EDITORIAL COMMENT

Platelet Polymorphisms and Ischemic Heart Disease: Moving Beyond Traditional Risk Factors*

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A single butterfly flapping its wings today produces a tiny change in the state of the atmosphere ... 
Chaos: Making a New Science, James Gleick (1)

Because of the cumulative effect of inherited minute alterations of multiple genes, what the cardiovascular system actually does over a lifetime wanders away from what it would have done. In other words, a dreadful process of atherosclerosis that would have devastated the cardiovascular system of an individual does not happen, or maybe one that was not going to happen does. What was seemingly too complex to predict, the genetic contribution to the development of complex traits like atherosclerosis and other common forms of cardiovascular disease, might become affordable. We owe this new opportunity in part to the ability to sequence the human and related genomes. Single nucleotide polymorphisms (SNPs) represent the most frequent and simplest alteration of this sequence. Unprecedented efforts are underway to identify both SNPs and more complex polymorphisms and to establish their relationship to susceptibility for common ailments and to drug response for patients with heart disease.

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Ischemic heart disease and adverse events following revascularization procedures represent a complex interaction of vascular injury, inflammation and thrombosis. Within the past decade, however, our understanding of ischemic heart disease has become even more sophisticated as recent discoveries have revealed the influence of gene variants on the development of atherosclerotic disease and arterial thrombosis. The pioneers of the field have already studied the association of a platelet receptor variant that was not going to happen does. What was seemingly too complex to predict, the genetic contribution to the development of complex traits like atherosclerosis and other common forms of cardiovascular disease, might become affordable. We owe this new opportunity in part to the ability to sequence the human and related genomes. Single nucleotide polymorphisms (SNPs) represent the most frequent and simplest alteration of this sequence. Unprecedented efforts are underway to identify both SNPs and more complex polymorphisms and to establish their relationship to susceptibility for common ailments and to drug response for patients with heart disease.

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affected individuals to increased thrombotic risk (3). Finally, a T to C single nucleotide substitution at position −5 from the ATG start codon characterizes the Kozak sequence polymorphism. Although it does not alter structure, the Kozak polymorphism may increase surface expression of GPIbα (2,4). In one study, GPIb-IX-V receptor density on the platelet surface correlated with genotype; TT homozygous platelets expressed the least GPIbα, whereas CC homozygous platelets expressed the most (4). Importantly, these findings have not been verified in subsequent research (5).

Adding to the controversy over platelet polymorphisms are studies associating GPIbα variants with an increased risk of ischemic events (6–8). The interpretation of these studies is further blurred by variations in study design, patient demographics and clinical presentation. In this issue of the Journal, Meisel et al. (2) add to our understanding of the GPIbα receptor as a potential risk factor for coronary artery disease and adverse events complicating catheter-based interventions. In this case-controlled study, the investigators genotyped nearly 1,000 patients with coronary artery disease and compared the frequency of the Kozak polymorphism to matched controls. In a second part, they examined the role of the −5C allele as a predictor of short-term complications following percutaneous coronary interventions. Compared to the wild-type allele (−5T/T), carriers of the −5C allele were more likely to present with an unstable coronary syndrome and/or experience a peri-procedural adverse event following balloon angioplasty.

Unlike previous studies examining the role of the −5C allele in ischemic heart disease, the study by Meisel et al. (2) is the first to associate the GPIb polymorphism with an increased risk of developing an unstable coronary syndrome or ischemic complication following percutaneous coronary intervention. Among nearly 2,500 patients undergoing angioplasty, Santoso et al. (9) found no relationship between the Kozak polymorphism and ischemic events, except for possibly a greater severity of coronary artery disease in younger patients who were homozygous with the −5C allele. Still other smaller studies have failed to confirm the association between the Kozak sequence polymorphism and ischemic events (10,11).

