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Variant: NM_000173.7(GP1BA):c.1620G>A (p.Trp540Ter)

Version: 1.0

CA116663

4157 (ClinVar)

Gene: GP1BA (HGNC:2811)
Condition: Bernard-Soulier syndrome (MONDO:0009276)
Inheritance Mode: Autosomal recessive inheritance
UUID: 315ba369-6ff6-45a0-b82a-1532bf01de7f
Approved on: 2025/9/4
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HGVS expressions

NM_000173.7(GP1BA):c.1620G>A (p.Trp540Ter)
NM_000173.7:c.1620G>A
NC_000017.11:g.4934224G>A
CM000679.2:g.4934224G>A
NC_000017.10:g.4837519G>A
CM000679.1:g.4837519G>A
NC_000017.9:g.4778260G>A
NG_008767.2:g.6930G>A
ENST00000329125.6:c.1620G>A
ENST00000649830.1:c.-888+118C>T
ENST00000329125.5:c.1620G>A
ENST00000611961.1:c.1542G>A
NM_000173.6:c.1620G>A

Pathogenic

Met criteria codes 6

PP4 PM3 PVS1_Strong PM2_Supporting PS3_Supporting PP1_Strong

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 for GP1BA Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The c.1620G>A (p.Trp540Ter) variant in GP1BA is a nonsense variant that may cause a premature stop codon that is predicted to escape nonsense mediated decay. However the truncation includes the functionally important transmembrane domain (removes amino acids 540-553) in a gene where loss-of-function is an established disease mechanism (PVS1_Strong; PMID:9639514). The Grpmax Filtering allele frequency in gnomAD v4.1.0 is 0.000009540 (based on 18/1179684 alleles) in the European (non-Finnish) population, which is lower than the ClinGen PD VCEP threshold (<0.0001114; PM2_Supporting). Surface expression of GP1a measured by flow cytometry in CHO cells

transiently co-transfected with the p.Trp540Ter variant in GP1a and wild type GP1b, and GP9 was barely detectable compared to controls, indicating that this variant impacts protein function (PMID:9639514)(PS3_supporting). This variant has been detected in at least 6 individuals with Bernard-Soulier syndrome. At least one individual had excessive mucocutaneous bleeding and macrothrombocytopenia and absent expression of GPIba measured by flow cytometry (PP4 - PMID:25370924). Two of those individuals were homozygous for this variant (PMID:25370924, 9233564). Two individuals were compound homozygous for this variant and the p.Cys81Arg variant and confirmed in trans by family testing, but was used for that curation (PMID:25370924). Another proband (different publication and authorship) was compound homozygous for this variant and the p.Cys81Arg variant and confirmed in trans by family testing, but was used for this curation (PMID: 9639514) for a total of 2 points (PM3). The variant has been reported to segregate in a homozygous proband plus 2 compound heterozygotes (PMID:25370924) and a proband plus 1 additional compound heterozygous affected sibling (PMID: 9639514) meeting PP1_strong. In summary, this variant meets the criteria to be classified as pathogenic for Bernard-Soulier syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: PVS1_strong, PM3, PP4, PP1_moderate, PM2_supporting, PS3_supporting (Platelet VCEP GP1BA specifications version 1).

Met criteria codes

PP4	✔	At least one patient (Kalstad homozygote in PMID:25370924) with this variant had absent (< less than 10%) expression of GPIba measured by flow cytometry, which is highly specific for Bernard-Soulier syndrome. Additionally, the patient had excessive mucocutaneous bleeding and macrothrombocytopenia which are consistent with Bernard-Soulier syndrome (PP4).
PM3	✔	This variant has been detected in at least 5 probands with Bernard-Soulier syndrome. Two of those individuals were homozygous for this variant (1 point). Two probands were compound homozygous for this variant and the p.Cys81Arg variant and confirmed in trans by family testing, but was used for the p.Cys81Arg curation so not used for this curation (0 points). Another proband (different publication and authorship) was compound homozygous for this variant and the p.Cys81Arg variant and confirmed in trans by family testing, but was used for this curation and not used for the p.Cys81Arg curation (1 point). Total points: 2 (PM3).
PVS1_Strong	✔	The c.1620G>A (p.Trp540Ter) variant in GP1BA is a nonsense variant that may cause a premature stop codon that is predicted to escape nonsense mediated decay. However the truncation includes the functionally important transmembrane domain (removes amino acids 540-553) in a gene where loss-of-function is an established disease mechanism (PVS1_Strong; PMID:9639514).
PM2_Supporting	✔	The Grpmax Filtering allele frequency in gnomAD v4.1.0 is 0.000009540 (based on 18/1179684 alleles) in the European (non-Finnish) population, which is lower than the ClinGen PD VCEP threshold (<0.0001114; PM2_Supporting).
PS3_Supporting	✔	Surface expression of GP1a measured by flow cytometry in CHO cells transiently co-transfected with the p.Trp540Ter variant in GP1a and wild type GP1b, and GP9 was barely detectable compared to controls, indicating that this variant impacts protein function (PMID:9639514)(PS3_supporting).
PP1_Strong	✔	The variant has been reported to segregate in a homozygous proband plus 2 compound heterozygotes and 7 additional heterozygous relatives with macrothrombocytopenia that were not scored due to lack of data for each heterozygote (2 points: PMID:25370924). The variant has also been reported to segregate in a proband plus 1 additional compound heterozygous BSS affected sibling (1 point: PMID: 9639514). Total segregation pts: 3 pts.

Curation History

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