# Platelet receptor polymorphisms and thrombotic risk

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**Plaque rupture and/or endothelial damage lead to exposure of von Willebrand factor and collagen which facilitate the adhesion of circulating platelets via glycoprotein Ib-IX-V and the integrin $\alpha_2\beta_1$, respectively, to the damaged vessel wall. This process activates the platelet and leads to a conformational change of a second integrin $\alpha_{IIb}\beta_3$ that facilitates fibrinogen binding and platelet aggregation. Thrombin generated at the blood-plaque interface converts fibrinogen to fibrin, which stabilizes thrombus growth. Therefore, any genetic differences that might alter surface expression or activity of these receptors could influence risk for adverse outcomes as a result of the haemostatic process. In the last 5 years, there has been a rapid accumulation of the literature concerning the relationship between genetic variations in platelet glycoproteins and risk for coronary heart disease.**

**In this chapter, we present a comprehensive review of the impact of platelet receptor polymorphisms and thrombotic risk.**

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Ischemic vascular disease is one of the most common causes of morbidity and mortality in the developed world. Recent data suggest that this disease is also increasing among Asians[1,2]. In recent years, there is increasing evidence that this disease is the result of complex interactions between genetic susceptibility, long-lasting environmental influences (hormone, smoking, overweight) and intercurrent disorders (diabetes, hypertension, dyslipidemia, hyperhomocysteinemia). The most feared complication of these disorders is acute myocardial infarction, which results from the formation of an occlusive thrombus at the site of a ruptured atherosclerotic plaque. Nowadays, the crucial role of platelets in this process is well accepted[3].

## Platelet glycoprotein polymorphisms

Several allelic variants of key platelet glycoproteins (GP) are known to exist within the human gene pool, creating diversity in the expression, function and immunogenicity of these important adhesion receptors components.

Historically, platelet GP polymorphisms have been of clinical interest because of their ability to elicit the production of platelet specific alloantibodies. These antibodies cause enhanced platelet clearance and/or destruction leading to thrombocytopenia and/or hemorrhagic diatheses in three clinically-defined conditions, neonatal alloimmune thrombocytopenia, post-transfusion purpura, and post-transfusion refractoriness[4]. Currently, five human platelet alloantigen (HPA) systems residing on the platelet receptors GPIb-IX-V, $\alpha_2\beta_1$, and $\alpha_{IIb}\beta_3$ are officially recognized. In addition, a number of low frequency alloantigens have been described[5]. Since the first report in 1996 on the association of the $Pl^{A2}$ (HPA-1b) allele of the integrin subunit $\beta_3$ as a risk factor for coronary thrombosis[6], human platelet alloantigens have received widespread and ever increasing attention that extends beyond the field of platelet immunology.

**Polymorphisms of $\alpha_{IIb}\beta_3$.** The integrin $\alpha_{IIb}\beta_3$ is the most abundant receptor on the platelet membrane surface, at about 80 000 copies per platelet, and is known as the receptor for fibrinogen or von Willebrand factor that mediates platelet cohesion, i.e., the formation of platelet aggregates. This receptor is also characterized by several heritable dimorphisms, such that there are four alleles of the $\alpha_{IIb}$ subunit and eight alleles of the $\beta_3$ subunit[5]. The two most common and clinically important $\beta_3$ alleles en-

code Leu33 ($Pl^{A1}$ or HPA-1a) and Pro33 ($Pl^{A2}$ or HPA-1b), with gene frequencies of 0.85 and 0.15, respectively, in the Caucasian population.

Weiss et al.[6] reported that the gene frequency of the $Pl^{A2}$ allele was 3.6 times higher among younger patients (< 60 years of age) with myocardial infarction or unstable angina as compared to age-matched controls (odds ratio 6.2). The impact of $Pl^{A2}$ polymorphism as genetic risk factor of ischemic vascular disease has been given credence by some, but not all, subsequent studies[7]. At the time this review is being written, there are at least seven reports that confirm an association between the $Pl^{A2}$ allele and risk for myocardial infarction in younger individuals[8-14]. On the other hand, there are at least eleven studies that have failed to find such an association[15-25]. Despite the controversy surrounding these clinical correlations, current investigations indicate that the $Pl^{A}$ phenotype has a possible effect on platelet function supporting the contention that it is a clinical risk factor for thrombosis. The $Pl^{A2}$ phenotype seems to confer a lower threshold for agonist-induced platelet responses[26,27], and Vijayan et al.[28] demonstrated that the $Pl^{A2}$ polymorphism alters $\alpha_{IIb}\beta_3$-mediated functions, such as adhesion, spreading and clot retraction.

