Platelet polymorphisms as risk-factors in thrombophilia: promising facts or optimistic suggestions?

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During the last four years, the possible association between platelet polymorphisms and increased thrombotic risk has been a topic of debate. This review summarizes the most significant contributions on both sides (favorable and unfavorable) in order to understand if the hypothesis that supports this possible association is based on reliable facts. The bibliographic material has been collected through electronic databases such as the Science Citation Index®, Medline®, the Institute for Scientific Information®, and abstracts presented at recent conferences.

The association between polymorphisms of the GP Ia-IIa and GP Ib-IX and arterial thrombosis is supported by a few but convincing contributions; regarding the association between thrombotic risk and polymorphisms of glycoprotein GP IIIa, the judgment of published works is contradictory. Contributions in favor of the association between thrombotic risk and polymorphisms of GP IIIa refer to studies on a small scale, while works performed on a larger scale seem to disregard such association. Despite the obvious possibility that studies performed on a small scale may have statistical analysis flaws, it is also possible that small and homogeneous patient groups may reveal underestimated or unknown clinical variants if analyzed in the light of low-frequency polymorphisms. The debate is promising and remains open to new contributions.

Key words: thrombophilia, thrombosis risk, platelet polymorphisms, platelet glycoproteins.

The ancient Greek term διατεσις (Latin diathesis) means disposition to something. Relating to medicine, diathesis means disease susceptibility: an individual, familial, or even racial condition enhancing the possibility to be affected by certain diseases. The concept of diathesis arises from the deepest history of Western medicine (i.e. Hippocratic school). Diathesis became an important concept of scientific medicine, born around the XVI-XVII century, and it was particularly addressed by the French medical school at the end of the XIX century. At the early opening of the XX century, Sir Archibald Garrod joined the term diathesis together with his concept of chemical individuality. The chemical basis of human individuality was particularly stressed by Leone Lattes (Italian school of Pavia) who investigated chemical individuality at the level of blood antigen relating to transfusion and forensic medicine. Modern genetic medicine has produced an enormous set of evidences supporting the linkage between disease susceptibility and molecular individuality. Today, the strict relationship among gene assessment, protein structure, and disease susceptibility is a paradigm of molecular medicine: such paradigm includes susceptibility to thrombosis.

Physiologic hemostasis is the result of a complex network of molecular, cellular, and humoral mechanisms which maintain blood fluidity within blood vessels. In response to endovascular injury, whatever the cause, blood-clotting enzymes and platelets interact, promoting vascular repair and reconstitution of endothelial integrity. Diseases owing to hypercoagulable states arise through imbalance between prothrombotic and anticoagulant physiologic mechanisms, when the former are predominant.

According to the most recent view, hypercoagulable state does not represent, in general, a systemic disorder, signalling pathway being differentially affected in different segments of the vascular tree, leading to characteristic thrombotic phenotypes.

While local anticoagulant pathways are relevant at the district level, blood-clotting factors and platelets intervene locally, being recruited as systemic available cofactors.
Along with local predisposing factors, clotting enzyme- and platelet-predisposing factors (individual phenotypes) are or and may be relevant in promoting thrombophilic states.

Many individual risks are known to be associated with thrombosis: i.e. hyperlipidemia, hypertension, diabetes mellitus, sex, obesity, cigarette smoking, and others. Most of these predisposing factors have genetic bases. Clinical evidences for molecular driven defects leading to thrombophilia began to be disclosed during the past eighties. During the nineties many demonstrations appeared, correlating specific molecular defects, or polymorphisms, and individual risks to develop thrombosis. Single-gene and multiple-gene abnormalities of coagulation factors are implicated: some of these defects have been recently addressed.

Much more recently, platelet polymorphisms conquered the honour of the stage as possible actors playing an active role in the thrombosis tragedy. This short review should not visit the established role of molecular variants of coagulation factors; it will focus on the debate recently opened about the putative role of platelet polymorphisms as independent risk-factors in thrombophilic states.

