The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000212.2:c.2113del

Version: 1.0

CA8623443

953051 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann's thrombasthenia (MONDO:0010119)
Inheritance Mode: Autosomal recessive inheritance
UUID: 655285f6-312a-42c6-a721-9f9a8fa8843f
Approved on: 2020/9/6
Published on: 2021/1/28

HGVS expressions

NM_000212.2:c.2113del
NC_000017.11:g.47302819del
CM000679.2:g.47302819del
NC_000017.10:g.45380185del
CM000679.1:g.45380185del
NC_000017.9:g.42735184del
NG_008332.2:g.53978del
ENST00000696963.1:c.2113del
ENST00000559488.7:c.2113del
ENST00000559488.5:c.2113del
ENST00000560629.1:c.2078del
NM_000212.3:c.2113del

Pathogenic

Met criteria codes 5

PVS1 PP4_Strong PP1_Strong PM2_Supporting PM3

Evidence Links 3

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The frameshift variant NM_000212.2:c.2113del results in the creation of a premature stop codon in exon 13 of 15, which is expected to result in NMD. It occurs at an extremely low allele frequency with a MAF of 0.0000932 in the East Asian population on gnomAD. It has been reported in at least 4 homozygotes and three compound heterozygous patient with a phenotype highly specific to GT, as well as at least 7 family members (PMIDs: 31088191, 30792900, 25728920). In summary, based on the available evidence at this time, the variant is classified as Pathogenic. GT-specific criteria applied: PVS1, PM2_Supporting, PM3, PP1_Strong, PP4_Strong.

Met criteria codes

PVS1 ✔

This frameshift variant occurs in exon 13 of 15 where it generates a premature stop codon, which is expected to result in NMD.

PP4_Strong	✔	At least one proband been reported (PMID: 25728920) with this variant that 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.
PP1_Strong	✔	There are a minimum of 7 segregations across 2 families with affected individuals homozygous for this variant (PMID: 30792900).
PM2_Supporting	✔	This variant is at an extremely low frequency (below the <1/10,000 threshold) with an overall allele frequency from gnomAD of 0.000007955 and MAF of 0.0001087 (2/18,394 alleles) in the East Asian population of gnomADv2.1.1 plus an additional 3,052 East asian alleles not carrying the variant in gnomADv3 for an overall MAF of 0.0000932.
PM3	✔	At least four homozygous probands have been reported (PMID: 30792900). An additional three compound heterozygotes have not been included here to avoid circularity.

PubMed:31088191
PubMed:30792900
PubMed:25728920

Curation History

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