Published in final edited form as:

Arterioscler Thromb Vasc Biol. 2010 December ; 30(12): 2372–2384. doi:10.1161/ATVBAHA.110.218131.

Genetic Regulation of Platelet Receptor Expression and Function: Application in Clinical Practice and Drug Development

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Abstract

Understanding genetic contributions to platelet function could have profound clinical ramifications for personalizing platelet-directed pharmacotherapy, by providing insight into the risks and possible benefits associated with specific genotypes. This article represents an integrated summary of presentations related to genetic regulation of platelet receptor expression and function given at the *Fifth Annual Platelet Colloquium* in January 2010. It is supplemented with additional highlights from the literature covering 1) approaches to determining and evidence for the associations of genetic variants with platelet hypo- and hyperresponsive phenotypes, 2) the ramifications of these polymorphisms with regard to clinical responses to antiplatelet therapies, and 3) the role of platelet function/genetic testing in guiding antiplatelet therapy.

Platelet aggregation is a key component for development of acute thrombosis in coronary, cerebral, and peripheral arterial diseases. Endogenous and environmental factors—age, cholesterol levels, hypertension, diabetes mellitus, and cigarette smoking—explain only part of the variation in platelet function observed in persons with these conditions. Although inherited and genetic factors have known links to bleeding disorders and prothrombotic phenotypes, the evidence for genetic influences that enhance platelet function is much weaker. Understanding the genetic contributions to platelet function could have profound clinical ramifications for personalizing platelet-directed pharmacotherapy, by providing insight into the risks and possible benefits associated with specific genotypes.

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*Participants for the 2010 *Platelet Colloquium* are listed in the Appendix.

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Disclosures

Drs. Williams, Weiss, Bray, Bahou, and L.C. Becker and Ms. French have no conflicts to disclose.

This review, based on information presented at the fifth annual *Platelet Colloquium* held in Washington, DC in January 2010, focuses on the genetic regulation of and variations in platelet receptor expression, function, and responses to antiplatelet therapies and how emerging knowledge in these areas might be applied clinically.

Evidence for Genetic Regulation of Platelet Function

Several well-characterized inherited disorders result from molecular defects that disrupt platelet function and therefore lead to bleeding phenotypes. Studies of platelet-related bleeding disorders such as Glanzmann thrombasthenia, caused by mutations in integrins αIIb (glycoprotein [GP] IIb) and/or β3 (GP IIIa), and Bernard Soulier syndrome, caused by mutations in GP Ib, have provided important insight into platelet function.

Focus has recently shifted to understanding genetic variants that might enhance platelet function. Although definitions for platelet responsiveness tend to differ among studies, it is now widely accepted that platelet aggregation ex vivo in response to agonist stimulation varies considerably among healthy individuals. In an analysis of 359 healthy people, Yee et al[1] noted that a minority consistently showed hyperresponsiveness (≥65% maximal platelet aggregation) after stimulation with ADP, collagen, epinephrine, collagen-related peptide (CRP), or ristocetin. Female sex and higher fibrinogen levels were significantly associated with hyperresponsiveness,[1] and hyperreactivity to 1 agonist tended to persist with others in the assays studied.

Several epidemiological and twin studies suggest that the extent of platelet aggregability may be heritable.[2–9] Analysis of 2413 subjects without known atherosclerotic disease in the Framingham Heart Study showed significant correlation in platelet aggregation among siblings in response to epinephrine, ADP, and collagen lag time.[10] Similarly, a study of 1008 Americans who had ≥1 family member with premature coronary artery disease (CAD), which included a family history of early myocardial infarction and sudden cardiac death, showed evidence for moderate to strong heritability in epinephrine- and ADP-induced aggregation responses (h2 of 0.36–0.42 in white subjects and >0.71 in black subjects).[11] In this latter study, the contribution from established cardiac risk factors to any given platelet phenotype was smaller than that from platelet-specific factors. Although by no means conclusive, these studies suggest an inherited component to platelet responses that may predispose individuals to acute arterial thrombosis.