Polymorphism of the $\alpha_{IIb}$ gene is responsible for the expression of the Bak (HPA-3) alloantigen system. The allele Ile843 confers the $Bak^a$ (HPA-3a) alloantigenic determinant (frequency 0.616), whereas Ser843 represents the $Bak^b$ (HPA-3b) epitope. Large studies have not found an association between the Bak polymorphism and coronary artery disease, myocardial infarction, or post-stent thrombosis or stenosis[25,29].

**Polymorphisms of glycoprotein Ib-IX-V.** The GPIb-IX-V complex is the second most abundant receptor on platelets, at 25 000 copies per platelet, and is known as receptor for von Willebrand factor[30].

Three dimorphisms of the GPIbα gene have attracted interest for their potential relevance in thrombotic risk. The first dimorphism Thr145Met is responsible for the formation of Ko alloantigenic determinants (HPA-2). This dimorphism is in linkage disequilibrium with a variable number of tandem repeats (VNTR) polymorphism within the mucin-like macroglycopeptide region of GPIbα resulting in the duplication of a 13-amino acid sequence either once (VNTR D), twice (VNTR C), thrice (VNTR B) or 4 times (VNTR A)[31-33]. The largest phenotype (VNTR A) might be uniquely distributed among oriental populations[34] and North American Indians[35].

A limited number of studies demonstrated an association between Met145 (VNTR A or B) and risk for the prevalence and severity of coronary artery disease[36-38], while one report has found that there is no such association[39]. At the same time, no association was found between the Thr145Met dimorphism and myocardial infarction in young patients[13,40]. While some authors have reported an association of VNTR A or B with risk for stroke[37,41], others have not found this association[42,43]. Even now it is not clear whether these variations may affect platelet function. Studies *in vitro* showed that platelet aggregation response induced by ristocetin and botrocetin and the binding kinetics of von Willebrand factor to both GPIbα isoforms (Met145 and Thr145) are identical[44,45]. The length of GPIbα is thought to be critical for the stability of platelet binding to von Willebrand factor under shear forces, but the effects of different GPIbα size variants on platelet function has not been directly examined.

The third dimorphism is termed C-5T Kozak polymorphism and was originally reported to be important in translation efficiency of GPIbα. Afshar-Khargan et al.[46] reported an association between the C-5 allele and increased GPIb-IX-V receptor density. However, subsequent studies failed to confirm an association of this dimorphism with clinical risk for arterial thrombosis[47-49].

**Polymorphisms of $\alpha_2\beta_1$.** $\alpha_2\beta_1$ is one of the most well-characterized but not the only platelet collagen receptor. Interestingly, the expression of $\alpha_2\beta_1$ on the platelet surface differs markedly among normal subjects (< 1000 to 3000 molecules/platelet) and depends upon the inheritance of linked, allelic polymorphisms within the coding sequence of the $\alpha_2$ gene that correlate with platelet $\alpha_2\beta_1$ density[50,51]. These observations led to further characterization of the integrin $\alpha_2$ alleles. Four $\alpha_2$ alleles can be defined: allele 1 (807T/1648G/2531C) is associated with increased levels of $\alpha_2\beta_1$, while allele 2 (807C/1648G/2531C) and allele 3 (807C/1648A/2531C) are each associated with decreased levels of this receptor. The gene frequencies of these three alleles in the Caucasian population are: allele 1, 0.394; allele 2, 0.529; and allele 3, 0.076. The very rare allele 4 (gene frequency < 0.01) uniquely expresses 807C/1648G/2531T[52]. Within the coding sequence, two single point missense dimorphisms have been described: A1648G (Lys505Glu) and C2531T (Thr799Met) are responsible for the formation of the $Br^a/Br^b$ (HPA-5) and $Sit^a$ alloantigens (HPA-12bw), respectively[52,53]. Neither dimorphism can be directly implicated in the reported expression differences, since these dimorphisms segregate independently of $\alpha_2$ alleles 1 and 2.

