

Variant: *NM_000419.4:c.2113T>C*

Version: 1.0

CA8602816 [↗](#)

953058 (ClinVar) [↗](#)

Gene: ITGA2B ([HGNC:3674](#))

Condition: Glanzmann's thrombasthenia ([MONDO:0010119](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 7aedd940-ac73-454f-a226-ca36dee0f6c2

Approved on: 2020/9/6

Published on: 2021/1/22

HGVS expressions

NM_000419.4:c.2113T>C

NC_000017.11:g.44377772A>G

CM000679.2:g.44377772A>G

NC_000017.10:g.42455140A>G

CM000679.1:g.42455140A>G

NC_000017.9:g.39810666A>G

NG_008331.1:g.16734T>C

ENST00000262407.6:c.2113T>C

ENST00000648408.1:c.1544T>C

ENST00000262407.5:c.2113T>C

ENST00000592462.5:n.908T>C

NM_000419.3:c.2113T>C

NM_000419.5:c.2113T>C

Pathogenic

Met criteria codes **5**

PM3_Strong

PP3

PP4_Strong

PP1_Moderate

PM2_Supporting

Not Met criteria codes **1**

PS3

Evidence Links **7**

Expert Panel

Platelet Disorders VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

Platelet Disorders VCEP

The c.2113T>C (p.Cys705Arg) variant has been reported in at least 7 probands (3 homozygotes and 4 compound heterozygotes; PMIDs: 20020534, 12424194, 12083483, 25728920, 25539746, 9920835); at least two with a phenotype highly specific to GT (PMIDs: 9920835, 25539746). The variant cosegregated with disease in one of these probands and two additional relatives (PMID: 12424194). The variant is found at an extremely low frequency, with an the overall allele frequency on gnomAD is 0.000003977 (1/113,742 alleles in the non-Finnish European population). Multiple lines of computational evidence support a deleterious effect on the gene/gene product (REVEL score of 0.878). Expression in CHO cells was strongly attenuated, shown by immunoprecipitation and flow cytometry (~70% reduction), in cells

coexpressing normal GPIIb. In summary, this variant meets criteria to be classified as Pathogenic for GT. GT-specific criteria applied: PM2_Supporting, PM3_Strong, PP1_Moderate, PP3, and PP4_Strong.

Met criteria codes

PM3_Strong



At least 3 homozygotes (1pt) have been reported in the literature as well as 4 compound heterozygotes. The in trans variants include pathogenic c.624+2C>A (1pt), as well as c.1440-13_1440-1del, Ile405Thr and c.3060+2T>C (which were not included in the evaluation of this variant to avoid circularity).

Patient GT-3 is homozygous for Cys705Arg (reported as Cys674Arg). [PubMed:25539746](#)

GT49 is compound heterozygous for c.1440-13_1440-1del and Cys705Arg. Phase not confirmed. This Cys705Arg variant is used in the assessment of c.1440-13_1440-1del so will not be used here to avoid a circular argument.

[PubMed:25728920](#)

Three GT patients were identified to have the Cys705Arg variant. Patient BM was heterozygous for this variant, however the second variant was not identified in this patient. Patients CE and LRI were both homozygous for Cys705Arg. [PubMed:12083483](#)

Patient GT-12 is compound heterozygous for Cys705Arg and c.3060+2T>C (curated as Likely Pathogenic by the ClinGen Platelet Disorders VCEP; this Cys705Arg variant can be used in the assessment of c.3060+2T>C so will not be used here to avoid a circular argument). Confirmation of trans phase was not reported. [PubMed:20020534](#)

Patient C is compound heterozygous for the Ile405Thr (reported as Ile374Thr) variant derived from the mother and the Cys705Arg (reported as Cys674Arg) from the father. This Cys705Arg variant can be used in the assessment ofIle405Thr so will not be used here to avoid a circular argument. [PubMed:12424194](#)

The proband is a compound heterozygote with the paternally derived c.624+2C>A variant and the maternal c.2113T>C (p.Cys705Arg). [PubMed:9920835](#)

PP3



SIFT, PolyPhen, and MutationTaster agree that there is a deleterious effect caused by this variant; the REVEL score of 0.878 is greater than the >0.7 threshold.

PP4_Strong



At least 7 probands have been described in the literature, at least 2 of whom (PMID: 12083483 and PMID: 25728920) meet the criteria for PP4_Strong; including mucocutaneous bleeding, impaired aggregation with all agonists except ristocetin, and reduced surface expression measured by flow cytometry. ITGA2B and ITGB3 were sequenced across all exons and intron/exon boundaries.