In certain conditions, platelets adhere to exposed subendothelial connective tissue, in particular to collagen. Such adhesion is a receptor mediated event, involving both integrin and non-integrin receptors. The most important platelet receptors for collagen are glycoprotein (GP) Ia-IIa, GP IV (CD36), GP VI. Primary adhesion of resting platelets to subendothelial tissues involve also von Willebrand factor associated with collagen: von Willebrand factor bind to the platelet membrane glycoprotein complex Ib-IX-V. Following such binding, resting platelets become activated. One of the most representative platelet integrin receptor, GP IIb-IIIa, undergoes conformational changes leading to exposition of fibrinogen binding sites. Fibrinogen-platelet interactions enhances platelet adhesion and promotes platelet aggregation. Platelet activation takes place also following thrombin interaction with GP Ib. Other ligand-receptor reactions are implicated in platelet adhesion-activation process: among these, GP Ic-IIa-fibronectin, GP Ic-IIa-laminin, GP IV-thrombospondin, must be mentioned. The process involves also the recruitment of non-platelet cells such as monocytes and granulocytes through P-Selectin (CD62) and PECAM-1 (CD31). The entire chain of the events regulating platelet glycoprotein interactions with subendotelial matrix has been clearly illustrated by Clemetson and Polgár. The haemostatic relevance of such receptors become self-evident looking at the haemostatic impairment of the platelet function owing to defective GP Ib-IX-V complex (Bernard-Soulier syndrome) or GP IIb-IIIa complex (Glanzmann's disease). Membrane associated glycoproteins involved in platelet adhesion and activation phases have been found to be encoded by two or more allelic isoforms that differ by a single nucleotide. The aminoacid polymorphisms that results from such base substitutions cause small localized conformational change in the glycoprotein three-dimensional structure. Such changes are likely to be recognized by allogeneic immune competent cells; from the functional point of view, such changes may also influence the ligand-receptor interaction. Sixteen glycoprotein alloantigen systems have been recognised. They are located in GPIa, GPIb, GPIIb, and GPIIIa and all are characterised by a substantial allele unbalance (Table I).

Such allele unbalance rises questions upon its evolutive and functional significance.

Megakaryocyte-derived non-nucleated platelets are found only in mammals. Their sudden phylogenetic appearance (400 million years ago) seems to be a typical example of the evolutionary concept of punctuated equilibria by introducing a marked separation between mammals and all other taxa. Such separation includes the dichotomy between haemostatic-procoagulant function of platelets and anti-bacterial capacities, both retained by pre-mammalian and non-mammalian platelet precursors such as Limulus amaebocytes or ascidian Halocynthia roretzi haemocytes. The evolutive conjunction ring between mammalian platelets and non-mammalian platelet precursors seem to be the monotreme echidna (Zaglossus and Thachiglossus), while the other monotreme platypus (Ornithorynchus anatinus) has mammalian-like platelets.

Platelet and platelet precursor glycoproteins are very well conserved proteins and show very similar structure and function. Furthermore, strict structural similarities have been shown between animal and vegetal αβ3 complexes. Both plant and animal αβ3 complexes react to similar stimulators and interact with adhesive proteins by the RGD recognition sequence.

The final question arising from such brief evolutive excursion is again: the human platelet allelomorphic unbalance of such conserved glycoproteins may have some functional, ever clinical, significance?

The logic of the selective pressure applied to high conserved proteins suggests that the most useful aminoacid sequences have evolved through hundred millions years, predominant alleles being favoured and low-frequency variants being discouraged. Allele unbalance may be the simple result of evolutive selection. In addition, one must consider the fact that platelet glycoprotein polymorphisms are highly immunogen, and variants may be therefore immunologically eliminated just at their
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Table I: nomenclature, molecular genetics, and frequencies of human platelet-specific alloantigen polymorphisms

<table>
<thead>
<tr>
<th>Antigen Synonym</th>
<th>Glycoprotein location</th>
<th>Nucleotide substitution</th>
<th>Aminoacid substitution</th>
<th>Antigen frequency (%)</th>
<th>Ref.</th>
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<td>Thr 145</td>
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<tr>
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<td>15</td>
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<tr>
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<td>Arg 143</td>
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emergence by maternal immunisation. Neonatal alloimmune thrombocytopenic purpura is a strong clinical evidence of it, and it can function as a selective mechanism sufficient to keep the frequency of mutant polymorphisms low. Then, one may assume that low-frequency platelet specific alloantigens, along being unfavoured by selection, are, or may be, associated with function abnormalities. Up to now, no in vitro evidence, neither morphological nor clinical, has been found to support such hypothesis.

However, in an article published by the New England Journal of Medicine, Weiss et al. have firstly indicated the platelet alloantigen polymorphisms as independent risk factors for coronary thrombosis. Starting from this clinical evidence, this review should summarise some of the most intriguing data relating to platelet glycoprotein polymorphisms and their clinical significance, particularly of those suspected to be associated to thrombophilia.