The next section reviews approaches to determining molecular variants associated with enhanced platelet responses, including candidate gene-association studies, genome-wide association studies (GWAS), and assessment of gene expression by messenger RNA (mRNA) profiling. It will soon be possible to perform individual genome (DNA) sequencing and/or transcriptome (RNA) analysis. For all of the approaches discussed below, the importance of careful phenotyping for interpretation of genetic associations cannot be overemphasized.

Selected Platelet Polymorphisms and Platelet Function

A brief summary of some of the more prominent candidate genes is presented below. The section provides examples of some of the observations and controversies in the field and is not meant to be an exhaustive cataloging of all available data. For additional information on candidate genes associated with differences in platelet phenotypes, readers are referred to a recent comprehensive review on this topic.[12]

Glycoprotein Ia/IIa (α2β1)

The rate of platelet attachment to Type I collagen under conditions of high shear relates directly to the density of GP Ia/IIa (α2β1) receptor; if density is high, there may be a propensity for thrombosis, and if low, the risk of bleeding may be increased.[13] Several polymorphisms exist in the coding region for this gene. Two silent polymorphisms are in complete linkage disequilibrium—807C/T and 873G/A—and 2 others show linkage disequilibrium—837C/T and 1648A/G (human platelet antigen [HPA]-$Br^{a/b}$).[14] Most recently, a new polymorphism has been identified in the 5′ regulatory region of the α2 gene (52T/C).[15] The 807T allele is associated with increased density of the GP Ia/IIa receptor, and the presence of the 807C allele is associated with reduced receptor density.[14,15] Figure 1 illustrates the relationship between specific variants of this gene and receptor density as shown on real-time epifluorescence video microscopy.[13]

Table 1 summarizes the clinical studies examining the association between the 807T/C variant and thrombotic disorders.[16–41] For CAD, other arterial thrombosis, major adverse cardiac events within 30 days after stenting, and venous thrombosis, studies have generally not shown a significant link with the 807T allele. In the most recent meta-analyses, the 807T allele was not shown to be a significant risk factor for CAD,[42,43] although evidence is split for an association with the risk for ischemic stroke [27–33] Polymorphisms such as 807T, which are located in the coding region of the α2 gene, also might interact with variants in the regulatory region, such as −52C/T and −92C/G, to alter changes in receptor density.[15] Finally, given the wide range in frequency of variants among populations,[40,44] it is critical to select the appropriate controls when evaluating genetic contributions to vascular disease risk. This latter phenomenon and publication bias may contribute to some of the conflicting results in the literature.

Glycoprotein 1bα

The major function of the GP Ib-IX-V receptor complex relates to adhesion of platelets to immobilized vWF in areas of high shear stress, resulting in platelet activation. The complex also binds thrombin and P-selectin and mediates platelet–leukocyte interactions,[45] and the subunits are encoded by distinct genes. Four of the known polymorphisms of the gene coding GP Ibα are categorized by the variable number of tandem repeats (VNTR A–D) of a 39-bp sequence.[46] Another (VNTR-E) appears to be a deletion mutation, with no bp sequence repeated,[47] and the HPA-$2^{a/b}$ (Ko) polymorphism, consisting of a C/T transition at nucleotide 1018, results in a single amino-acid substitution at residue 145 (Thr^{a}/Met^{b}).[48] This polymorphism shows strong linkage disequilibrium with the VNTR polymorphisms.[48] Platelet plug formation under high shear stress may be influenced by the VNTR-CD versus -

CC genotype.[49] The HPA-2 (Ko) polymorphism has been associated with higher affinity for vWF ristocetin- or botrocetin-induced binding conditions, but this variant does not appear to affect α-thrombin binding.[48]

Several clinical studies have assessed the functional effects of these polymorphisms (Tables 2, 3).[25,30,32–35,50–71] Although these studies have shown conflicting results, the preponderance of the evidence indicates a lack of significant association of the VNTR and HPA-2 polymorphisms with MI, stroke, CAD, and venous thromboembolism. In a recent meta-analysis of 8 studies, presence of the HPA-2^b allele was associated with an adjusted OR of 1.43 (95% CI, 1.13–1.81) for ischemic stroke.[72]

