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_000419.4:c.3060+2T>C

Version: 1.0

CA290944108

627296 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann's thrombasthenia (MONDO:0010119)
Inheritance Mode: Autosomal recessive inheritance
UUID: 87ce3bc8-52e8-4b5a-bc39-f9db1ce33a75
Approved on: 2020-09-04
Published on: 2021-08-20

HGVS expressions

NM_000419.4:c.3060+2T>C
NC_000017.11:g.44374352A>G
CM000679.2:g.44374352A>G
NC_000017.10:g.42451720A>G
CM000679.1:g.42451720A>G
NC_000017.9:g.39807246A>G
NG_008331.1:g.20154T>C
ENST00000262407.6:c.3060+2T>C
ENST00000648408.1:c.2374+307T>C
ENST00000262407.5:c.3060+2T>C
ENST00000587295.5:c.253+1481T>C
ENST00000588098.1:c.37+307T>C
ENST00000592462.5:n.2761T>C
NM_000419.3:c.3060+2T>C
NM_000419.5:c.3060+2T>C

Pathogenic

Met criteria codes 4

PP4_Strong PVS1_Strong PM2_Supporting PM3_Supporting

Evidence Links 0

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The NM_000419.4:c.3060+2T>C variant is a splice site variant that causes aberrant splicing and results in the deletion of 38 amino acids in the transmembrane domain (PMID: 9215749). It is present in a very low frequency in gnomAD (0.00003876). It is seen in four individuals in the compound heterozygous state in the published literature. In summary, based on the available evidence at the time the c.3060+2T>C variant is classified as pathogenic. GT-specific criteria applied: PVS1_Strong, PM2_Supporting, PP4_Strong, PM3_Supporting.

Met criteria codes

PP4_Strong	✔	Compound heterozygous individual, GT9, from PMID: 25373348 meets criteria for PP4_strong with bleeding symptoms, impaired platelet aggregation in response to collagen, ADP, AA, adrenaline, epinephrine but near-normal response to ristocetin. Western blotting and flow cytometry revealed reduced integrin expression. Full sequencing of both ITGA2B and ITGB3 was performed. [1 unpublished individual heterozygous for this variant from internal laboratory data, does not meet PP4: 10yo female with history of easy bruising, gingival bleeding, iron deficiency anemia and seizure. She had an inconsistently high PFA but never with both epinephrine and ADP being abnormal at the same draw. Platelet count, PT, aPTT, and VWF studies were normal. Decreased expression levels of αIIbβ3 observed on flow cytometry, consistent with heterozygous state. The individual was tested with the "platelet function disorder" panel.]
PVS1_Strong	✔	The variant results in alternative splicing and an in-frame deletion of 38 amino acids in the transmembrane domain which is critical to protein function (PMID: 25617834).
PM2_Supporting	✔	The variant is reported in 5/128992 non-Finnish European alleles, at a frequency of 0.00003876 in gnomAD. This is lower than the threshold of <1/10000 alleles and meets PM2.
PM3_Supporting	✔	The variant is seen in trans with Cys705Arg (classified as Pathogenic by the ClinGen Platelet Disorders VCEP, 0.5pt), c.3092_3093dup (not considered here to avoid circularity), Ile596Thr (classified as VUS, does not meet PM2 0pt) and Asp396Asn (not included to avoid circularity) in four unrelated probands. A total of 0.5 pts is applied that meets PM3_Supporting.

Curation History

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