Generally speaking, platelet receptor polymorphisms, not necessarily those due to platelet alloantigen systems, are known to induce sometime platelet dysfunction, mostly related to haemorrhagic diathesis. The Cam variant, involving the 119Asp/Tyr substitution in GP IIIa, leads to haemorrhagic diathesis owing to a loss of RGD-binding function; in fact, such substitution is included in the sixty-three RGD aminoacid sequence (109-171). Curiously, the Yuk/Pen polymorphism (GPIIIa143Arg/Gln = HPA-4a/b), which is also located into the RGD sequence, does not seem to be associated with function disturbance. A great variety of molecular variants are associated with platelet impaired function such as Glanzmann's thrombasthenia (GPIIb-IIIa variants) and Bernard-Soulier syndrome (GPIb-IX-V variants). It has been also suggested that some
variant altering the tandem repeats extension of GP Ibα may increase the susceptibility for pathologic thrombi to form67.

The FCγRIIA is a low affinity receptor for aggregated or antigen-bound IgG. Such small glycoprotein is expressed on a variety of cell including platelets. Three FCγRIIA polymorphic forms are due to the His/Arg substitution in amino-acid position 131. When histidin is present in this position, platelets are much more easily activable by anti PF4/heparin antibodies; homozygous 131His platelets are more activable by anti-PF4/heparin antibodies than heterozygous53. Predictably, patients with 131His polymorphism of FCγRIIA can be more susceptible to heparin-induced thrombocytopenia which have frequent thrombotic complications. The platelet alloantigen system Bra/Brb (HPA-5a/b) is generated by GPIa 505Glu/Lys amino acid substitution. Such polymorphism belongs to the VLA-2 collagen receptor, but this mutation is not known to affect platelet function in physiologic conditions. Bra/Brb polymorphisms are in linkage disequilibrium with two silent polymorphisms of the GPIa gene, at codon 224Phe (807 C/T polymorphism) and at codon 242The (873 G/A polymorphism). Such silent polymorphisms regulate the VLA-2 density on the platelet external surface; such receptor density may vary by a factor 10 according with the allelic forms54-56. One may assume that such a high variation of VLA-2 density might modulate platelet adhesion/aggregation in those pathologic conditions which are characterised by subendothelial collagen exposition57,58.

In the same way by which venous thromboembolism seems to be strongly related to a multigenic polymorphism interaction59-62, platelet polymorphisms may interact in a multigenic fashion, possibly together with other polymorphisms, thus creating the conditions for an increased risk to develop arterial thrombosis.

Following the observation reported by Weiss and colleagues on a cohort of 71 patients67, the association of increased risk for thrombosis and human platelet polymorphisms carried by GP IIb-IIIa, GP Ib-IX, and GP Iα-IIa was investigated. The great majority of the studies refers to GP IIb-IIIa complex polymorphism, in particular those related with the HPA-1a/b (Leu33Pro, PlA1/2, Zwa/b) alleles. The first two paper published on this topic were two letters published on Lancet. Osborn et al. did not find any correlation between GP IIIa polymorphism and myocardial infarction in a series of 233 patients64. Similar results were showed by Odawara and colleagues in a cohort of 370 diabetic patients with coronary disease64. Since these letters have been published, at least nine authoritative papers appeared denying association of platelet polymorphisms and thrombotic diseases by evaluating small and large groups of patients. Here I will resume the most significant data reported in such papers.

Carlsson et al. did not find differences between HPA-1, 2, 3, and 5 polymorphisms in 218 consecutive patients with stroke, 165 patients with cerebral vascular disease and 321 healthy controls65. Ridker and colleagues reported similar HPA-1b frequencies in 374 patients with myocardial infarction, 209 patients with stroke, 121 patients with venous thrombosis and in a control group in a eight-year long prospective study of 14,916 enrolled subjects66. Peter J Newman defined unlikely the linkage between Leu33Pro polymorphism of GP IIIa and the increased risk of thrombosis owing to "more sticky fibrinogen receptor" in the HPA-1b form67, adding convincing experimental evidences in support to his statement68. Most of the articles published prior 1998 limited their analysis to the comparison of phenotype frequencies of patients and controls: both patients and controls were taken as broad and homogeneous groups. Papers published afterwards tried to consider, when possible, more clinical variables. Zott et al., in 1998, evaluating the coronary artery disease on 124 patients with and 83 patients without premature myocardial infarction, stated that HPA-1b phenotype "does not represent a risk factor for coronary artery disease itself but appears to be associated with increased platelet thrombogenicity"69. Wagner and colleagues, while stating that PlA2 polymorphism of GP IIIa is not associated with stroke in young women, affirmed that "subgroup analyses showed that the PlA2 polymorphism appeared to be associated with stroke risk among white women with clinically identified probable aetiology for their stroke", suggesting that PlA2 allele could interact with other conditions predisposing to stroke30. Scaglione et al. studied 98 patients with premature myocardial infarction70. They did not find significant difference in the PlA1/PlA2 allele distribution within patients and controls, arguing that GP IIIa PlA2 gene polymorphism can not be used as a predictor of premature myocardial infarction. Nevertheless, they presented a table of the results indicating an higher prevalence, albeit not significant, of PlA2 homozygous subjects within the patient group.

