Are Platelet Membrane Glycoprotein Polymorphisms Predictive of Arterial Thrombosis?

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Key words: platelet polymorphisms, myocardial infarction, stroke, GPIIIa, GPIa, GPIb

IMAJ 2002;4:458–459

Arterial thrombotic syndromes are the leading cause of morbidity and mortality in the western world. Since platelets play a pivotal role in the formation of arterial thrombi, it has been suggested that markers of platelet activation would be potentially useful to identify patients at increased risk for arterial thrombosis.

The characterization of platelet glycoprotein polymorphisms paved the way for evaluation of their prevalence in populations of patients with arterial thrombotic syndromes, including myocardial infarction and stroke. Platelet membrane glycoproteins are highly polymorphic, and the allelic variations encoding the major platelet glycoproteins – $\alpha 2\beta 3$ (GPIIbIIIa), GPIa-IIa and GPIb-IX – are very common.

The platelet GPIIbIIIa is a receptor for fibrinogen and von Willebrand factor. Pl^A is the alloantigen most frequently implicated in immune mediated platelet destruction. The Pl^{A2} polymorphism (proline at position 33 of the β-3 subunit) was initially suggested to be more common in coronary artery disease patients. However, of 18 studies only 8 demonstrated a positive association, while 10 showed no association between Pl^{A2} and coronary artery disease [1]. The possibility that Pl^{A2} is a risk factor for coronary atherosclerosis but not for arterial thrombosis may explain the discrepancies between some of these studies [2]. The risk conferred by Pl^{A2} is particularly increased in young smokers.

A number of studies focused on the platelet collagen receptor to evaluate the correlation between inheritance of the integrin alpha-2 allele-1 coding for increased platelet alpha-2 beta-1 density and risks of adverse outcome in patients with thrombotic disorders. In patients with myocardial infarction, three studies [3–5] demonstrated a positive correlation, with odds ratio of 2.2–3.3, while three others showed no difference [6–8]. In addition, two studies in coronary artery disease patients and one in patients who had restenosis after coronary stenting were negative [4,9,10]. In stroke patients, three studies [11–13] showed a positive association, with odds ratio of 2.0–3.0, while another study was negative [9]. Furthermore, three studies in venous thrombosis patients were negative [9,14,15]. Thus, the bulk of evidence suggests that this platelet collagen receptor polymorphism is not helpful in predicting thrombotic risk.

In this issue of *IMAJ*, Rosenberg et al. [16] report the results of a case-control study, in young males with a first episode of acute myocardial infarction and healthy controls, carefully designed to evaluate the risks exerted by a number of platelet glycoprotein polymorphisms in the GpIIIa, GPIa and the GPIb alpha genes. The study groups were different for smoking and other acquired metabolic risk factors, suggesting that their size was sufficiently large to detect significant clinically relevant differences. However, the prevalence of the studied platelet glycoprotein polymorphisms, including HPA-1 a/b in GPIIIa, 807C/T in GPIa, HPA-2a/b, VNTR and Kozak-C/T in GPIb alpha, were not significantly different in patients compared to controls.

Evaluation of platelet glycoprotein polymorphisms is elaborate and costly. Since studies of currently available glycoproteins by and large do not add information to trivial metabolic risk factors, the role of any of these polymorphisms as predictors of arterial thrombosis remains controversial. Furthermore, the confounding influences of age, gender, environment and metabolic risk factors should be rigorously assessed by studies of platelet glycoprotein polymorphisms in thrombosis patients and controls.

If indeed platelet glycoprotein polymorphisms will prove non-predictive for arterial thrombosis, the information gathered in these studies could still be potentially useful. For example, some of these glycoproteins may serve as receptors for anti-platelet agents. Single nucleotide polymorphisms attract considerable interest in the rapidly evolving field of pharmacogenomics. It is possible that these single nucleotide polymorphisms on the platelet surface may differentiate between variable responses to anti-platelet agents. Functional studies in patients from the Framingham Offspring Study demonstrated increased aggregation of Pl^{A2} platelets [17]. Furthermore, it was suggested that Pl^{A1A2} platelets may be more sensitive to inhibition of aggregation by aspirin or abciximab [18]. The clinical relevance of these findings on drug interactions has yet to be determined by epidemiologic studies.

