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Reviews

The Role of Platelet Glycoprotein Ib and IIb Polymorphism in Coronary Artery Disease

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In Western society atherosclerotic disease is one of the commonest causes of increased morbidity and mortality[1,2]. Atherosclerosis is a multifactorial disease and many different environmental factors such as physical inactivity, cigarette smoking, hormonal and genetical or acquired (inherited dyslipidaemia, hypertension, diabetes, positive family history of cardiovascular disease[3,4]) combine in order to determine its onset and outcome.

Especially within the last decade, several genes and their polymorphisms involved in the atherosclerotic process, have been found to increase thrombotic predisposition and risk of acute coronary syndromes. Among these genes, platelet glycoprotein polymorphisms have been studied intensely.

This article is a review regarding the role of two platelet glycoprotein polymorphisms Ib and IIb in cardiovascular thrombosis. It is also worth mentioning the difference between polymorphism and mutation. Mutation is defined any change (heritable or not) in DNA sequence while polymorphism is the difference in DNA sequence among individuals. The term polymorphism describes genetic variations occurring in more than 1% of the population.

Platelet receptors and their role in thrombosis

Most platelet receptors are protein complexes with two or more polypeptide subunits non-covalently associated with the platelet membrane[5]. In all stages of platelet adhesion and aggregation, these receptors interfere with subendothelial matrix. Following vascular injury and under high shear stress conditions[6], platelets adhere to the surface bound von Willebrand factor (vWF) through the platelet glycoprotein (GP) Ib/X/V. This adhesion is made more stable and secure by subsequent multiple interactions between glycoprotein Ia/IIa with collagen and GPIIb/IIIa and Ic/IIa with vWF and fibronectin respectively[6].

Given the importance of platelet glycoproteins in primary haemostasis, it is reasonable to suggest that in certain circumstances, inherited differences in these platelet receptors may contribute, by altering their activity, to an increased risk of acute coronary events. A platelet polymorphism, for instance, in a regulatory gene region may alter the expression of the receptor on the platelet surface. Moreover a nucleotide polymorphism that results in an amino acid substitution may change the tertiary structure of the receptor and subsequently change platelet adhesive function.

Glycoprotein GPIb/IX/V- Structure and polymorphism

This receptor consists of four subunits (proteins: GPIba, GPIbβ, GPIX and GPV) that are the products of distinct genes[7]. These subunits have similar structural features and belong to the "leucine-rich family" of glycoproteins[8]. There are approximately 25.000 copies of this receptor per platelet[9,10]. Glycoprotein Ib is composed of two disulfide- linked polypeptides, glycoprotein Iba and glycoprotein Ibβ and this complex is non-covalently associated with glycoproteins GPIX and GPV[8,11,12]. The GPIb/IX/V receptor mediates the initial adhesion of platelets to the extracellular matrix under conditions of high shear stress via the binding of von Willebrand factor (vWf) to the amino acid terminal domain of glycoprotein Iba[13]. Given the importance of the GPIb/IX/V receptor in platelet adhesion it is reasonable to suggest that small alterations in GPIb structure can influence the platelet's functional responses and subsequently the thrombotic risk[14].

Two polymorphisms of the glycoprotein Iba gene that affect the structure have been described and a third one that may lead to altered gene expression of this subunit. In the first polymorphism, a cytosine (C) to thymidine (T) substitution, results in the amino acid methionine[15] in the place of threonine at position 145 and is responsible for the HPA-2 platelet antigen system[16]. This dimorphism is in linkage disequilibrium with a variable number of tandem repeat (VNTR) polymorphism within the macroglycopeptide region of GPIa resulting in the duplication of a 13 amino acid sequence[17]. This last fragment can be present as a single copy or repeated up to four times.

In the third polymorphism of GPIba, a T to C single nucleotide substitution at position 5 from the initiator methionine codon is termed Kozak polymorphism and is thought to alter the translational efficiency of glycoprotein Iba[18]. Moreover, an association between the C-5 allele and increased GPIb / IX/V receptor density has been documented[19-21].

GPIb/IX/V polymorphism and cardiovascular disease

GPIb/IX/V receptor is responsible for the initial platelet adhesion to the subendothelium under high shear stress conditions and several studies have assessed its polymorphisms as potential independent risk factors for myocardial infarction. In a Japanese study of 91 patients with non-fatal myocardial infarction or angina and 105 healthy controls, the Met 145 allele was associated with increased risk of coronary heart disease among a subgroup of patients under the age of 60[22]. At the same time other studies[23,24] failed to confirm this association even when analysis was limited in younger female patients with myocardial infarction[25].

