Platelet Glycoprotein IIb/IIIa Receptors and Glanzmann's Thrombasthenia

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Platelet aggregation and fibrin formation are essential for the maintenance of normal hemostasis, a system designed to act quickly and effectively to arrest hemorrhage. This system is also triggered by pathogenic events, such as the rupture of an atherosclerotic plaque, which can lead to thrombotic vaso-occlusion, ischemia, and infarction. Platelets are a major contributor to these damaging and life-threatening thrombotic phenomena because of their adhesive properties, which result in the release of soluble mediators, platelet aggregation, and enhancement of thrombin generation.[1] The platelet glycoprotein IIb/IIIa (GPIIb/IIIa) receptor is a key component in the pathway to platelet aggregation; consequently, this receptor has become the target for therapeutic intervention. A paradigm of this antiplatelet treatment modality is found naturally in the inherited disorder Glanzmann's thrombasthenia. A key feature of this disease is that patients present with mucocutaneous bleeding but only rarely demonstrate spontaneous central nervous system hemorrhage,[2] a feared complication of anticoagulant and antiplatelet therapy. All of the mutations that have been identified in patients with Glanzmann's thrombasthenia result in a functional deficiency of GPIIb/IIIa receptors,[2,3] and a hallmark of this disease is the absence of agonist-induced platelet aggregation. The molecular characterization of mutations causing Glanzmann's thrombasthenia has provided a wealth of information on structure-function relations of the GPIIb/IIIa receptor. This review will briefly summarize those mutations that affect ligand-binding domains and receptor activation and present them in the context of predicted structures. More comprehensive coverage can be found in reviews discussing the structure and function of the GPIIb/IIIa receptor complex[4,5] and the clinical and molecular basis of Glanzmann's thrombasthenia.[2,3]

GPIIb/IIIa Receptor

Platelets are the first line of defense in preventing blood loss from injured blood vessels via recognition and adhesion to components of the subendothelial matrix. This event is followed by formation of a platelet plug due to recruitment of additional platelets by binding and cross-linking of large ligand molecules, such as fibrinogen and von Willebrand factor. In addition, activated platelets provide a surface for blood coagulation components, thus facilitating the generation of thrombin.[6,7] Platelet aggregation is mediated by the GPIIb/IIIa receptor (integrin αIIbβ3), one of the most abundant cell surface receptors ($\approx$80 000 per platelet),[8] which represents $\approx$15% of total surface protein.[9] On quiescent platelets, this receptor exhibits minimal binding affinity for von Willebrand factor and plasma fibrinogen. In an activated state, "inside-out" signal transduction mechanisms[5] trigger a conformational change in the receptor to a high-affinity ligand-binding state that is competent to bind adhesive glycoproteins and form a platelet plug. After ligand binding, "outside-in" signal transduction mechanisms[5] mediate integrin-cytoskeleton interactions. These have been shown to be requirements for postligand occupancy events, such as cell spreading and formation of focal adhesion sites.[10]

Ligand recognition motifs for integrin receptors require an acidic amino acid for activity. The first example of an acidic peptide conferring integrin recognition was the Arg-Gly-Asp (RGD) sequence in fibronectin.[11] Other extracellular matrix molecules were found to contain this sequence, and the concept of RGD as a common recognition motif was adopted.[12] The RGD motif is found in ligands of GPIIb/IIIa receptors including the α chain of fibrinogen and von Willebrand factor, but a Lys/Gly-Asp (K/GD) recognition motif, found within a unique dodecapeptide sequence in the fibrinogen γ chain, is necessary and sufficient for fibrinogen-mediated platelet aggregation.[13]

Because of the absence of a crystal structure, less precise information is available concerning the sites within integrin receptors that recognize ligands. Structural information is available for 1 ligand-binding region, which is the von Willebrand factor A or I (inserted) domain.[14] The I domain is expressed by a subset of α-chain subunits, and high-resolution crystallography has established this domain as part of a unique metal coordination site designated the metal ion-dependent adhesion site (MIDAS).[14] The I domain is not present in the GPIIb (αIIb) subunit, but structural studies have identified a region of similar cation-binding characteristics in integrin β subunits.[15] A number of structural models have been generated showing the conformational association of amino acid residues predicted to play a direct role in ligand binding.[16–18]

Received April 20, 1999; revision accepted July 14, 1999.