Exactly why carriers of the −5C allele experience a higher rate of adverse events following balloon angioplasty, but not after atherectomy or stenting, is puzzling. As the investigators hypothesized, it seems intuitive that any mutation promoting platelet adhesion would increase the risk of complications following a procedure that intentionally disrupts the endothelium. However, the increased risk associated with the Kozak polymorphism is found only with balloon angioplasty and not with other interventions known to injure the endothelium or involve angioplasty (e.g., predilation with balloon angioplasty prior to stenting). Moreover, established predictors of adverse events following catheter-based interventions (e.g., diabetes, lesion morphology, among others) vary considerably among the groups in the present study, and the use of GPIIb-IIIa inhibitors (known to reduce periprocedural ischemic complications) was not specified. Although we do not have a molecular mechanism to explain the discrepancy between various angioplasty procedures relative to the Kozak polymorphism, the data, if confirmed, could be useful in the selection of the appropriate procedure for individual patients.

**PLA2 polymorphism of GPIIIa.** Glycoprotein IIIa, together with GPIIb, constitutes the fibrinogen receptor (GPIIb-IIIa, or integrin α2β3), whose engagement represents the final common pathway for platelet aggregation (Fig. 2). Due to the substitution of a cytosine for a thymidine at position 1565 in exon 2 of the GPIIIa gene, the platelet antigen 2 (PLA2) variant displays a proline instead of a leucine at amino acid 33. The structural change in GPIIIa-IIIa that is induced by the PLA2 variant is the...
cause for a severe form of neonatal alloimmune thrombocytopenia.

Similar to the GPIbα polymorphism, PlA2 has been implicated in arterial thrombosis and the development of unstable coronary syndromes. Specifically, a high prevalence of the PlA2 allele has been reported in patients with unstable angina or myocardial infarction (MI) and in siblings of patients with a history of premature ischemic heart disease (12,13). Mikkelsen et al. (14) also reported a higher prevalence of PlA2 among victims of sudden cardiac death whose coronary arteries contained thrombus. Still other studies have not confirmed the association between PlA2 and MI (15), maintaining the controversy over the influence of the PlA2 polymorphism. Despite the variance in epidemiologic data, most studies examining the molecular effect of the PlA2 polymorphism on GPIIb-IIIa function have been consistent, showing that the mutation results in increased platelet responsiveness (16,17).

Platelet antigen 2 polymorphism has also been related to a higher incidence of adverse ischemic events following catheter-based procedures. As previously described, catheter-based interventions with coronary stenting are a major stimulus for platelet activation. Although the use of intracoronary stents has improved both short- and long-term clinical outcomes by maximizing acute procedural luminal gain and reducing the incidence of restenosis, the disruption of the endothelium and the placement of a metallic stent promote platelet adhesion and thrombus formation. Both platelet adhesion and aggregation also contribute substantially to restenosis by promoting the migration and growth of smooth muscle cells. Walter et al. (18) reported a higher incidence of acute stent thrombosis and MI among PlA2–positive individuals following percutaneous revascularization. Although the incidence of stent thrombosis did not vary with PlA1/A2 status, Kastrati et al. (19) found that PlA2 carriers were more likely to experience periprocedural death and Q-wave MI. In a multivariate model, the risk of an adverse event after coronary stenting was approximately 2.5 times for PlA2 homozygous individuals compared to the PlA1/A1 genotype. Among 653 patients undergoing either coronary stenting or directional coronary athrectomy, Laule et al. (20) observed a trend toward worse 30-day outcomes following intervention for PlA2–positive individuals, though these results did not achieve statistical significance.

Although these studies differ in their conclusion relative to the strength of the impact of PlA2 on adverse events, substantial differences in the design and end points among the studies must be noted. In addition, the antithrombotic regimen varied considerably among these studies. We have previously reported on the gradual beneficial effect of improved antiplatelet regimens on the occurrence of thromboembolic complications in stent patients displaying the PlA2 polymorphism (21). Hence, with the use of thienopyridine derivatives and GPIIb-IIIa blockers, outcome differences between PlA1/A1 homozygous and PlA1/A2 heterozygous individuals seem to become blurred. However, PlA2/A2 homozygous patients appear to remain at higher risk despite therapeutic advances (19,22).