Glycoprotein IIb/IIIa

The integrin $\alpha_{IIb}\beta_3$ receptor binds fibrinogen, vWF, fibronectin, and vitronectin. The primary polymorphism for this receptor is the substitution of proline for leucine at position 33 (T1565C; Pl^{A1}/Pl^{A2}).[73] Presence of the Pl^{A1} allele has been associated with increases in P-selectin, fibrinogen, and activated GP IIb/IIIa receptor density.[73] The presence of the Pl^{A2} allele may be associated with an increase in platelet aggregation after stimulation with ADP,[74,75] epinephrine,[74] or collagen[75] and more production of thromboxane A_2.[75] In contrast, the homozygous Pl^{A1} genotype appears to be more sensitive to arachidonic acid and thromboxane analogs but not to thrombin or ADP.[76] In clinical studies, as with other polymorphisms, findings have conflicted regarding a significant association between the Pl variant and the risk of MI, CAD, cerebrovascular disorders, and arterial or venous thrombosis (Table 4).[25,32–34,36,58,68,77–91] Even the results of meta-analyses are divided: some have shown no significant link between the $P1^{A2}$ allele and the risk of MI,[92,93] cerebrovascular disease/stroke,[94,95] or CAD,[43] whereas others have shown slight but significant associations between this polymorphism and the risk of CAD[95–97] and of ischemic coronary events after revascularization.[96]

Mutations in $\alpha_{IIb}\beta_3$ and GPIb are established culprits in inherited disorders of hemostasis. Both were obvious initial candidates to examine associations between genetic variability and thrombosis tendency; yet, despite extensive analysis, no clear association(s) have emerged. Despite the critical and nonredundant nature of these proteins in hemostasis, organisms likely have adapted to tolerate relative small changes in their levels or functions without developing overt thrombosis. Additionally, the assays used to detect platelet responsiveness may not be ideally suited detecting enhanced function(s) of these proteins. Alternatively, their contribution to platelet phenotypes and clinical outcomes may be very small and require large population analysis to detect. The next section discusses other possible methods for identifying genetic-driven differences in platelet reactions to stimulation.

Genome-Wide Association Studies to Identify Genetic Determinants of Platelet Aggregation

The many benefits of GWASs include the fact that they can be unbiased, identify non-platelet genes affecting platelet function, provide data on both sequence and copy-number variations, and identify common genetic variants (minor allele frequency >5%) linked to

various diseases. However, the results are not always replicable, typically do not identify the genes themselves (most loci identified in GWASs are not located in exon coding regions and thus are not associated with amino acid changes), and cannot provide information about context or mechanisms. In addition, most variants have been associated with only minor increases in risk, and thousands of subjects are required to identify significant associations with clinical outcomes.

In the classic GWAS, a clinical outcome such as MI is tracked.[98] One method to reduce the need for excessively large samples is to use an intermediate phenotype for analysis. For example, if genes 1 and 2 affect platelet reactivity, it might be more feasible to measure their physiological effects rather than the clinical outcome of MI. This approach requires that the measured variable directly relate to the clinical outcome, and appropriate intermediate phenotypes may not always exist or be readily detectable. With these caveats in mind, several investigations have used this approach to generate provocative and hypothesis-generating findings (Table 5).[99–106]

Although many of the associations have mapped to proteins of known function in platelets, GWAS have also suggested roles for novel mediators. One example is the platelet endothelial aggregation receptor (PEAR)1. This Type 1 platelet membrane protein[107] undergoes agonist-induced phosphorylation in a GP IIb/IIIa-dependent manner. Herrera-Galeano and colleagues[108] genotyped PEAR1 for 10 SNPs from 1486 healthy people in 2 generations of families with premature CAD enrolled in the GeneSTAR study. The C allele of SNP rs2768759 [A/C], located in the promoter region of the gene, was much more frequent in whites than blacks (70.2% vs. 17.7%) and was generally associated in both groups with increased platelet aggregation in response to all agonists at baseline. After aspirin treatment, the associations were stronger and more consistent and remained significant when aggregation was adjusted for baseline responses, consistent with the C allele playing a role in reduced platelet responsiveness to aspirin. The PEAR1 SNP explained up to 6.9% of the locus-specific genetic variance in blacks and up to 2.5% of the genetic variance in whites after aspirin treatment. Thus PEAR1 appears to play an important role in the response to aspirin in both whites and blacks.