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(*Arterioscler Thromb Vasc Biol.* 2000;20:607-610.)

***Arterioscler Thromb Vasc Biol.* is available at http://www.atvbaha.org**

A structural model of the ligand-binding domain of an integrin α chain has been predicted by computer modeling.[19] The minimal ligand-binding sequence of GPIIb is composed of the amino-terminal 450 amino acids, which contain 7 homologous repeats with 4 cation-binding sites.[20] These repeats are composed predominantly of β strands,[21] which have been predicted to fold into a β-propeller structure.[19] The β propeller is highly conserved in evolution, and the model for an integrin α chain contains 7 repeats of β sheets that are arranged as propeller blades around a central axis.[19] Ligand binding has been proposed to take place on the face opposite the cation-binding sites that lie on the bottom of this structure.[19]

Glanzmann's Thrombasthenia

Glanzmann's thrombasthenia is an autosomal recessive disease that results in a functional deficiency of GPIIb/IIIa receptors.[2] This lifelong disorder is characterized by mucocutaneous bleeding, with epistaxis and purpura being common in childhood and menorrhagia being common during child-bearing years and causing significant morbidity. The hallmark of this disease is severely reduced or absent platelet aggregation in response to multiple physiological agonists. This disease is caused by mutations in the genes encoding GPIIb or GPIIIa that result in qualitative or quantitative abnormalities of the platelet membrane proteins.[2,3] The molecular characterization of Glanzmann's thrombasthenia in patients and their families has permitted DNA-based carrier detection and prenatal diagnoses to be performed.[22,23] In recent years, the number of mutations that have been identified at the molecular level has increased,[3] thus forming the basis of an Internet database that includes clinical, biochemical, and mutation information on reported patients (http://med.mssm.edu/glanzmanndb).

Mutations Within the β-Propeller Sequence of an Integrin α Chain

Different groups of Glanzmann's thrombasthenia mutations that are located within the GPIIb β propeller are beginning to emerge. One group of mutations is located within and surrounding the calcium-binding domains, and another group is located within and around the third blade of the propeller (Figure 1). Four missense mutations and 1 in-frame deletion mutation in 7 patients have been identified within and surrounding the calcium-binding domains, which are located within the fourth to seventh blades of the propeller. These mutations affect transport of the GPIIb/IIIa complex to the cell surface and include a G273D(G242D) substitution (patient FLD),[24] which precedes the first calcium-binding domain; E355K(E324K) (patients FL and Swiss)[25,26] and R358H(R327H) (patients KJ and Mila-1)[27,28] substitutions, located between the second and third calcium-binding domains; a G449D(G418D) (patient LM)[29] substitution, which precedes the fourth calcium-binding domain; and a V425D426 (patient LeM)[30] deletion at the beginning of the fourth calcium-binding domain. Another group of mutations is located within the vicinity of the third blade (W3) of the β propeller, which contains a predicted β-turn structure that has been implicated in ligand-binding of GPIIb/IIIa and other integrin receptors.[31,32] Four missense mutations in 5 patients result in functionally defective receptors. A T207I(T176I)

