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Variant: NM_000419.4:c.1214T>C

Version: 1.1

CA290950815

953004 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann's thrombasthenia (MONDO:0010119)
Inheritance Mode: Autosomal recessive inheritance
UUID: 07a984a0-d52d-4aab-b0dc-90af6f65f302
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HGVS expressions

NM_000419.4:c.1214T>C
NC_000017.11:g.44381058A>G
CM000679.2:g.44381058A>G
NC_000017.10:g.42458426A>G
CM000679.1:g.42458426A>G
NC_000017.9:g.39813952A>G
NG_008331.1:g.13448T>C
ENST00000262407.6:c.1214T>C
ENST00000648408.1:c.645T>C
ENST00000262407.5:c.1214T>C
ENST00000592226.5:n.454T>C
ENST00000592462.5:n.9T>C
NM_000419.3:c.1214T>C
NM_000419.5:c.1214T>C

Pathogenic

Met criteria codes 4

PP1_Moderate PP4_Strong PM2_Supporting PM3_Strong

Not Met criteria codes 2

PS3 PP3

Evidence Links 4

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The c.1214T>C (p.Ile405Thr) variant has been reported in at least four compound heterozygous probands (PMIDs: 12424194, 12083483, 24418945, 25728920) with a phenotype highly specific to GT. In one case the variant cosegregated with disease in the proband and two siblings (PMID: 12424194). It is absent from Exac and gnomAD. In summary, this variant meets criteria to be classified as Pathogenic for GT. GT-specific criteria applied: PM3_Strong, PM2_Supporting, PP1_Moderate, PP3 and PP4_Strong.

Met criteria codes

PP1_Moderate ✔

The Ile405Thr variant segregated with disease in the proband and two siblings (PMID: 12424194).

The maternally derived Ile405Thr variant segregated with disease in the proband (Patient C) and two siblings. PubMed:12424194

PP4_Strong ✔

This variant has been reported in at least 4 probands in the literature. At least two (PMIDs: 25728920, 12083483) meet 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 C was reported to have been diagnosed with GT based on "typical laboratory findings and clinical history". The details were not provided however some were available from the GT database (entry 71) including bleeding symptoms of bruising, gingival bleeding, and epistaxis. Aggregation in response to ADP was absent but no other agonists were reported. Expression was not measured by flow cytometry or Western blot but by immunoblot there was 10-50% GPIIb expression and surface expression by radiolabeled antibody was <10% GPIIb/GPIIIa. Normal platelet counts were not reported. PubMed:12424194

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

Patient GT74, a compound heterozygote, had a history of mucocutaneous bleeding (gingival bleeding, heavy bruising, GI bleeding, and melena) and a WHO bleeding score of 3. There was absent platelet aggregation with at least three agonists but normal ristocetin-induced aggregation. Severely reduced (<5%) platelet expression of alphaIIb-beta3 was confirmed by flow cytometry. No mention was made of normal platelet count. PubMed:25728920

The proband meets all the GT criteria. A normal platelet count is reported and bleeding phenotypes include epistaxis, gingivorrhagia, easy bruising, menorrhagia, bleeding after tooth extraction, haemorrhage after surgery and haemarthrosis. Aggregometry results showed failure of ADP, collagen and adrenalin to induce platelet aggregation, but ristocetin-induced platelet aggregation (RIPA) was normal. Platelet surface glycoprotein analysis by flow cytometry revealed a severe αIIbβ3 deficiency (<10% according to Glanzmann Thrombasthenia database record 325). PubMed:24418945

PM2_Supporting ✔

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

PM3_Strong ✔

This variant has been reported in the literature in a compound heterozygous state in at least four probands. The confirmed in trans variants of Cys705Arg and Pro176Ala are classified as Pathogenic by the ClinGen Platelet Disorders VCEP and meet the criteria to apply PM3_Strong with 2pt for this variant.

Patient C is compound heterozygous for the Ile405Thr (reported as Ile374Thr) variant derived from the mother and the Pathogenic variant Cys705Arg (reported as Cys674Arg) from the father. 1pt PubMed:12424194

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. Pro176Ala has been classified as Pathogenic by the ClinGen Platelet Disorders VCEP. 1pt PubMed:12083483

Patient GT74 is compound heterozygous for c.1214T>C (p.Ile405Thr) and Pathogenic variant c.1440-13_1440-1del, however confirmation of the trans phasing is not reported. However, to avoid circularity the proband was counted only towards the classification of c.1440-13_1440-1del not Ile405Thr. PubMed:25728920

The proband is reported to be compound heterozygous for c.1214T>C (p.Ile405Thr) and Pathogenic variant c.1234G>A (p.Gly412Arg) however confirmation of the trans phasing is not reported. However, to avoid circularity

the proband was counted only towards the classification of Gly412Arg not Ile405Thr. PubMed:24418945

Not Met criteria codes

PS3

Flow cytometry found that in transfected (Ile405Thr with WT ITGB3) 293T cells the expression of αIIbIle405Thr/β3 was 11% of control (PMID: 12424194). However, this evidence was not used to support PS3 at any level of strength because the level of αIIbβ3 cell surface expression was not measured, only whether cells were positive or negative for surface αIIbβ3. Other experiments reported in this publication (immunoprecipitation of αIIb in lysates from the transfected cells and pulse-chase analyses) also did not meet the requirements to apply PS3 at any level of strength.

Flow cytometry found that in transfected (I405T with WT ITGB3) 293T cells only 5% ± 3% of cells were positive for surface expression. They also performed IP and pulse-chase experiments to assess maturation; found only pro-αIIb subunits were detected, and only at the early time points, suggesting that they were retained in the endoplasmic reticulum and subsequently degraded. Function was not assessed. PubMed:12424194

PP3

REVEL score of 0.573 is below the threshold of >0.7

Curation History

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