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_000174.5(GP9):c.466G>A (p.Ala156Thr)

Version: 1.0

CA202222

196227 (ClinVar)

Gene: GP9 (HGNC:2815)
Condition: Bernard-Soulier syndrome (MONDO:0009276)
Inheritance Mode: Autosomal recessive inheritance
UUID: 05e16eb5-5bb2-4243-b0b3-5cc2381f8cf5
Approved on: 2025-02-11
Published on: 2025-02-17

HGVS expressions

NM_000174.5:c.466G>A
NM_000174.5(GP9):c.466G>A (p.Ala156Thr)
NC_000003.12:g.129062205G>A
CM000665.2:g.129062205G>A
NC_000003.11:g.128781048G>A
CM000665.1:g.128781048G>A
NC_000003.10:g.130263738G>A
NG_008715.1:g.6404G>A
ENST00000307395.5:c.466G>A
ENST00000307395.4:c.466G>A
NM_000174.4:c.466G>A

Benign

Met criteria codes 3

BA1 PS3_Supporting BP4

Not Met criteria codes 4

PP4 PM3 BS2 BP2

Evidence Links 1

Expert Panel

Platelet Disorders VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Platelet Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GP9 Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Platelet Disorders VCEP

The c.466G>A (p.Ala156Thr) variant in GP9 is a missense variant predicted to cause substitution of alanine by threonine at amino acid 156. At least one patient (Case in PMID:15351858 or internal) with this variant had aggregation absent for ristocetin and present for all other agonists, which is highly specific for Bernard-Soulier syndrome. Additionally, the patient had excessive mucocutaneous bleeding and macrothrombocytopenia which is consistent with Bernard-Soulier syndrome, however this variant has a Grpmax Filtering allele frequency in gnomAD v4.1 is 0.2194 (based on 9530/42710 alleles) in the East Asian population, which is higher than the ClinGen PD VCEP threshold (>0.001), and therefore meets this criterion (BA1). The computational predictor REVEL gives a score of 0.187, which is below the ClinGen PD VCEP threshold of <0.290 and predicts no damaging effect on GP9 function and splicing predictor SpliceAI predicts no impact on

splicing with delta scores of 0.00 (BP4). Surface expression of GPIBa and GP9 measured by flow cytometry in CHO cells in cells transiently co-transfected with the c.466G>A variant and wild type GP1a and GP1b showed decreased expression at very low (<25%) WT levels, indicating that this variant impacts protein function (PMID:15351858)(PS3_supporting). In summary with BP4 (-1), BA1, PS3_supporting (+1), the other criteria cancel out and BA1 alone provides a Benign classification, ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP.

Met criteria codes

BA1 ✔

The Grpmax Filtering allele frequency in gnomAD v4.1 is 0.2194 (based on 9530/42710 alleles) in the East Asian population, which is higher than the ClinGen PD VCEP threshold (>0.001), and therefore meets this criterion (BA1).

PS3_Supporting ✔

Surface expression of GPIBa and GP9 measured by flow cytometry in CHO cells in cells transiently co-transfected with the c.466G>A variant and wild type GP1a and GP1b showed decreased expression at very low (<25%) WT levels, indicating that this variant impacts protein function (PMID:15351858)(PS3_supporting).

Surface expression of [GP1a, GP1b, and/or GP9] measured by [flow cytometry/Western blot] in CHO cells in cells transiently co-transfected with the p.Ala156Thr variant GP9 and wild type GP1a and GP1b showed decreased expression at XX% (<25%) WT levels, indicating that this variant impacts protein function (PMIDs)(PS3_supporting). PubMed:15351858

BP4 ✔

The computational predictor REVEL gives a score of 0.187, which is below the ClinGen PD VCEP threshold of <0.290 and predicts no damaging effect on GP9 function and splicing predictor SpliceAI predicts no impact on splicing with delta scores of 0.00 (BP4).

Not Met criteria codes

PP4 ✖

At least one patient (Case in PMID:15351858) with this variant had aggregation absent for ristocetin and present for all other agonists, which is highly specific for Bernard-Soulier syndrome (PP4). Additionally, the patient had excessive mucocutaneous bleeding and macrothrombocytopenia which is consistent with Bernard-Soulier syndrome. This is not considered here because BA1 is met.

PM3 ✖

Not evaluated for variants meeting BA1 or BS1.

BS2 ✖

This variant has been observed in 1 homozygous individual who is unaffected with Bernard Soulier Syndrome (proven with flow cytometry and normal platelet count and normal platelet size), a condition with high penetrance at an early age (PMID:20497174) Because the group threshold is >1 unaffected probands, this criteria is not met. CONFIRM HOMOZYGOSITY - CONFLICTING INFO IN PAPER

BP2 ✖

This variant has been observed in cis with the variant c.450G>A (p.Trp150Ter) (PMID:20497174) which is classified as likely pathogenic by the ClinGen PD VCEP in an individual with Bernard-Soulier syndrome. The phase of the variants was confirmed by parental/family testing. Because p.Trp150Ter is not classified as pathogenic, this criteria is not met.

Curation History

Showing 1 to 1 of 1 rows