

INHERITED PLATELET GPIV DEFICIENCY: FIRST DESCRIPTION OF TWO PATIENTS WITH BLEEDING DIATHESIS

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Background and Aims. Platelet glycoprotein (GP) IV, also known as CD36, is expressed on multiple cell types, where it plays a role in lipid metabolism, immune regulation, and vascular biology. In platelets, GPIV serves as a receptor for thrombospondin-1 and collagen, mediating adhesive interactions and intracellular signaling events regulating platelet activation. Genetic variants in CD36 cause GPIV deficiency, a rare inherited condition. *Cd36*^{-/-} mice show low bone mass due to defective osteoblast differentiation but not bleeding(1). Despite its involvement in platelet activation, GPIV deficiency in humans has not been associated so far with a bleeding phenotype, and platelet aggregation was generally normal(2). Our aim was to describe two unrelated patients carrying heterozygous CD36 variants associated with markedly reduced platelet GPIV expression and bleeding manifestations.

Methods. Platelet aggregation was evaluated by light transmission aggregometry, glycoprotein expression by flow cytometry, and α - and δ -granule content and release by P-selectin expression, β -TG release, mepacrine uptake/release, and ATP secretion by lumiaggregometry. Platelet adhesion to collagen under flow was assessed using a perfusion chamber. Clinical exome sequencing was performed using a capture-based NGS approach.

Results. Patient 1 (P1) was a 22-year-old woman with easy bruising and prolonged bleeding after dental extractions (ISTH-BAT score 5); she previously clinically diagnosed with joint hypermotility but no Ehlers-Danlos syndrome mutations were found. Patient 2 (P2) was a 50-year-old woman with life-long mucocutaneous bleeding, gynecological bleeding and an ISTH-BAT score of 10; she also had bone-related abnormalities, including osteolipomas. Blood clotting assays, platelet number and volume, LTA and granule secretion were all normal in both patients, but PFA-100 closure time was prolonged in P1 and bleeding time in P2. Flow cytometric analysis showed markedly reduced expression of CD36 in platelets from both patients and also in monocytes from P1 suggesting type I CD36 deficiency in P1 and type II in P2 (Figure 1 A-B). Platelet adhesion to collagen under flow conditions at high shear rates was reduced (Figure 1C). Von Willebrand factor (VWF) values in P1 were slightly reduced (VWF:Ag 54%, normal values 61-152%; VWF:RCo 50%, normal values 58-175%; VWF:CBA 61%, normal values 50-400%) and moderately reduced in P2 (VWF:Ag 57-65%, VWF:RCo 48-61%). Clinical exome sequencing identified two heterozygous frameshift

variants in the CD36 gene: the CD36 (NM_001001548.3):c.660_669del (p.Asn220Lysfs*4), Pathogenic, in P1 and the CD36 (NM_001001548.3):c.338_339del (p.Ser113Phefs*20), Likely Pathogenic, in P2. No variants in the VWF gene were observed.

Conclusions. These cases expand the clinical spectrum of inherited GPIV deficiency, suggesting that heterozygous CD36 variants may, in rare instances, be associated with mild to moderate bleeding. The associated collagen- and bone-related features are consistent with the role of CD36 in vascular integrity and skeletal homeostasis. Low levels of VWF in both patients are consistent with emerging genetic evidence showing that loss-of-function mutations in CD36 are associated with lower VWF levels in large population studies(5).

References

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