GPIa polymorphisms. The two polymorphisms in the gene for GPIa occur at nucleotides 807 (C or T) and 873 (G or A) and are associated with up to 10-fold variation in receptor density on the platelet surface. Because these polymorphisms do not result in an amino acid substitution, they are considered silent polymorphisms and do not produce alloantigens. A third polymorphism at nucleotide 1642 results in the substitution of glutamic acid for lysine. Despite the possibility that these polymorphisms may result in an increased number of collagen receptors on the platelet surface, studies examining the role of GPIa mutations in acute coronary syndromes have reported conflicting results (23–25).
TRANSLATING GENETIC STUDIES INTO Clinical Practice

With so many conflicting results from epidemiologic studies of platelet polymorphisms, how should clinicians interpret the findings by Meisel et al. (2)? Should health care providers begin potentially costly screening programs to predict cardiovascular risk or instead dismiss these results as inconclusive evidence? Although it is appealing to attribute much of the disagreement among studies to design or patient populations, it is also important to recognize that the clinical diagnosis of acute coronary syndromes includes a broad range of phenotypic characteristics. Moreover, the relative impact of platelet polymorphism such as GPIbα may vary according to multiple factors such as age, gender, smoking history, diabetes or medications. Although platelet polymorphisms are a promising addition to more established cardiovascular risk factors, identifying genetic variants as a single cause of cardiovascular disease would be an oversimplification; instead, the contribution of these polymorphisms should also be considered in the context of nongenetic factors.

It appears most appropriate to accept the present study as part of a growing body of evidence to define the role of inherited platelet polymorphisms in cardiovascular disease. To date, no single trial has conclusively established the importance of platelet polymorphisms. Until a large database involving thousands of patients is able to reconcile divergent findings satisfactorily, the controversy will remain.

Considering inheritance patterns, the accuracy of genotyping and the impact of environmental factors, the required sample size to have adequate power has been estimated to include several thousands of patients (26). Therefore, studies should encourage carefully supervised genetic sampling as part of larger clinical trials or even routine patient care to create larger databases.

Aside from describing a relationship between platelet polymorphisms and cardiovascular disease, such studies should also motivate scientists to define the biologic effects of inherited platelet traits more accurately. In the case of GPIbα, for example, there is uncertain evidence whether the mutation definitely results in a greater number of platelet membrane receptors. Understanding the interaction of platelet polymorphisms with cardiovascular risk factors and endovascular procedures may also influence treatment strategies targeting a specific susceptibility gene implicated in coronary thrombosis. Considering the increased risk of the PlA2 polymorphism for adverse events in patients undergoing coronary stenting, affected patients might benefit from a more intensive antithrombotic regimen of extended therapy with both aspirin and clopidogrel (21). Platelets from PlA2-positive patients may be more resistant to inhibition with aspirin than those from PlA1/A1 homozygous patients in the presence of collagen. However, treatment with the combination of aspirin and clopidogrel in PlA2-positive patients appears to attenuate collagen-induced platelet aggregation, such that their platelet inhibition is no longer different from that of PlA1/A1 patients receiving aspirin alone (P. J. Goldschmidt-Clermont, personal communication, 2001). In addition, statin therapy following coronary stenting may abolish the increased incidence of restenosis observed among PlA2 carriers compared to PlA1/A1 homozygotes (27).

Despite the substantial research activity in the genetics of coronary artery disease, relatively little coordinated effort has been made to confirm the associated risks of specific gene polymorphisms. As a result, identifying risk associated with genetic discoveries and translating this knowledge into clinical practice will likely occur gradually rather than by one revolutionary discovery. To solve this problem, future studies should consist of larger studies that adhere to the same standards as contemporary large-scale randomized trials for drug development. Including mechanistic studies as part of clinical trials will also facilitate our understanding of the functional significance of these polymorphisms, help define the impact of these mutations on clinical outcomes and validate case-control association studies. A spin-off effect of these studies might be a better definition of phenotypes for the group of syndromes that we have somewhat arbitrarily assembled under the generic name of “acute coronary syndromes.” Only through a larger collective effort will the role of platelet polymorphisms and other susceptibility genes for cardiovascular disease be defined. Then, the translation of the human genome project into information that is directly relevant to the betterment of our patients may become a reality. Just as the “butterfly flapping its wings today produces a tiny change in the state of the atmosphere” (1), the impact of slight changes within relevant genes for heart disease will become, once and for all, measurable.

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