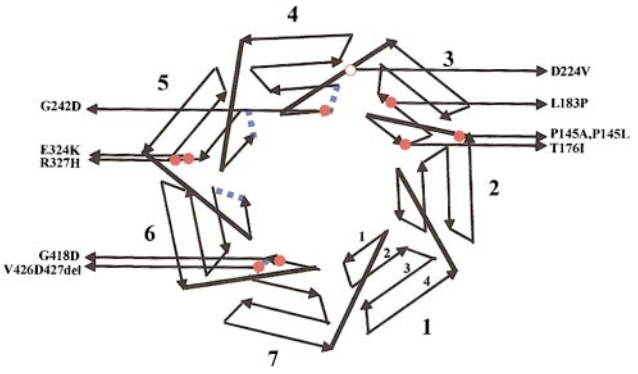

Figure 1. Glanzmann's thrombasthenia and in vitro–generated mutations located within a β-propeller structure of an integrin α-chain subunit. A schematic drawing of a 7-blade β-propeller structure predicted to represent the ligand-binding region of an integrin α-chain subunit.[19] Each blade (1 to 7) is composed of antiparallel β strands (arrows numbered 1 to 4, as shown in blade 1) that are connected by hairpin loops. The 4 calcium-binding domains (blue dotted lines) are included within the 1-2 connecting loops within blades 4 to 7. These domains have been hypothesized to be located on the bottom of the propeller and lie opposite the ligand-binding sites.[19] The locations of 8 missense mutations and 1 deletion mutation identified in 12 patients with Glanzmann's thrombasthenia are represented by red circles; the in vitro–generated mutation located between the third and fourth blades of the propeller is represented by an open circle in red.

(Frankfurt I)[33] substitution is located in the 1-2 connecting strand, a L214P(L183P) (patient LW)[34] substitution is located at the end of the second β strand near the 2-3 connecting strand, and P176A(P145A) (Mennonite)[35] and P176L(P145L)[35] substitutions are located within the 4-1 connecting strand between the second and third blades of the propeller. Independent support for the functional importance of this region has been shown by a D255V(D224V) mutation,[36] located within the 4-1 connecting strand between the third and fourth blades of the propeller. This mutation was identified from in vitro–generated mutant GPIIb/IIIa receptors expressed on the surface of Chinese hamster ovary cells[37] and disrupts ligand-binding function of the receptor.

Mutations Within the MIDAS of GPIIIa

Eight missense mutations identified in 9 patients with Glanzmann's thrombasthenia are located within the cation-binding sphere of the GPIIIa MIDAS domain (Figure 2). Two mutations, D145Y(D119Y) (Cam variant)[38] and D145N(D119N) (patient NR),[39] are located within the conserved DXSXS amino acid motif; 3 mutations, R240W(R214W) (Strasbourg I variant and patient CM),[40,41] R240Q(R214Q) (patient ET),[42] and R242Q(R216Q) (patient SH),[43] are located near the putative coordinating sites[17]; and 3 mutations, D143W(D117W) (patient MK),[44] S188L(S162L) (patient BL),[45] and L288P(L262P) (patient LD),[46] are located within the sphere of the MIDAS domain. The mutations at residue D119 result in severe abnormalities of GPIIb/IIIa function but do not affect surface expression, whereas the mutation at D117 results in the intracellular retention of misfolded receptor complexes. The mutations at residues R214 and R216 result in surface-expressed GPIIb/IIIa receptors that are abnormally sensitive to dissociation by calcium chelation, and the mutations at residues S162 and L262 result in surface expression levels $\approx$30% of normal but also show sensitivity to dissociation by calcium. The importance of these sites is reinforced by the identification of a group of in vitro–generated