Patient GT-3 has platelets normal in number and size with a history of bleeding. There was impaired aggregation to ADP and arachidonic acid but normal or only mildly reduced agglutination with ristocetin. Based on flow cytometry he was classified as type II GT (αIIbβ3 expression between 5% and 20%). [PubMed:25539746](#)

Patient GT49, compound heterozygous for Cys705Arg, had a history of mucocutaneous bleeding (ecchymosis, epistaxis, and post-traumatic hematomas) and a WHO bleeding score of 2. There was absent platelet aggregation with ADP and severely reduced with at least two additional agonists but normal ristocetin-induced aggregation. There was residual (5-10%) platelet expression of alphaIIb-beta3 confirmed by flow cytometry. No mention was made of platelet count. [PubMed:25728920](#)

Patient BM, heterozygous for Cys705Arg, had a history of epistaxis, aggregation absent in response to ADP, thrombin, and epinephrine but normal for ristocetin. There was <10% of normal GPIIb/GPIIIa by flow cytometry.

Patient CE, homozygous for Cys705Arg, had a history of gastrointestinal bleeding, aggregation absent in response to ADP and epinephrine but normal for ristocetin (and thrombin according to the GT database). Patient LRI, homozygous for Cys705Arg, had a history of gastrointestinal bleeding, aggregation absent in response to ADP, thrombin, and epinephrine but normal for ristocetin. No platelet counts were provided. [PubMed:12083483](#)

Patient CabGT-12 was classified as type II GT with 19% GPIIb determined by flow cytometry. No details were provided on bleeding phenotypes, aggregation studies, or platelet count. [PubMed:20020534](#)

Patient C was reported to have been diagnosed with GT based on "typical laboratory findings and clinical history". The details were not provided however some were available from the GT database (entry 71) including bleeding symptoms of bruising, gingival bleeding, and epistaxis. Aggregation in response to ADP was absent but no other agonists were reported. Expression was not measured by flow cytometry or Western blot but by immunoblot there was 10-50% GPIIb expression and surface expression by radiolabeled antibody was <10% GPIIb/GPIIIa. Normal platelet counts were not reported. [PubMed:12424194](#)

The proband has a normal platelet count of 286,0000/ul with a history of bleeding episodes, including unprovoked bruising. Platelets failed to aggregate either spontaneously or in response to adenosine diphosphate (ADP), epinephrine, or collagen, but showed a normal response to ristocetin. Surface level of platelet GPIIb-IIIa was analyzed by flow cytometry and it was found that GPIIb and GPIIIa were about 10% of the control values. [PubMed:9920835](#)

- PP1_Moderate

i

✓

The Cys705Arg variant segregated with disease in the compound heterozygous proband, and his two compound heterozygous siblings (PMID: 12424194). The homozygous Cys705Arg father was also affected but is not considered here since his genotype differs from the affected siblings.

The Cys705Arg variant segregated with disease in the compound heterozygous proband, his homozygous father, and two compound heterozygous siblings. [PubMed:12424194](#)
- PM2_Supporting

i

✓

The variant is found at an extremely low frequency (below the <1/10,000 threshold) with an overall allele frequency on gnomAD of 0.000003977 with a MAF of 0.000008792 (1/113,742 alleles) in the non-Finnish European population.

Not Met criteria codes

- PS3

i

✗

Transient cotransfections were performed in CHO cells with GPIIIa and either normal or Cys705Arg GPIIb cDNA. The cells coexpressing normal GPIIb and GPIIIa showed surface exposure of GPIIb-IIIa complexes which was strongly attenuated, shown by immunoprecipitation and flow cytometry (~70% reduction), in cells coexpressing normal GPIIIa with the mutant GPIIb. This does not meet the requirement for 5-25% expression to meet PS3_Moderate.

Transient cotransfections were performed in CHO cells with GPIIIa and either normal or Cys705Arg GPIIb cDNA. The cells coexpressing normal GPIIb and GPIIIa showed surface exposure of GPIIb-IIIa complexes which was strongly attenuated, shown by immunoprecipitation, in cells coexpressing normal GPIIIa with the mutant GPIIb. [PubMed:9920835](#)

Expanded upon the transfection studies done in PMID: 9920835 to include analysis by flow cytometry which showed that the mutation Cys705Arg decreased by approximately 70% the surface expression of transfected GPIIb-IIIa. [PubMed:11313253](#)

Curation History

▼

▼

Showing 1 to 1 of 1 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.