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Variant: NM_000419.5:c.2374del

Version: 1.0

CA915940267

1879050 (ClinVar)

Gene: ITGA2B (HGNC:3674)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: b77bdc24-e8dd-45ca-b3c9-461c30d877ee
Approved on: 2022/4/7
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HGVS expressions

NM_000419.5:c.2374del
NC_000017.11:g.44376160del
CM000679.2:g.44376160del
NC_000017.10:g.42453528del
CM000679.1:g.42453528del
NC_000017.9:g.39809054del
NG_008331.1:g.18347del
ENST00000262407.6:c.2374del
ENST00000648408.1:c.1805del
ENST00000262407.5:c.2374del
ENST00000587295.5:c.26del
ENST00000592462.5:n.1169del
NM_000419.3:c.2374del
NM_000419.4:c.2374del

Pathogenic

Met criteria codes 4

PM2_Supporting PVS1 PM3_Supporting PP4_Strong

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_000419.5(ITGA2B):c.2374del (p.Val792TrpfsTer34) frameshift variant leads to to a premature stop codon in biologically-relevant-exon 25/30 and is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). At least one patient (Patient GT1 in PMID:25373348) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia. Additionally, αIIbβ3 surface expression was severly reduced, as measured by flow cytometry while αIIb was absent on Western blot and β3 was decreased. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries (PP4_strong). GT1 of PMID: 25373348 is homozygous for c.2374del (PM3_supporting). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). In summary, this variant meets the criteria to be

classified as Pathogenic for autosomal recessive Glanzmann Thrombasthenia based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PVS1, PP4_strong, PM2_supporting, PM3_supporting. (VCEP specifications version 2; date of approval 01/18/2022)

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PVS1	✔	The c.2374del variant in exon 24 causes the p.Val792TrpfsTer34 frameshift variant leading to a premature stop codon in biologically-relevant-exon 25/30 and is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PM3_Supporting	✔	GT1 of PMID: 25373348 is homozygous for c.2374del (parents confirmed carriers). 0.5pt
PP4_Strong	✔	At least one patient (Patient GT1 in PMID:25373348) with this variant displayed mucocutaneous bleeding and impaired aggregation with all agonists except ristocetin, which is highly specific for Glanzmann thrombasthenia. Additionally, αIIbβ3 surface expression was severly reduced, as measured by flow cytometry while αIIb was absent on Western blot and β3 was decreased. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries. (PP4_strong)

Curation History

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