Table 1. The GPIba Met 145/VNTR A or B polymorphism and thrombotic risk.

Positive correlation	Negative correlation
Coronary artery disease	
Murata et al[22]	Ito T et al[24]
Gonzalez-Conejero et al[27]	
Myocardial infarction	
Mikkelson J et al[31]	Hato T et al[23]
	Ardissimo D et al[25]
	Mercier B et al[32]
Cardiovascular disease/stroke	
	Carlsson LE et al[29]
	Carter AM et al[30]

The preliminary data, regarding the role of the VNTR polymorphisms in acute ischaemic events, are also conflicting[26] (Table 1). A limited number of studies have demonstrated an association between Met 145 (VNTR A or B) and risk of cardiovascular disease[15,22,27,28] while others have not found this association[29,30]. In a recent study the HPA-2 Met/VNTR B allele was associated with increased occurrence of myocardial infarction and sudden death in middle age patients[31] (Table 1).

Studies have discrepancies in assessing the risk of GPIb/IX/V polymorphism in different ethnic groups. Among European populations the VNTR B/C genotype was associated with a 2-3 fold increase in risk of coronary artery disease in a Spanish population[27] but no association was detected in a French population[32]. Furthermore, in a prospective study of middle-aged Americans the VNTR C/C genotype was associated with a decreased risk of coronary events[28,33] (Table 1).

The data regarding the role of the Kozak polymorphism of the GPIba variant are also inconclusive. The study by Meisel et al[34] is the first that associated the 5C allele of this polymorphism with an increased risk of unstable angina or ischaemic complication following percutaneous coronary intervention. The same finding was confirmed recently by Kenny et al[35]. In this last study the T-5C polymorphism in GPIb alpha was associated with the risk of MI in a population with unstable angina[35] (Table 2).

Several studies[21,28,36] failed to confirm an association between this dimorphism and clinical risk for arterial thrombosis while others reported a trend

Table 2. Kozak polymorphism and thrombotic risk.

Positive correlation with myocardial infarction	Negative correlation with myocardial infarction
Douglas H et al[37]	Croft S et al[21]
Meisel C et al[34]	Corral J et al[36]
Kenny J et al[35]	Frank MB και συν[38]
	Sperr WR et al[57]

towards protection against myocardial infarction by the 5C allele[37,38]. This discrepancy in the results can be explained partly by differences in the selection of the study population and the choice of the control group (Table 2).

A careful review of the published studies, does not allow us to reach a conclusion regarding the role of GPIb/IX/V polymorphisms in coronary artery disease. Further studies are needed to clarify the role of the polymorphisms of this receptor in coronary artery disease.

Glycoprotein GPIIb/IIIa - Structure and polymorphism

GPIIb and GPIIIa are present in platelet membrane as a heterodimeric complex whose formation requires the presence of divalent cations[39]. Two chains of GPIIb are associated non-covalently with one chain of GPIIIa for the formation of GPIIb/IIIa complex[40,41]. There are approximately 80,000 copies of GPIIb/IIIa per platelet[39] and its major ligands are fibrinogen and vWF either when they are immobilised or in solution after platelet activation.

The genes that encode GPIIb and GPIIIa are both in 17q21 chromosome[42]. A number of point mutations have been described in GPIIb/IIIa's gene and there are data suggesting their interference in the etiology of acute coronary syndromes. Polymorphisms of GPIIb as well as GPIIIa have the ability to produce platelet specific alloantibodies. These antibodies are the main cause of several disorders i.e. post-transfusion purpura and neonatal alloimmune thrombocytopenia[43]. There are at least seven GPIIIa alleles but the most common polymorphism in GPIIIa is described by the human alloantigen system HPA-1 (Pl^{A})[39] with frequencies of 97.9% for HPA-1a and 26.5% for HPA-1b in the Caucasian population[44]. Due to the substitution of a cytosine from a thymidine at position 1565 in exon 2 of the GPIIIa gene, the platelet antigen Pl^{A2} variant displays a proline instead of a leucine at position 33[39]. A rare leucine 40/arginine40 polymorphism on platelet glycoprotein IIIa is linked to the human platelet antigen 1b[45]. Four other rare polymorphisms in GPIIIa gene have been described and are related with the alloantigen system HPA-4[46,47], HPA-6[48], HPA-7[49], HPA-8[50].

A thymine (T) to guanine (G) transversion in exon 26 of the glycoprotein IIb gene that encodes an Ile to Ser substitution at amino acid 843 has been reported and is responsible for the expression of the HPA-3 alloantigen system[51].

