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Variant: NM_000212.2:c.565C>T

Version: 1.0

CA291224669

812736 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann's thrombasthenia (MONDO:0010119)
Inheritance Mode: Autosomal recessive inheritance
UUID: fd701e2d-bd2e-4499-a8bf-f519215e51f0
Approved on: 2020/9/6
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HGVS expressions

NM_000212.2:c.565C>T
NC_000017.11:g.47284646C>T
CM000679.2:g.47284646C>T
NC_000017.10:g.45362012C>T
CM000679.1:g.45362012C>T
NC_000017.9:g.42717011C>T
NG_008332.2:g.35805C>T
ENST00000696963.1:c.565C>T
ENST00000559488.7:c.565C>T
ENST00000559488.5:c.565C>T
ENST00000560629.1:c.530C>T
ENST00000571680.1:c.565C>T
NM_000212.3:c.565C>T

Pathogenic

Met criteria codes 6

PS3_Moderate PM3_Strong PP4_Strong PM2_Supporting PP1 PP3

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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 NM_000212.2:c.565C>T (p.Pro189Ser) missense variant has been reported in at least three homozygotes and two compound heterozygous probands with phenotypes highly specific to GT (PMIDs: 31565851, 25728920, 24236036, 22250950). The variant has been shown to segregate in at least one family with two affected individuals (PMID: 31565851). This variant is at an extremely low frequency with a MAF of 0.00002638 in the South Asian population of gnomAD and multiple lines of computational evidence support a deleterious effect on the gene /gene product (REVEL score of 0.976). Pro189Ser has been expressed in CHO cells and found to have a 94% reduction in surface expression (PMID: 24236036). In summary, based on the available evidence at this time, the variant is classified as Pathogenic. GT-specific criteria applied: PS3_Moderate, PM2_Supporting, PM3_Strong, PP1, PP3, PP4_Strong.

Met criteria codes

PS3_Moderate	✔	In PMID: 24236036, the mutation was introduced into a β3 expression construct and transient expression in CHO cells was performed with co-expression of normal human αIIb. There was a 94% reduction in surface expression of the αIIbβ3 receptor in CHO cells expressing P163Sβ3 compared to those expressing WTβ3. The mutation was introduced into a β3 expression construct and transient expression in CHO cells was performed with co-expression of normal human αIIb. There was a 94% reduction in surface expression of the αIIbβ3 receptor in CHO cells expressing P163Sβ3 compared to those expressing WTβ3, measured by flow cytometry. PubMed:24236036
PM3_Strong	✔	This variant has been reported in two homozygotes and two compound heterozygotes with pathogenic variant c.2113del and likely pathogenic variant Cys210Ser. PubMed:31565851 PubMed:25728920
PP4_Strong	✔	At least three probands have been reported with this variant that meet the criteria for PP4; including mucocutaneous bleeding, impaired aggregation with all agonists except ristocetin, and reduced surface expression of αIIbβ3. At least one (PMID: 25728920) meets criteria for PP4_strong as ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries. PubMed:22250950 PubMed:24236036
PM2_Supporting	✔	This variant is at an extremely low frequency (below the <1/10,000 threshold) with an overall allele frequency from gnomAD of 0.00001193 and MAF of 0.00002638 (3/113,730 alleles) in the South Asian population.
PP1	✔	The proband and affected brother share the compound heterozygous genotype of Pro189Ser and Cys210Ser (PMID: 31565851).
PP3	✔	SIFT (Damaging), Polyphen2-HDIV 1 (probably Damaging), and Mutation Taster (disease causing) agree that this variant has a deleterious effect and the REVEL score is 0.976, above the >0.7 threshold.

Curation History

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