References

1. Bray PF. Integrin polymorphisms as risk factors for thrombosis. *Thromb Haemost* 1999;82:337–44.
2. Franco RF, Reitsma PH. Gene polymorphisms of the haemostatic system and the risk of arterial thrombotic disease. *Br J Haematol* 2001;115:491–506.
3. Moshfegh K, Wuillemin WA, Redondo M, et al. Association of two silent polymorphisms of platelet glycoprotein Ia/IIa receptor with risk of myocardial infarction: a case-control study. *Lancet* 1999;353:351–4.
4. Santoso S, Kunicki TJ, Kroll H, et al. Association of the platelet glycoprotein Ia C_{807} T gene polymorphism with myocardial infarction in younger patients. *Blood* 1999;93:2449–53.

5. Roset M, Sixma JJ, Wu YP, et al. Platelet adhesion to collagen in healthy volunteers is influenced by variation of both alpha 2 beta 1 density and von Willebrand factor. *Blood* 2000;96:1433–7.
6. Croft SA, Hampton KK, Sorrell JA, et al. The GPIa C807T dimorphism associated with platelet collagen receptor density is not a risk factor for myocardial infarction. *Br J Haematol* 1999;106:771–6.
7. Morita H, Kurihara H, Lmai Y, et al. Lack of association between the platelet glycoprotein la C807T gene polymorphism and myocardial infarction in Japanese, an approach entailing melting curve analysis with specific fluorescent hybridization probes. *Thromb Haemost* 2001;85:226–30.
8. Anvari A, Janisiw M, Turel Z, et al. Platelet glycoprotein la gene dimorphism alpha2-807 in malignant arrhythmia in coronary artery disease. *Thromb Res* 2000;98:281–6.
9. Corral J, Gonzales-Conejero R, Rivera J, et al. Role of the 807 C/T polymorphisms of the alpha 2 gene in platelet GP la collagen receptor expression and function. *Thromb Haemost* 1999;81:951–6.
10. Von Beckerath N, Koch W, Mehilli J, et al. Glycoprotein la gene C807T polymorphism and risk for major adverse cardiac events within the first 30 days after coronary artery stenting. *Blood* 2000;95(11):3297–301.
11. Carlsson LE, Santoso S, Spitzer C, et al. The alpha2 gene coding sequences T_{807}/A_{873} of the platelet collagen receptor integrin alpha2 beta1 might be a genetic risk factor for the development of stroke in younger patients. *Blood* 1999;93:3583–6.
12. Sacchi E, Taglibue L, Duca F, et al. A C807T substitution in the coding sequence of the platelet collagen receptor integrin 1 as a genetic risk factor for stroke in young patients [Abstract]. *Thromb Haemost* 1999;(Suppl):848.
13. Reiner AP, Kumar PN, Schwartz SM, et al. Genetic variants of platelet glycoprotein receptors and risk of stroke in young women. *Stroke* 2000;31:1628–33.
14. Hessner MJ, Dinauer DM, Luhm RA, et al. Contribution of the glycoprotein la 807TT, methylene tetrahydrofolate reductase 677TT and prothrombin 20210GA genotypes to prothrombotic risk among factor V 1691(Leiden) carriers. *Br J Haematol* 1999;106:237–9.
15. Carlsson LE, Potzsch B, Santoso S, et al. The GPIa-C807T polymorphism on the platelet collagen receptor GPIa-lIa and the development of deep vein thrombosis [Abstract]. *Thromb Haemost* 1999;(Suppl):254.
16. Rosenberg N, Zivelin A, Chetrit A, Dardik R, Kornbrot N, Inbal A. Effects of platelet membrane glycoprotein polymorphisms on the risk of myocardial infarction in young males. *IMAJ* 2002;4:411–14.
17. Feng D, Lindpaintner K, Larson MD, et al. Increased platelet aggregability associated with platelet GPIIIa PI^{A2} polymorphism. The Framingham offspring study. *Arterioscler Thromb Vasc Biol* 1999;19:1142–7.
18. Michelson AD, Furman MI,Goldschmidt-Clermont P, et al. Platelet GP III_a PI (A) polymorphisms display different sensitivities to agonists. *Circulation* 2000;101:1013–18.

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