Another variant of the PEAR1 gene, the intron 1 variant (rs12041331A/G), has shown an even stronger association with its expression.[109] The G allele was associated with increased platelet aggregation in response to all agonists, before and after aspirin treatment, in 2076 healthy persons enrolled in GeneSTAR. Frequency of the G allele was 91% in whites and 63% in blacks, and accounted for up to 3% and 15%, respectively, of the total phenotypic variance in these groups. This SNP is located at a predicted leucine zipper factor binding site (AliBaba2.1), suggesting a potential mechanism for PEAR1 regulation by the variant.

Platelet Expression Profiling

Proteomic and transcriptonomic analyses have identified important differences in gene expression, genetic pathways, class predictions/diagnostics, protein phosphorylation patterns, protein interactions, and possible therapeutics targets.[110–115] Our discussion focuses on gene expression profiling.

Although human platelets are anucleate fragments of megakaryocytes, they retain cytoplasmic mRNA and can translate proteins.[110] Young platelets contain particularly high concentrations of mRNA. Estimates place the number of platelet individual transcripts at 1,600–3,000.[113] Regulation of transcription is enhanced by agonists such as α-thrombin, controlled by ligation of integrins such as $\alpha_{IIb}\beta_3$ and $\alpha_2\beta_1$, and associated with cytoskeletal translocation of eukaryotic translation initiation factor 4E (eIF4E).[116–118] Initial platelet-profiling studies focused on the use of microarrays and serial amplification of genetic expression (SAGE) evaluations.[110,113,119–122] We focus on data generated in 3 specific contexts: 1) normal individuals who display differences in platelet aggregation responses, 2) individuals presenting with acute MI, and 3) patients with essential thrombocytosis.

In a recent analysis, platelet RNA was isolated from 288 healthy subjects who had been phenotyped for platelet responsiveness.[123] Gene expression patterns in individuals defined as being hyperreactive (n=18) were compared with those having hyporeactive platelets (n=11). The hyperreactive subjects had 120 upregulated genes and 170 downregulated genes compared with hyporeactive subjects. In particular, expression of genes involved in intracellular signaling and calcium flux differed between the 2 groups. Platelet hyperreactivity was significantly associated with increased levels of mRNA for vesicle-associated membrane protein (VAMP) 8/endobrevin, a vesicle-soluble NSF attachment protein receptor (v-SNARE) required for platelet granule secretion. A VAMP8 SNP (rs1010) has also been associated with platelet reactivity in an age-dependent manner. A role for VAMP8 in platelet reactivity is supported by observations that the rs1010 polymorphism is associated with the risk of MI.[124–126]

Interpreting the results of transcriptional profiling in acute MI is challenging because changes in gene expression can reflect events triggering or consequences of plaque rupture and thrombosis. Healy and colleagues[127] profiled platelet mRNA from patients with acute ST-segment-elevation MI (STEMI, n=16) or stable CAD (n=44), analyzed the transcriptomes, and constructed single-gene models to identify candidate genes with differential expression. Of the 54 differentially expressed transcripts, the most strongly linked to STEMI were CD69 and myeloid-related protein-14 (MRP-14). Plasma levels of MRP-8/14 heterodimer were doubled in patients with STEMI compared with stable CAD (17.0 versus 8.0 μg/mL; $P<0.001$).

To validate the findings, a prospective, nested, case-control study of 255 pairs of women was conducted within the Women's Health Study. The risk of nonfatal MI, stroke, or cardiovascular death increased significantly with increasing quartile of MRP-8/14, with women in the highest quartile having a 3.8-fold increase in risk compared with those in the lowest quartile, independent of traditional risk factors or C-reactive protein.[127] In another nested case-control study (237 case–control pairs) conducted among patients enrolled in a Phase III trial, the median MRP-8/14 level was significantly higher in patients who died or had nonfatal MI at 30 days compared with patients without these events.[128] The risk of a repeat cardiovascular event increased with increasing quartile of MRP-8/14 level; patients in the highest quartile had twice the risk of a recurrent event versus patients in the lowest quartile, even after adjusting for standard risk indicators, treatment assignment, and C-reactive protein. Thus, expression of MRP-14 appears to be increased before STEMI, and

plasma concentrations of MRP-8/14 might predict the risk of future cardiovascular events in healthy individuals.[129]

