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_000212.3:c.777+1G>A

Version: 1.0

CA8623036

850886 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann's thrombasthenia (MONDO:0010119)
Inheritance Mode: Autosomal recessive inheritance
UUID: e4899cc1-99c5-43c2-9c95-ac0668ade48f
Approved on: 2021-03-05
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HGVS expressions

NM_000212.3:c.777+1G>A
NC_000017.11:g.47286423G>A
CM000679.2:g.47286423G>A
NC_000017.10:g.45363789G>A
CM000679.1:g.45363789G>A
NC_000017.9:g.42718788G>A
NG_008332.2:g.37582G>A
ENST00000559488.7:c.777+1G>A
ENST00000559488.5:c.777+1G>A
ENST00000560629.1:n.742+1G>A
ENST00000571680.1:c.777+1G>A
NM_000212.2:c.777+1G>A

Pathogenic

Met criteria codes 3

PVS1 PP4_Strong PP1

Not Met criteria codes 3

PM2 PM3 PP3

Evidence Links 0

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.777+1G>A is a canonical splice donor variant which is predicted to cause skipping of exon 5, with a frameshift resulting in NMD. It has been reported to occur in one homozygous and one compound heterozygous proband, and at least one of those individuals satisfies clinical and laboratory criteria for GT phenotype (PMID: 25728920). This variant was reported to co-segregate in at least two affected members of a family (PMID: 25728970). This variant meets GT specific criteria for PVS1, PP4_strong, and PP1 and is therefore classified as Pathogenic.

Met criteria codes

PVS1	✔	c.777+1G>A is a canonical splice donor variant which is predicted to cause skipping of exon 5 of 15, causing a frameshift with a premature stop codon in exon 6, leading to NMD.
PP4_Strong	✔	This variant has been reported in 3 probands by PMID 25728920. And at least one proband (GT30) meets criteria for PP4_Strong - which includes history of significant mucocutaneous bleeding, absent platelet aggregation with physiological agonists except ristocetin, flowcytometric demonstration of reduced (<5%)surface expression of αIIbβ3 expression. Sanger sequencing was done to ensure full coverage of all exons and intron of the IGTB3 and ITGA2B genes. (PMID:25728920) PP4_strong applied
PP1	✔	c.777+1G>A variant has been reported to segregate in one proband (GT35a) plus one affected relative (sister - GT35b) in PMID 25728920. Both siblings are compound heterozygous for c.777+1G>A and Arg131Pro. Meets criteria for PP1_supporting.

Not Met criteria codes

PM2	✖	Although the overall allele frequency in gnomAD is 0.00008560 (24/280376), the MAF in the Latino subpopulation is 0.0006774 (24/35432), which is above the threshold of <0.01%. Therefore, PM2_supporting is not met.
PM3	✖	The c.777+1G>A variant was reported in two probands in PMID:25728920, one in the homozygous state (GT30) and one in the compound heterozygous state (GT35a) along with a missense variant (p.Arg131Pro). PM3 cannot be applied here because PM2_supporting is not met.
PP3	✖	Multiple insilico splicing tools(maxentscan,spliceAI) predict this variant to cause disruption of the canonical splice donor site and exon 5 skipping. However since PVS1 has been applied, PP3 is not applied here.

Curation History

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