In 1999, Laule et al. evaluated, at 30-day composite endpoint, 653 patients undergone angioplasty intervention (271 coronary angioplasty, 102 directional coronary atherectomy, 280 stenting) without finding any correlation of Leu33Pro polymorphism of GP IIIa and the clinical outcome at the end of the follow-up period31. Cenarro and colleagues did not find a correlation between PlA2 polymorphism frequency and coronary syndromes in a cohort of 40 patients with heterozygous familial hypercholesterolemia73.
Along such negative or dubitative results, other equally authoritative results have been published during the same period of time (1997–1999), supporting the association of PlA2 polymorphism and thrombotic risk. Carter et al., looking for an association of PlA2 allele with the fibrinogen Bb448 polymorphism in 405 patient submitted to angiography, reported the association of PlA2 allele with myocardial infarction (odds ratio, 1.66) and multiple vessel thrombosis (odds ratio, 1.5)74. Walter et al., evaluated prospectively for a 30-day follow-up period 318 consecutive patients submitted to coronary stenting. They demonstrated an increased risk of stent thrombosis in patients with PlA2 allele (odds ratio, 5.26)75. Kastrati and colleagues performed coronary angiography in 1,150 patients submitted six months earlier to coronary stent. They evidenced a higher stent-thrombosis rate in patients with- than those without- PlA2 allele, the influence of PlA2 polymorphism being more pronounced in women. The investigators argued that PlA2 allele were an independent risk factor for restenosis76. Anderson et al. have studied 791 patients undergoing angioplasty and they have found PlA2 variant allele weakly associated with non-fatal myocardial infarction and not associated with coronary artery disease per se77. Very recently, Goodall and colleagues, in a cohort of 70 patients, have found that the rate of myocardial infarction was high, albeit not significantly (p = 0.58), in patients with HPA-1b. More interestingly, they have found that fibrinogen binding to ADP-stimulated platelets was significantly higher in HPA-1b patients (p<0.0001)78. The Authors argued that, by this way, the HPA-1b allele may predispose patients to higher risk of thrombosis. Undas et al. have also demonstrated very recently that reduction of thrombin generation following aspirin administration is lower in patients carrying the PlA2 allele. The Authors strongly support the hypothesis that the PlA2 allele reduces the antithrombotic action of aspirin79. Such possibility was previously suggested by Alan Nurden80. The clinical impact of such hypothesis is very serious, the large majority of patients with prothrombotic risk assuming aspirin prophylactically. From the clinical point of view, this is to be consider much more seriously at the light of the observation that ADP aggregates platelets from aspirin-treated patients at concentration three time less than those of untreated patients81. The mechanism of this unexpected effect of aspirin is the up-regulation of platelet ADP receptor. By this view aspirin, in spite of reducing, may enhance the thrombotic risk at the local-lesion level, where the ADP concentration may be relatively higher than in other lesion-free districts. If this is the case, aspirin treatment of patients with PlA2 allele should be reconsidered.

Observations regarding thrombosis associated platelet polymorphisms other than those carried by GP IIb-IIIa are rare. Moshfegh and colleagues described a three-to-six fold increment (twenty fold if smokers) of myocardial infarction risk in patients carrying two silent (no specific alloantigen phenotypic expression) and linked polymorphisms within the glycoprotein Ia gene (807 C/T, 873 G/A) of glycoprotein GP Ia-IIa complex82. Such silent polymorphisms seem to be involved in the mechanisms of membrane expression of GP Ia-IIa: the amount of membrane expressed GP Ia-IIa is then strictly related to collagen binding capacity of platelets83. The clinical observations reported in this article seem to have proper cause-effect relationship sustained by polymorphism driven molecular assessment. Santos0 et al. have investigated 640 patients in this regard, and they have confirmed that the 807T allele of glycoprotein Ia gene is associated with myocardial infarction (odds ratio, 1.55, p<0.05) and with coronary artery disease (odds ratio, 1.94, p<0.05)84. Nevertheless, the same group of investigation showed also that 807 T allele is not correlated with the development of stroke and thrombosis in patients with heparin induced thrombocytopenia85. A size polymorphism within GPIbα chain of GP Ib-IX-V complex has been indicated as an independent risk factor for coronary artery disease and for cerebrovascular disease86,87, but it seems without a significant role in venous thrombosis. The implicated allele codes for tandem repeats of a 13 amino acid sequence; elongation of this chain increases von Willebrand factor binding to GP Ib-IX complex, thus increasing three to eight fold the risk of coronary artery disease.