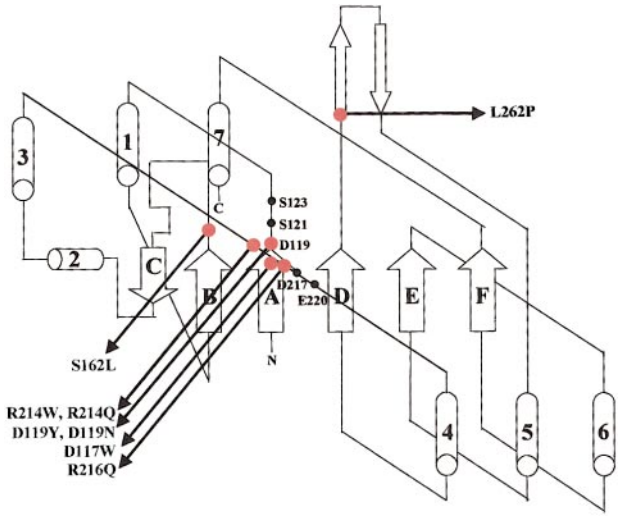

Figure 2. Glanzmann's thrombasthenia mutations located within the vicinity of the MIDAS domain of GPIIIa (β3). A schematic drawing shows the predicted folding pattern of a von Willebrand factor A domain structure of GPIIIa in which a MIDAS domain is located at the center of the structure.[17] This drawing has been modified to include mutations identified in patients with Glanzmann's thrombasthenia. Arrows A to F represent predicted β sheets, and cylinders 1 to 7 represent predicted α-helix structures. The cation-binding $D^{119}XS^{121}XS^{123}$ motif and coordinating residues D^{217} and E^{220} are shown in black circles. The locations of 8 mutations identified in 9 patients with Glanzmann's thrombasthenia are represented by red circles.

mutant GPIIb/IIIa receptors expressed in Chinese hamster ovary cells.[37] The mutations D119N, R214W, D217N, E220Q, and E220K were identified as functional defects, providing independent support for the importance of the MIDAS domain in ligand binding.

Mutations That Affect Receptor Activation

Two Glanzmann's thrombasthenia mutations that disrupt the activation state of the GPIIb/IIIa receptor have been identified. Both mutations are located within the GPIIIa cytoplasmic domain, which is important for integrin activation and the regulation of ligand binding.[47] The mutations are a R750X(R724X) nonsense mutation (patient RM),[48] which results in the deletion of the carboxy-terminal 39 residues of GPIIIa, and a S778P(S752P) missense mutation (patient P or Paris I).[49] Resting platelets from both patients express significant levels of stable GPIIb/IIIa complexes that are unresponsive to agonists but responsive to conformational activators. Functional analyses show normal adhesion to immobilized fibrinogen but abnormal cell spreading. The S778P(S752P) mutation shows reduced focal adhesion plaque formation, and the R750X(R724X) mutation shows undetectable tyrosine phosphorylation of focal adhesion kinase $pp125^{FAK}$. These mutations provide support for the role of the GPIIIa cytoplasmic tail in the function of the GPIIb/IIIa receptor complex.

Conclusion

Our appreciation for the diversity of abnormalities that underlie Glanzmann's thrombasthenia has been enriched by the molecular characterization of mutational defects identified in patients affected by this disorder. Mutations can be precisely defined, and distinct groups of mutational defects can now be identified. The molecular characterization of patients with this disorder has provided the foundation for DNA-based carrier detection and prenatal diagnoses of Glanzmann's thrombasthenia. As the structural basis of integrin receptors begins to unfold, the identified mutations will shed light on mechanisms of receptor-ligand complex formation. The information generated from these studies will continue to provide insight into the biogenesis, structure, and function of the GPIIb/IIIa and integrin family of adhesion receptors.