A final example of profiling to identify gene-expression patterns associated with platelet responses is the use of essential thrombocytosis (ET) as a model. Patients with ET have thrombotic complications, hemorrhagic symptoms, or both. Among the first discoveries to emerge from the use of this model were that distinct subtypes of steroidogenic 17β-hydroxysteroid dehydrogenases (HSDs) are functionally present in human platelets and that their differential expression is associated with ET.[111]

A primary drawback of using ET to model platelet profiling is that it can be difficult to distinguish ET from reactive thrombocytosis (RT). In an attempt to develop class-prediction algorithms, Gnatenko et al. studied the platelet transcript profiles of 38 patients with RT, 40 patients with ET (24 of whom carried the JAK2V(617)F mutation, a marker of myeloproliferative disorders), and 48 normal control subjects.[115] The normal and ET groups showed little variation by sex (<1% of genes differed), but about 3% of the genes in the RT group were skewed toward men. A subset of 11 biomarker genes was 86.3% accurate in discriminating among the 3 groups, 93.6% accurate in distinguishing between ET and RT, and 87.1% accurate in prospective classification of a new group.[115] In addition, a set of 4 biomarker genes predicted JAK2 wild-type ET in >85% of samples. Genetic biomarker subsets obtained from routine blood sampling might be used to predict thrombocytosis class.

The newest method for platelet profiling involves a multiplexed-based platform for simultaneous quantification of platelet transcripts using fluorescent microspheres and intact platelet-rich plasma or gel-filtered platelets lysed in vitro.[113] With this method, which bypasses the need to isolate RNA, 17 platelet transcripts can be profiled accurately and simultaneously from only 100 μL of whole blood, even for low-abundance platelet transcripts. Results of this method correlate exceptionally well with those from platelet Affymetrix microarrays (r^2 = .949; P<0.001) and show no correlation with in-kind–derived leukocyte profiles. This method might be adapted for situations where rapid molecular profiling using whole blood would be valuable.

Although platelet profiling using proteomic/transcriptonomic technologies is feasible, several challenges remain, including small amounts of target mRNA, concern for contaminating nonplatelet cells in the preparations, and the challenge of extrapolation to more common platelet disorders and prohibitive costs. To maximize the applicability of profiling methods, consortia must be developed for interinstitutional data exchange and enrollment. Future research should include both pharmacogenomic studies in platelets and comparative pharmacological effectiveness studies by sex and ethnicity.

Genetic Polymorphisms and the Response to Antiplatelet Therapies

The use of antiplatelet therapies is a mainstay in the settings of ACS and PCI, particularly dual therapy with aspirin and clopidogrel. Recently, genetic variations associated with hyporesponse to antiplatelet therapy have been associated with poorer outcomes. For example, in a meta-analysis[130] of 9 studies that collectively enrolled 9684 patients receiving clopidogrel (91% of the patients had undergone PCI, 65% had ACS), 28.5% of patients were

carriers of ≥1 reduced-function allele of gene CYP2C19. These carriers had a 61% higher risk of a major adverse cardiac event compared with noncarriers. Other studies have linked the presence of CYP2C19 reduced-function variants with greatly increased risks for stent thrombosis with and without cardiac mortality[131]; cardiovascular ischemic events or death[132]; and death, MI, or nonfatal stroke[136]; and the presence of increased-function variants with bleeding risk.[134] Moreover, if both CYP2C19 and ABCB1 reduced-function alleles are taken into account, up to half of the ACS population undergoing PCI might have a genotype associated with an increased risk of major cardiac events while receiving clopidogrel.[135]

In May 2009, the U.S. Food and Drug Administration (FDA) called for addition of information about “poor metabolizers” to the labeling for Plavix (clopidogrel bisulfate).[136] In March 2010, the agency announced the requirement for a “black-box” warning on the label, specifying that poor metabolizers are at higher risk for cardiovascular events. The labeling defines “poor responders” as persons who are homozygous for any of the CYP2C19*2–18 alleles. The labeling notes that genetic testing can be performed to identify poor responders and that physicians should consider alternative treatment strategies for these persons.[136] At present, however, the FDA has approved no agent for specific use in poor responders to clopidogrel, or in those with a heightened response to the drug.

