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Variant: NM_000212.3:c.1871G>A

Version: 1.0

CA400032726

996162 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann's thrombasthenia (MONDO:0010119)
Inheritance Mode: Autosomal recessive inheritance
UUID: c881c2c9-1906-4660-83a4-6516d8673ba9
Approved on: 2020/11/10
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HGVS expressions

NM_000212.3:c.1871G>A
NC_000017.11:g.47299488G>A
CM000679.2:g.47299488G>A
NC_000017.10:g.45376854G>A
CM000679.1:g.45376854G>A
NC_000017.9:g.42731853G>A
NG_008332.2:g.50647G>A
ENST00000696963.1:c.1871G>A
ENST00000559488.7:c.1871G>A
ENST00000559488.5:c.1871G>A
ENST00000560629.1:c.1836G>A
NM_000212.2:c.1871G>A

Pathogenic

Met criteria codes 5

PP3 PM3 PP4_Strong PS3_Moderate PM2_Supporting

Evidence Links 4

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

NM_000212.3(ITGB3):c.1871G>A (p.Cys624Tyr) is a missense variant and has been reported in at least two probands in the literature who satisfy the diagnostic criteria for GT phenotype (PMIDs: 25728920, 22250950). This variant is absent from all major population cohorts (gnomAD, 1000 Genomes, ExAC). It has been predicted to be deleterious by multiple in silico tools (REVEL score = 0.951). Heterologous expression studies have demonstrated significantly reduced surface expression of αIIbβ3 (PMID: 11507099).This variant has been reported to occur in heterozygous state with two other variants (Leu222Pro and Arg242Ter) that have been classified as Pathogenic by ClinGen Platelet VCEP. This variant meets the GT specific criteria for PP4_strong, PS3_Moderate , PM3, PM2_Supporting, and PP3 and is therefore classified as Pathogenic.

Met criteria codes

PP3	✔	REVEL score = 0.951 which is above the GT specific threshold of 0.70 for PP3
PM3	✔	PMID:25728920 has reported this variant to be in compound heterozygosity with another missense variant p.Leu222Pro. However no information about the phase of these variants is available.The Leu222Pro variant has been classified as Pathogenic by ClinGen Platelet VCEP (phase unconfirmed) - 0.5 points. PMID: 22250950 has reported this variant in another non-related individual in compound heterozygozity with a nonsense variant, p.Arg242Stop (phase unconfirmed), which has been classified as Pathogenic by the ClinGen Platelet VCEP. 0.5 points. Total points = 0.5+0.5 = 1.0 points, and therefore PM3 is applied. PubMed:20438394 PubMed:22250950
PP4_Strong	✔	Patient GT9 had a history of moderate mucocutaneous bleeding, platelet aggregation was absent with three physiological agonists (but normal aggregation with ristocetin) and reduced (<5%) surface expression of αIIbβ3 demonstrated by flow cytometry. Sanger sequencing ensured coverage of exons and splice sites of the ITGA2B and ITGB3 genes as well as untranslated regions. PMID: 25728920 PP4_strong applied. PubMed:25728920
PS3_Moderate	✔	Chen et al, 2001 performed transfection studies using CHO cells. Flow cytometry showed reduced (~10%) surface expression of αIIbβ3. No disruption of protein function (reduced binding with fibrinogen or ligand mimetic antibodies like PAC-1) was demonstrated by the authors. (PMID: 11507099) PS3 is therefore applied at a moderate strength. Chen et al,2001 performed transfection studies using CHO cells. Flowcytometry showed reduced (~10%) surface expression of β3Cys598Tyr (β3Cys624Tyr) when compared with wildtype αIIbβ3 expression. Immunochemical analysis of the mutated receptors by SDS-PAGE and Western blot revealed a lower than normal electrophoretic mobility of β3 under nonreducing conditions, while their mobility was identical to wild type β3 under reducing conditions. Interestingly, this variant is found to be partially activating, allowing the spontaneous binding of the activation-dependent monoclonal antibody PAC-1 to transfected CHO. PS3 is therefore applied at moderate strength. PubMed:11507099
PM2_Supporting	✔	Absent from major population cohorts (gnomAD, 1000 Genomes, ExAC)

Curation History

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