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Variant: NM_000407.5:c.439T>A

Version: 1.2

CA410677511

Gene: GP1BB (HGNC:2812)
Condition: Bernard-Soulier syndrome (MONDO:0009276)
Inheritance Mode: Autosomal recessive inheritance
UUID: fc507081-3d5a-4b36-8128-048f109aef1a
Approved on: 2025/2/18
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HGVS expressions

NM_000407.5:c.439T>A
NC_000022.11:g.19724282T>A
CM000684.2:g.19724282T>A
NC_000022.10:g.19711805T>A
CM000684.1:g.19711805T>A
NC_000022.9:g.18091805T>A
NG_007974.1:g.5740T>A
ENST00000366425.4:c.439T>A
ENST00000366425.3:c.439T>A
ENST00000431044.5:c.*1524T>A
NM_000407.4:c.439T>A
NR_037611.1:n.4179T>A
NR_037612.1:n.2683T>A

Likely Pathogenic

Met criteria codes 6

BS3_Supporting PP3 PP4 PM1 PM3 PM2_Supporting

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 GP1BB Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The variant NM_000407.5(GP1BB):c.439T>A (p.Cys147Ser) has been found in at least one individual with Bernard-Soulier syndrome. This patient (PMID:16978236) is compound heterozygous for this variant inherited from the father and c.448del inherited from the mother (PM3). He had aggregation absent for ristocetin and present for all other agonists, which is highly specific for Bernard-Soulier syndrome (PP4). Additionally, the patient had reduced GP1ba, GPIbb, and GPIX platelet expression and macrothrombocytopenia which is consistent with Bernard-Soulier syndrome. The variant is absent from gnomADv4.1 (PM2_supporting). The computational predictor REVEL gives a

score of 0.687, which is above the ClinGen PD VCEP PP3 threshold of >0.644 and predicts a damaging effect on GP1BB function (PP3). This variant resides at a disulfide bond residue, Cys147, of GP1BB that is defined as a critical functional domain by the ClinGen PD VCEP (PM1). However, with stable transfection in CHO cells this variant caused elimination of the GPIbb-GPIba disulfide linkage did not significantly affect GPIb/IX surface expression or the binding of soluble vWF to the GPIb/IX transfected CHO cells (PMID: 16978236; BS3_supporting). In summary, this variant meets the criteria to be classified as Likely Pathogenic for autosomal recessive Bernard-Soulier syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen PD VCEP: BS3_supporting, PP3, PM1, PM2_supporting, PM3 and PP4.

Met criteria codes

BS3_Supporting ✔

The wild-type GPIba or mutant GPIbb cDNA construct was transiently cotransfected with wild-type GPIba and GPIX cDNA constructs into 293T cells. The expression of GPIbb Ser1247 (referred to here as Ser122) polypeptide was similar to WT. Next, total expression of the recombinant GPIbb protein and the formation of disulfide bonds between GPIba and GPIbb in the transfected cells were investigated by immunoblot analysis. Only a small molecular weight band, corresponding to the individual GPIbb subunit, indicating there was not inter subunit disulfide bond. Chinese hamster ovary cells stably expressing GPIba/Ibb Ser147/IX were surface labeled and immunoprecipitated, resulting in equal precipitation with WT and localized to the cell membrane similar to WT. It also had the ability to bind soluble vWF, measured by flow cytometry, and to aggregate in the presence of ristocetin. These results suggest that despite disruption of the disulfide linkage between GPIba and GPIbb, GPIb/IX is formed. In summary, elimination of the GPIbb-GPIba disulfide linkage by the mutation C147S did not significantly affect GPIb/IX surface expression or the binding of soluble vWF to the GPIb/IX transfected CHO cells (PMID: 16978236; BS3_supporting). While the expression level of GPIb/IX on the patient's platelets was greatly decreased, the experiments in vitro demonstrated significant expression of GPIba/IbbSer122/IX on the surface of transfected cells. This discrepancy may be explained in part by the use of a forced-expression system with a eukaryotic expression vector, in which transcription is greatly exaggerated. Alternatively, and in the context of a mature megakaryocyte, the GPIbb Ser122 molecule may be more unstable and rapidly degraded. Pulse-chase experiments should clarify the biosynthesis and fate of the mutant GPIb/IX complex and explain the discrepancy

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PP3 ✔

The computational predictor REVEL gives a score of 0.687, which is above the ClinGen PD VCEP PP3 threshold of >0.644 and predicts a damaging effect on GP1BB function. And the computational splicing predictor SpliceAI indicated that the variant has no predicted impact on splicing.

PP4 ✔

At least one patient (Proband in PMID:16978236) 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 macrothrombocytopenia which is consistent with Bernard-Soulier syndrome.

PM1 ✔

This variant resides at a disulfide bond residue, Cys147, of GP1BB that is defined as a critical functional domain by the ClinGen PD VCEP (PM1).

PM3 ✔

This variant has been found in at least one individual with BSS. This individual was compound heterozygous for this variant and the frameshift, c.448del, classified Likely Pathogenic. This variant was confirmed to be in trans via parental testing (1 point, PM3).

PM2_Supporting ✔ Variant is absent from gnomADv4.1

Curation History

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