References

1. Coller BS. Augmentation of thrombolysis with antiplatelet drugs. *Coron Artery Dis*. 1995;6:911–914.
2. George JN, Caen JP, Nurden AT. Glanzmann's thrombasthenia: the spectrum of clinical disease. *Blood*. 1990;75:1383–1395.
3. French DL. The molecular genetics of Glanzmann's thrombasthenia. *Platelets*. 1998;9:5–20.
4. Calvete JJ. On the structure and function of platelet integrin αIIbβ3, the fibrinogen receptor. *Proc Soc Exp Biol Med*. 1995;208:346–360.
5. Shattil SJ, Kashiwagi H, Pampori N. Integrin signaling: the platelet paradigm. *Blood*. 1998;91:2645–2657.
6. Reverter JC, Beguin S, Kessels H, Kumar R, Hemker HC, Coller BS. Inhibition of platelet-mediated, tissue factor-induced thrombin generation by the mouse/human chimeric 7E3 antibody. *J Clin Invest*. 1996;98: 863–874.
7. Oliver JA, Monroe DM, Roberts HR, Hoffman M. Thrombin activates factor XI on activated platelets in the absence of factor XII. *Arterioscler Thromb Vasc Biol*. 1999;19:170–171.
8. Wagner CL, Mascelli MA, Neblock DS, Weisman HF, Coller BS, Jordan RE. Analysis of GPIIb/IIIa receptor number by quantitation of 7E3 binding to human platelets. *Blood*. 1996;88:907–914.
9. Jennings LK, Phillips DR. Purification of glycoproteins IIb and IIIa from human platelet plasma membranes and characterization of a calcium-dependent glycoprotein IIb-III complex. *J Biol Chem*. 1982;257: 10458–10466.
10. Yamada KM, Geiger B. Molecular interactions in cell adhesion complexes. *Curr Biol*. 1997;9:76–85.
11. Ruoslahti E, Pierschbacher MD. Arg-Gly-Asp: a versatile cell recognition signal. *Cell*. 1986;44:517–518.
12. Yamada KM. Adhesive recognition sequences. *J Biol Chem*. 1991;266: 12809–12812.
13. Farrell DH, Thiagarajan P, Chung DW, Davie EW. Role of fibrinogen α and γ chain sites in platelet aggregation. *Proc Natl Acad Sci U S A*. 1992;89:10729–10732.
14. Lee J-O, Rieu P, Arnaout MA, Liddington R. Crystal structure of the A domain from the α subunit of integrin CR3 (CD11b/CD18). *Cell*. 1995; 80:631–638.
15. Michishita M, Videm V, Arnaout M. A novel divalent cation-binding site in the A domain of the β2 integrin CR3 (CD11b/CD18) is essential for ligand binding. *Cell*. 1993;72:857–867.
16. Tozer EC, Liddington RC, Sutcliffe MJ, Smeeton AH, Loftus JC. Ligand binding to integrin αIIbβ3 is dependent on a MIDAS-like domain in the β3 subunit. *J Biol Chem*. 1996;271:21978–21984.
17. Tuckwell DS, Humphries MJ. A structure prediction for the ligand-binding region of the integrin β subunit: evidence for the presence of a von Willebrand factor A domain. *FEBS Lett*. 1997;400:297–303.
18. Takagi J, Kamata T, Meredith J, Puzon-McLaughlin W, Takada Y. Changing ligand specificities of αvβ1 and αvβ3 integrins by swapping a short diverse sequence of the β subunit. *J Biol Chem*. 1997;272: 19794–19800.
19. Springer TA. Folding of the N-terminal, ligand-binding region of integrin α-subunits into a β-propeller domain. *Proc Natl Acad Sci U S A*. 1997; 94:65–72.
20. Loftus JC, Halloran CE, Ginsberg MH, Feigen LP, Zablocki JA, Smith JW. The amino-terminal one-third of αIIb defines the ligand recognition specificity of integrin αIIbβ3. *J Biol Chem*. 1996;271:2033–2039.
21. Tuckwell DS, Humphries MJ, Brass A. A secondary structure model of the integrin α subunit N-terminal domain based on analysis of multiple alignments. *Cell Adhes Commun*. 1994;2:385–402.
22. Seligsohn U, Mibashan RS, Rodeck CH, Nicolaides KH, Millar DS, Coller BS. Prenatal diagnosis of Glanzmann's thrombasthenia. *Lancet*. 1985;2:1419. Letter.