The continuum of differences in platelet $\alpha_2\beta_1$ density among normal individuals belies a simple gene dosage effect and suggests the influence of additional, unlinked genetic factors. Inherited, single base substitutions are found at two positions, C-52T and C-92G, within the proximal 5'-regulatory region (within -1096 to +48) of the human integrin $\alpha_2$ gene[54]. The T-52 and G-92 sequences have a gene frequency of 0.35 and 0.15, respectively, in a typical Caucasian population, and the presence of either allele correlates with reduced densities of platelet $\alpha_2\beta_1$. The substitutions T-52 and G-92 independently downregulate gene transcription, while the

combination G-92/T-52 has an additive negative influence, in transfected human megakaryocytic cell lines. Thus, the natural dimorphisms C-52T and C-92G within the proximal 5'-regulatory region of the human integrin $\alpha_2$ gene contribute to the regulation of integrin $\alpha_2\beta_1$ expression on megakaryocytes and blood platelets and must thereby modulate collagen-related platelet functions *in vivo*.

The significance of the C807T dimorphism to arterial disease has been evaluated in several studies. The initial report described a correlation between allele 1 (T807) (high receptor density) and risk for myocardial infarction[55]. In a larger study with 2237 male patients undergoing angiography, an association between allele 1 (T807) and myocardial infarction was observed in younger patients[56]. Roest et al.[57] have more recently found that allele 1 (T807) was associated with increased vascular mortality in women who are heavy, chronic smokers. In addition, a significant association was also found in younger patients with stroke[58] and in patients with diabetic retinopathy[59]. On the other hand, some studies were unable to establish an association between allele 1 (T807) and myocardial infarction[60-62]. However, in two of these studies[60,61], the frequency of the homozygous TT genotype among the study controls was higher than that reported among normal Caucasian or Oriental populations, respectively[56,59], and may have markedly influenced the conclusions. It is evident that patient and control selection bias needs to be eliminated from clinical studies of this kind by careful consideration of ethnic and racial influences on allele frequencies.

The Lys505Glu amino acid substitution located in the cation binding domain of $\alpha_2$ is responsible for HPA-5b ($Br^a$) and HPA-5a ($Br^b$) epitope formation[53]. In a large study, Kroll et al.[63] found an association between Br dimorphism with coronary artery disease in low-risk patient subgroup. In this population the frequency of $Br^b$ homozygous individuals was overrepresented. This finding suggests that allele 3 (807C; $Br^a$) may decrease risk for thrombotic disease through a qualitative effect on $\alpha_2\beta_1$ function that is independent of genetic effects on expression levels.

**Other platelet glycoprotein polymorphisms.** *FcγRIIa.* Human platelets express a single Fc receptor, FcγRIIa, which exists in two isoforms His131 and Arg131. Several studies have examined the impact of His131Arg dimorphism on heparin-induced thrombocytopenia where thrombosis as complication is known[64,65]. Heparin treatment can induce antibodies that recognize a complex of heparin and platelet factor 4. These immune complexes activate platelets and endothelial cells via the FcγRIIa receptor[66,67]. Carlsson et al.[68] could demonstrate that the frequency of the Arg131 isoform (low-affinity receptor) is significantly elevated among patients with thrombotic events. These observations indicate that the reduced clearance of immune complexes in the Arg131 phenotype caused prolonged activation of platelets and endothelial cells leading to thrombotic complications.

*P-selectin.* P-selectin is a highly polymorphic platelet adhesion that mediates platelet-leukocyte interactions. Herrmann et al.[69] found that the frequency of Pro715 variant is reduced in patients with myocardial infarction, suggesting a possible protective effect. The molecular mechanisms underlying this association have not been yet identified.

## Summary

The importance of platelet GP polymorphisms as genetic risk factors for arterial thrombosis is a new area of human genomics that must be carefully evaluated. As is the case with many other previously proposed genetic risk factors, controversies and seemingly contradictory findings already abound. Many factors responsible for these controversies could be discussed in greater detail, but the resolution of these discrepancies most probably lies in understanding and minimizing differences in study design. Most of the studies differ by study size, ethnicity, bias in the selection of patients and controls, plurality in clinical endpoints and variation of environmental factors. Nonetheless, there is evidence that the $PI^{A2}$ allele of integrin $\beta_3$, the VNTR A or B alleles of GPIbα and allele 1 (T807) of integrin $\alpha_2$ contribute to the risk and morbidity of thrombotic disease. However, well-designed, large, prospective, genetic and epidemiologic studies are needed to clarify the role of these platelet receptor polymorphisms. In addition, *in vitro* studies of the functional relevance underlying these polymorphisms should be conducted to provide biologic plausibility for the clinical findings. Further interest and development in this area may give us the real opportunity to define adequate treatment strategies for the prevention of thrombotic disease.

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