.526C>G (p.Pro176Ala) variant has been reported, in the homozygous state, in at least one proband (PMID: 10607701) with a phenotype highly specific to GT. The variant cosegregated with disease in this proband and a sibling. Additionally two compound heterozygous cases have been reported (PMIDs: 10607701, 12083483). It is absent from Exac and gnomAD and multiple lines of computational evidence support a deleterious effect (REVEL score of 0.825). Expression of Pro176Ala in COS-1 and CHO cells demonstrated decreased surface expression and indicated the ability of αIIbβ3 to interact with immobilized fibrinogen was attenuated and abolished for soluble fibrinogen (PMID: 10607701). In summary, this variant meets criteria to be classified as Pathogenic for GT. GT-specific criteria applied: PS3, PM2_Supporting, PM3_Supporting, PP1, PP3, and PP4_Strong.

Met criteria codes

PM3_Supporting ✔

A homozygous proband was reported in PMID: 10607701. Additionally, this variant has been reported in trans with Ile405Thr and Arg977Ter (not included in this assessment to avoid circularity).

Patient MR is compound heterozygous for the Ile405Thr (reported as Ile374Thr) variant and Pro176Ala (reported as Pro145Ala). The variants were reported to have been confirmed to be in the trans phase. This variant is used as evidence to support PM3 for Ile405Thr, as such it is not used here to avoid a circular argument.
PubMed:12083483
PubMed:10607701

PS3 ✔

Expression of Pro176Ala in COS-1 and CHO cells demonstrated decreased surface expression and indicated that not only does mutation αIIbP176A attenuate the ability of αIIbβ3 to interact with immobilized fibrinogen, but it abolishes the ability of αIIbβ3 to bind soluble fibrinogen (PMID: 10607701).

Pro176Ala (reported here as Pro145Ala) was expressed in COS-1 cells with WT β3 and resulted in complexes without the heavy chain such that little αIIbβ3 was detectable on the surface of these cells by immunoprecipitation (neither flow cytometry or Western blotting was used to measure expression). Additionally, they stably expressed αIIbP145Aβ3 and wild-type αIIbβ3 in CHO cells and found 2.5-fold less spontaneous adhesion of immobilized fibrinogen, compared to WT, and little increase in adhesion following exposure to PT25-2 (which normally doubles adherence). For soluble fibrinogen; whereas there was substantial PT25-2–stimulated fibrinogen binding to cells expressing wild-type αIIbβ3, there was none to cells expressing αIIbP145Aβ3. These experiments indicate that not only does mutation of αIIbP145A attenuate the ability of αIIbβ3 to interact with immobilized fibrinogen, but it abolishes the ability of αIIbβ3 to bind soluble fibrinogen. PubMed:10607701

PP1 ✔

Two affected siblings, both homozygous, were reported in PMID: 10607701.

Two affected siblings, both homozygous, were reported as Patients LW and GW. PubMed:10607701

PP3 ✔

SIFT, PolyPhen, and MutationTaster agree that there is a deleterious effect caused by this variant; the revel score of 0.825 is greater than the >0.7 threshold.

PP4_Strong ✔

Patient MR of PMID: 12083483 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 MR has mucocutaneous bleeding including epistaxis (reported in the GT database), platelet aggregation was absent in response to ADP and epinephrine but normal for ristocetin. Surface expression was <10% as measured by flow cytometry. A normal platelet count was not reported. PubMed:12083483

The proband, Patient LW, meets all the GT criteria for PP4. There is a history of mucocutaneous bleeding, including epistaxis, purpura, and petechiae. The patient has a normal platelet count and the expected aggregation results; platelets fail to aggregate to thrombin, ADP, epinephrine, or collagen but agglutinate normally in the presence of ristocetin. Surface expression was reduced as measured by flow cytometry; with monoclonal antibodies specific for αIIb, β3, and αIIbβ3 revealed that they respectively bound ~10%, ~20%, and ~30%. Additionally platelets were unable to bind PAC-1 following platelet stimulation by phorbol myristate acetate. PubMed:10607701

PM2_Supporting	✔	This variant is absent from all population cohorts in gnomAD, ExAC, 1000 Genomes, and ESP.

Not Met criteria codes

PM5	✖	Two additional variants likely pathogenic variants 176Leu and 176His occur at the same amino acid residue as Pro176Ala, not included here to avoid circularity.

Curation History

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