23. French DL, Coller BS, Usher S, Berkowitz R, Eng C, Seligsohn U, Peretz H. Prenatal diagnosis of Glanzmann thrombasthenia using the polymorphic markers BRCA1 and THRA1 on chromosome 17. *Br J Haematol*. 1998;102:582–587.
24. Poncz M, Rifat S, Coller BS, Newman PJ, Shattil SJ, Parrella T, Fortina P, Bennett JS. Glanzmann thrombasthenia secondary to a Gly273Asp mutation adjacent to the first calcium-binding domain of platelet glycoprotein IIb. *J Clin Invest*. 1994;93:172–179.
25. Bourre R, Peyruchaud O, Bray P, Combrie R, Nurden P, Nurden AT. A point mutation in the gene for platelet GPIIb leads to a substitution in a highly conserved amino acid located between the second and the third Ca^{++}-binding domain. *Blood*. 1995;86:452a. Abstract.
26. Ruan J, Peyruchaud O, Alberio L, Valles G, Clemetson K, Bourre F, Nurden AT. Double heterozygosity of the GPIIb gene in a Swiss patient with Glanzmann's thrombasthenia. *Br J Haematol*. 1998;102:918–925.
27. Wilcox DA, Paddock CM, Lyman S, Gill JC, Newman PJ. Glanzmann thrombasthenia resulting from a single amino acid substitution between the second and third calcium-binding domains of GPIIb. *J Clin Invest*. 1995;95:1553–1560.
28. Ferrer M, Fernandez-Pinel M, Gonzalez-Manchon C, Gonzalez J, Ayuso MS, Parrilla R. A mutant (Arg327His) GPIIb associated to thrombasthenia exerts a dominant negative effect in stably transfected CHO cells. *Thromb Haemost*. 1996;76:292–301.
29. Wilcox DA, Wautier JL, Pidard D, Newman PJ. A single amino acid substitution flanking the fourth calcium binding domain of αIIb prevents maturation of the integrin αIIbβ3 complex. *J Biol Chem*. 1994;269:4450–4457.
30. Basani RB, Vilaire G, Shattil SJ, Kolodziej MA, Bennett JS, Poncz M. Glanzmann thrombasthenia due to a two amino acid deletion in the fourth calcium-binding domain of αIIb: demonstration of the importance of calcium-binding domains in the conformation of αIIbβ3. *Blood*. 1996;88:167–173.
31. Irie A, Kamata T, Puzon-McLaughlin W, Takada Y. Critical amino acid residues for ligand binding are clustered in a predicted β-turn of the third N-terminal repeat in the integrin α4 and α5 subunits. *EMBO J*. 1995;14:5550–5556.
32. Kamata T, Irie A, Tokuhira M, Takada Y. Critical residues of integrin αIIb subunit for binding of αIIbβ3 (glycoprotein IIb-IIIa) to fibrinogen and ligand-mimetic antibodies (PAC-1, OP-G2, and LJ-CP3). *J Biol Chem*. 1996;271:18610–18615.
33. Westrup D, Santoso S, Becker-Hagendorff K, Just M, Jablonka B, Siefried E, Kirchmaier CM. Transfection of GPIIbIle176/IIIa (Frankfurt I) in mammalian cells. *Thromb Haemost*. 1997;77:671. Abstract.
34. Grimaldi CM, Chen FP, Wu CH, Weiss HJ, Coller BS, French DL. Glycoprotein IIb Leu214Pro mutation produces Glanzmann thrombasthenia with both quantitative and qualitative abnormalities in GPIIb/IIIa. *Blood*. 1998;91:1562–1571.
35. Basani RB, French DL, Vilaire G, Brown DL, Chen F, Coller BS, Derrick JM, Gartner TK, Bennett JS, Poncz M. A naturally occurring mutation near the amino terminus of αIIb defines a new region involved in ligand binding to αIIbβ3. *Blood*. 2000;95:180–188.