Glycoprotein IIb Ile 843 Ser and cardiovascular risk

Studies regarding the functional consequences of this polymorphism have yielded conflicting results. Several investigators have observed no effect on *in vitro* platelet aggregation[52] while other reports indicated that platelets with the GPIIb Ser843 allele demonstrate increased *in vitro* platelet aggregation and decreased clot retraction compared to those lacking the allele[53].

Controversial are also the data regarding the role of this polymorphism in coronary artery disease. Reiner et al[54] reported an increased risk of myocardial infarction among women who possessed at least one copy of the GPIIb Ser 843 allele (Table 3). This increased risk was present only in a subgroup of women who had additional cardiovascular risk factors (cigarette smoking, hypercholesterolemia or had a positive family history of early myocardial infarction)[54]. In contrast studies involving male patients from Japan[23] or Central Europe[55-57] failed to detect the same association (Table 3). In addition in a study of 2178 patients with symptomatic coronary disease undergoing coronary stent placement, the Ser 843 allele was not related with the development of coronary stent thrombosis or restenosis[58] (Table 3).

With so many conflicting results from epidemiological studies it is difficult to recognize Iib Ile 843 Ser polymorphism as an important inherited determinant of atherothrombotic risk. The possible

Table 3. GPIIb polymorphism and thrombotic risk.

Positive correlation with myocardial infarction	Negative correlation with thrombosis
Reiner AP et al[54]	Sperr WR et al[57]
	Bottiger C et al[55]
	Hato T et al[23]
	Kroll H et al[56]
	Bottiger C et al[58]

association between the Ser 843 variant and increased risk of arterial thrombotic disease among premenopausal women requires confirmation in larger studies.

Genetics and antiplatelet therapy

Genetic factors are postulated to modulate drug response either in determining efficacy or the risk of side-effects. It has been hypothesised that the clinical efficacy of antiplatelet drugs (i.e aspirin) might be related to Pl^A polymorphism. Aspirin inhibition of platelets varies by Pl^A genotype[59,60]. In addition, a more specific antiplatelet therapy, GPIIb/IIIa antagonists, have been suggested to have different responses according to Pl^A genotype[61-63]. GPIIb/IIIa antagonists bind to the receptor and prevent platelet aggregation to all known agonists but oral GPIIb/IIIa antagonists have been proven to be ineffective and even harmful when administered in patients with acute coronary syndromes[61]. Whether the Pl^{A2} variant of the GPIIb/IIIa antagonists is more susceptible to the partial agonist activity induced by smaller ligands such as GPIIb/IIIa antagonists and whether this hypothesis can explain the observed variability in the response to these drugs in humans has yet to be addressed.

Conclusions

Platelet glycoprotein receptors play a primary role in the thrombotic process. They mediate the multiple interactions of platelets with the extracellular matrix and they interfere with coagulation mechanisms. Therefore, platelet glycoprotein polymorphisms may be involved in the process of thrombosis.

The preliminary data regarding the glycoprotein GPIb and GPIIb polymorphisms in ischaemic events as well as in the adverse thrombotic events after coronary interventions are inconclusive and often controversial. The discrepancy in the results of different studies may be explained partly by differences in the study design and the analysis. Many studies have a limited sample size, which is frequently too small to confirm or rule out the presence of a relevant epidemiological association between specific polymorphisms and cardiovascular disease. Moreover, studies differ in ethnicity, bias in selection of patients and controls, plurality in clinical endpoints and variation of environmental factors. Furthermore, as far as the correlations between genes and myocardial infarction are concerned, the true effect of genotype can be masked if mortality rates are the endpoint. Correlations between platelet polymorphisms and environmental risk factors reinforce this. Moreover, several genes are in linkage disequilibrium with other genes and simultaneous studies of several genes may reveal associations that at present seem to be weak. Regarding the correlations between genes and myocardial infarction, the true effect of genotype can be masked by whether patients died of acute coronary syndromes or when only survivors are included in the studies.

Considering that atherosclerosis is a multifactorial disease it is extremely difficult to conclude that genetic inheritance will be enough to explain the interindividual variations by itself. Correlations already noticed between platelet polymorphisms and environmental risk factors reinforce this assumption. It is difficult to arrive at a definite answer for the role of platelet polymorphisms and especially for GPIb and GPIIb polymorphism, as present reports are inconsistent. Understanding the interaction of platelet glycoprotein polymorphisms with cardiovascular risk factors and endovascular procedures may also influence treatment strategies targeting a specific susceptibility gene implicated in coronary thrombosis. Further studies are needed to clarify the potential association between platelet polymorphisms, coronary artery disease and myocardial infarction.

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