During the last four years, controversial results have been presented on the association of platelet polymorphisms and thrombosis risk. This is especially true for GP IIIa variants. Some reports showed quite opposite results investigating quite identical clinical cases. Researchers disclaiming the association of platelet polymorphisms and thrombosis risk assume that misleading associative conclusions may arise in small patient study groups, owing to low-frequency of the implicated alleles, or owing to variation of allele frequencies across ethnic groups87,88.

Such objections are scientifically correct, however they sound to me too much simplistic if applied to such a complex matter as multifactorial biological event such as thrombophilia8. Critically comparing the published data, it seems that in larger sample size studies the allele associated risk, if any, tends to disappear. Large-scale are much more valuable than small-scale investigation in term of reliability of the odds ratio value, statistical significativity of the differences, and epidemiological consistency. However, in this topic,
the question arises if large-scale studies tend to dilute the possible relationships among low-frequency risk factors (inheritable, environmental, behavioural) vanifing the efforts to find clinically valuable associations. Large-scale studies reduce the bias connected with patient and/or control selection.

Multivariate analysis of large-scale studies is used for finding significant relationships among known variables hidden into the mass of the experimental results. But if a significant variable is not yet known, multivariate analysis may fail to detect it. For this reason, small-scale studies giving significant differences between patient/control groups, such as reported in this review, should be considered with the greatest interest in order to find clinically important variables (underscored or underestimated) which fit with known parameters (platelet polymorphisms in this case).

According with the data currently available it seems quite clear that not all thrombophilic syndromes are equally associated with platelet polymorphic alleles; platelet polymorphisms do not influence venous thrombosis, while they seem to facilitate stent restenosis and possibly, in a variable extent, coronary artery disease.

In addition, no single polymorphism inherited as an allelic trait, neither in the homozygous nor in the heterozygous form, has been proved to be associated with in vitro demonstrable platelet dysfunction in physiologic conditions. Nevertheless, in some conditions characterised by a particularly perturbed equilibrium at the endothelial-platelet-coagulation-fibrinolysis interfaces, as some of those described here67,69,70,74-84,86-88, platelet polymorphisms should reasonably play a pathophysiologic role.

In conclusion, also in the case of undetectability of polymorphism-related platelet dysfunctions, this does not indicate necessarily that no potentially evocable dysfunctions exist at all. Potential dysfunctions could emerge on the pure clinical ground as the result of multifactorial events.

Many known, and eventually many unknown, traits and characters are influencing the individual response to agonists and to antagonists (naturally occurring or therapeutically administered); platelet polymorphisms can belong to, or interact with, such traits and characters. Some Author maintained that platelet polymorphisms play a role as cofactorial or independent risk factors in thrombophilic syndromes.

Other Authors are still sceptic. In any case, a way of investigation has been indicated. Much more study is still required to ascertain if thrombosis risk associated with platelet polymorphisms is a real fact or just an evanescent suggestion.

Abstract

During the last four years, the possible association between platelet specific polymorphisms and the increased risk for thrombophilia is object of debate. Authoritative papers have been published both in favour and against such associations. This review will summarise the outstanding contributes on both field (pro & con) in order to understand if the hypothesis for such association is supported by credit worthy evidences.

The material presented in this review has been collected among the articles and the abstracts published in journals covered by the Science Citation Index®, Medline®, those available through the Institute for Scientific Information®, and the abstracts published in abstract books of selected symposia. Association of GP Ia-IIa and GP Ib-IX polymorphisms and thrombotic artery disease are sustained by few but convincing investigations, while contradictory evidences have been published on thrombotic risk associated with GP IIIa polymorphisms. In general, paper arguing in favour of such association are showing the results obtained on small scale investigations.

Author disclaiming such association are mostly sustained by large patient-group studies. Albeit the possible statistical bias owing to small patient-group studies, it seem reasonable that underscored, or actually unknown, clinically relevant variables should be better detectable, if associated with low-frequency polymorphisms, in small-scale homogeneously-selected patient groups. The debate is promising and still opened to new findings.

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