36. Tozer EC, Baker E, Ginsberg MH, Loftus JC. A mutation in the α subunit of the platelet integrin αIIbβ3 identifies a novel region important for ligand binding. *Blood*. 1999;93:918–924.
37. Baker EK, Tozer EC, Pfaff M, Shattil SJ, Loftus JC, Ginsberg MH. A genetic analysis of integrin function: Glanzmann thrombasthenia *in vitro*. *Proc Natl Acad Sci U S A*. 1997;94:1973–1978.
38. Loftus JC, O'Toole TE, Plow EF, Glass A, Frelinger AL III, Ginsberg MH. A β3 integrin mutation abolishes ligand binding and alters divalent cation-dependent conformation. *Science*. 1990;249:915–918.
39. Ward CM, Chao YL, Kato GJ, Casella J, Bray PF, Newman PJ. Substitution of Asn, but not Tyr, for Asp119 of the β3 integrin subunit preserves fibrin binding and clot retraction. *Blood*. 1997;90:26a. Abstract.
40. Lanza F, Stierle A, Fournier D, Morales M, Andre G, Nurden AT, Cazenave J-P. A new variant of Glanzmann's thrombasthenia (Strasbourg I: platelets with functionally defective glycoprotein IIb-IIIa complexes and a glycoprotein IIIa Arg214Trp mutation. *J Clin Invest*. 1992;89:1995–2004.
41. Djaffer I, Rosa J-P. A second case of variant of Glanzmann's thrombasthenia due to substitution of platelet GPIIIa (integrin β_3) Arg214 by Trp. *Hum Mol Genet*. 1993;2:2179–2180.
42. Bajt ML, Ginsberg MH, Frelinger AL III, Berndt MC, Loftus JC. A spontaneous mutation of integrin αIIbβ3 (platelet glycoprotein IIb-IIIa) helps define a ligand binding site. *J Biol Chem*. 1992;267:3789–3794.
43. Newman PJ, Weyerbusch-Bottum S, Visentin GP, Gidwitz S, White GCI. Type II Glanzmann thrombasthenia due to a destabilizing amino acid substitution in platelet membrane glycoprotein IIIa. *Thromb Haemost*. 1993;69:1017. Abstract.
44. Basani RB, Brown DL, Vilaire G, Bennett JS, Poncz M. A Leu117Trp mutation within the RGD-peptide cross-linking region of β3 results in Glanzmann thrombasthenia by preventing αIIbβ3 export to the platelet surface. *Blood*. 1997;90:3082–3088.
45. Jackson DE, White MM, Jennings LK, Newman PJ. A Ser162Leu mutation within glycoprotein (GP) IIIa (integrin β3) results in an unstable αIIbβ3 complex that retains partial function in a novel form of type II Glanzmann thrombasthenia. *Thromb Haemost*. 1998;80:42–48.
46. Ward CM, Newman PJ. A Leu262Pro mutation in the integrin β3 subunit results in an αIIbβ3 complex which binds fibrin but not fibrinogen. *Blood*. 1997;90:25a. Abstract.
47. Shattil SJ, Gao J, Kashiwagi H. Not just another pretty face: regulation of platelet function at the cytoplasmic face of integrin αIIbβ3. *Thromb Haemost*. 1997;78:220–225.
48. Wang R, Shattil SJ, Ambruso DR, Newman PJ. Truncation of the cytoplasmic domain of β3 in a variant form of Glanzmann thrombasthenia abrogates signaling through the integrin αIIbβ3 complex. *J Clin Invest*. 1997;100:2393–2403.
49. Chen Y-P, Djaffar I, Pidard D, Steiner B, Cieutat A-M, Caen JP, Rosa J-P. Ser752Pro mutation in the cytoplasmic domain of integrin β3 subunit and defective activation of platelet integrin αIIbβ3 (glycoprotein IIb-IIIa) in a variant of Glanzmann thrombasthenia. *Proc Natl Acad Sci U S A*. 1992;89:10169–10173.

KEY WORDS: platelets ■ integrins ■ Glanzmann's thrombasthenia