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Variant: NM_000212.3(ITGB3):c.727G>C (p.Asp243His)

Version: 2.0

CA400023600

800945 (ClinVar)

Gene: ITGB3 (HGNC:3690)
Condition: Glanzmann thrombasthenia (MONDO:0100326)
Inheritance Mode: Autosomal recessive inheritance
UUID: 712094bd-7187-4f2b-bc0f-90c0275d5d2f
Approved on: 2024/8/20
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HGVS expressions

NM_000212.3(ITGB3):c.727G>C (p.Asp243His)
NM_000212.3:c.727G>C
NC_000017.11:g.47286372G>C
CM000679.2:g.47286372G>C
NC_000017.10:g.45363738G>C
CM000679.1:g.45363738G>C
NC_000017.9:g.42718737G>C
NG_008332.2:g.37531G>C
ENST00000696963.1:c.727G>C
ENST00000559488.7:c.727G>C
ENST00000559488.5:c.727G>C
ENST00000560629.1:c.692G>C
ENST00000571680.1:c.727G>C
NM_000212.2:c.727G>C

Likely Pathogenic

Met criteria codes 4

PP1_Moderate PM2_Supporting PM3 PP3

Not Met criteria codes 2

PM5 PP4

Evidence Links 0

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Platelet Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2.1*
PDF
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The ITGB3 missense variant NM_000212.3:c.727G>C replaces the aspartic acid residue with a histidine residue (p.Asp243His). The highest population minor allele frequency in gnomAD v4.0 is 0.000002856 (1/350098 alleles) in the European (non-Finnish) population, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting). This variant has been observed in homozygosity in three probands

(PM3) suspected to have Glanzmann's thrombasthenia (GT) (GT-11 and GT-15 in PMID: 30792900; Case 19 in PMID: 32680510), as well as two affected family members of GT-15 (PP1_moderate). However sufficient information to confirm if the individuals' phenotypes (or the phenotype of any affected family member) were specific for GT was not provided. In silico tools predict the variant is damaging to protein function; REVEL score of 0.983 is above the >.0.7 threshold to support a deleterious effect (PP3). In summary, this variant meets criteria to be classified as likely pathogenic for GT. GT-specific criteria applied: PP1_moderate, PM3, PP3, PM2_supporting.

Met criteria codes

PP1_Moderate	✔	This variant was observed in homozygosity in a proband (GT-15 in PMID: 30792900) and two affected family members (also in homozygosity; FAM-03 GT-16 and GT-17 in PMID: 30792900).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.0 is 0.000002856 (1/350098 alleles) in the European (non-Finnish) population, which is lower than the ClinGen PD VCEP threshold (<0.0001; PM2_Supporting).
PM3	✔	This variant has been observed in homozygosity in at least two probands (GT-11 and GT-15 in PMID: 30792900). Each occurrence earns 0.5 points, which is sufficient to apply PM3.
PP3	✔	REVEL score of 0.983 is above the >.0.7 threshold to support a deleterious effect.

Not Met criteria codes

PM5	✖	A different missense change at this amino acid residue (c.728A>T, p.Asp243Val) has been reported in a Glanzmann thrombasthenia patient (PMID: 18832906). However this evidence was not counted toward the interpretation of the c.727G>C variant to avoid circularity.
PP4	✖	This variant has been observed in at least two probands with a previous history of Glanzmann's thrombasthenia (GT-11 and GT-15 in PMID: 30792900), but sufficient platelet aggregation and surface protein expression information was not provided to apply PP4 at any strength level.

Curation History

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