This issue highlights a conundrum that can stem from improved insight into genetic associations, namely, the lack of a proven therapeutic strategy. For poor responders to clopidogrel, possible strategies include use of a higher dose of clopidogrel or alternate $P2Y_{12}$ antagonists such as prasugrel or ticagrelor, which are newer thienopyridines that depend less on CYP2C19 oxidation for effect and have not been linked to pharmacokinetic or pharmacodynamic differences based on CYP genotype.[137–139] Small studies have reported improved outcomes with higher doses of clopidogrel when nonresponsiveness was assessed ex vivo, but it is not clear whether these findings will translate to population benefit based on CYP genotype. The Gauging Responsiveness With A VerifyNow Assay-Impact On Thrombosis And Safety (GRAVITAS, clinicaltrials.gov #NCT00645918), is currently exploring the use of the VerifyNow test to guide antiplatelet therapy (tailored or standard clopidogrel dosing versus placebo) in 2800 patients undergoing planned stenting, measuring the outcomes of cardiovascular death, nonfatal MI, or definite or probable stent thrombosis within 6 months.[140] The results of this trial, which may be available in late 2010, should shed light on the value of test-guided antiplatelet therapy. Similar studies will be required to define optimal antiplatelet strategies based on genotype to ensure the best outcomes using a personalized medicine approach.

Conclusions/the Future

Candidate gene-association studies, GWASs, and gene expression profiling continue to reveal novel linkages between polymorphisms in genes coding for platelet function and both thrombotic and hemorrhagic phenotypes. These and ongoing investigations should bring us closer to the day when platelet-directed therapy can truly be individualized according to genomic and/or transcriptomic characteristics, in addition to endogenous and environmental factors.

Complete knowledge of the relationship between genotype and phenotype is insufficient, however. Alternative management strategies remain to be developed and tested for patients with genotypes linked to platelet hyporesponse, currently the case for clopidogrel and likely to emerge for other antiplatelet agents, as well as platelet hyperresponse.

Acknowledgments

Sources of Funding

The 2010 *Platelet Colloquium* and this manuscript were supported by unrestricted educational grants from AstraZeneca; Bristol-Myers Squibb/sanofi Pharmaceuticals Partnership; Daiichi Sankyo, Inc. and Lilly USA, LLC; Merck Research Laboratories, Regado Biosciences, Inc.; and The Medicines Company. These companies had no role in the development or editing of the manuscript.

Dr. Sabatine has received research grant support from Bristol-Myers Squibb, sanofi-aventis, AstraZeneca, and Schering-Plough; honoraria from Eli Lilly, and has consulted for BMS/Sanofi Partnership, sanofi-aventis, and Daiichi/Eli Lilly. Dr. Simon has received honoraria from BMS/Sanofi Partnership, Daiichi/Eli Lilly, Johnson & Johnson, Portola Pharmaceuticals, Schering Corporation, and The Medicines Company and consulted for BMS/Sanofi Partnership, Daiichi/Eli Lilly, Johnson & Johnson, Portola Pharmaceuticals, Schering Corporation, and The Medicines Company. Dr. Parise has received honoraria from SAB, Blood Center, Milwaukee. Dr. Dauerman has consulted for BMS/Sanofi Partnership and The Medicines Company. Dr. R.C. Becker has received grant support from AstraZeneca, BMS/Sanofi Partnership, Johnson & Johnson, Merck and Co., Regado Biosciences, Schering Corporation, and The Medicines Company; received honoraria from AstraZeneca and Daiichi/Eli Lilly; and consulted for Portola Pharmaceuticals, Regado Biosciences, and The Medicines Company. Dr. Smyth has received grant support from AstraZeneca, Daiichi/Eli Lilly, Schering Corporation, and The Medicines Company and consulted for BMS/Sanofi Partnership.

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Appendix: Participants in the 2010 Platelet Colloquium

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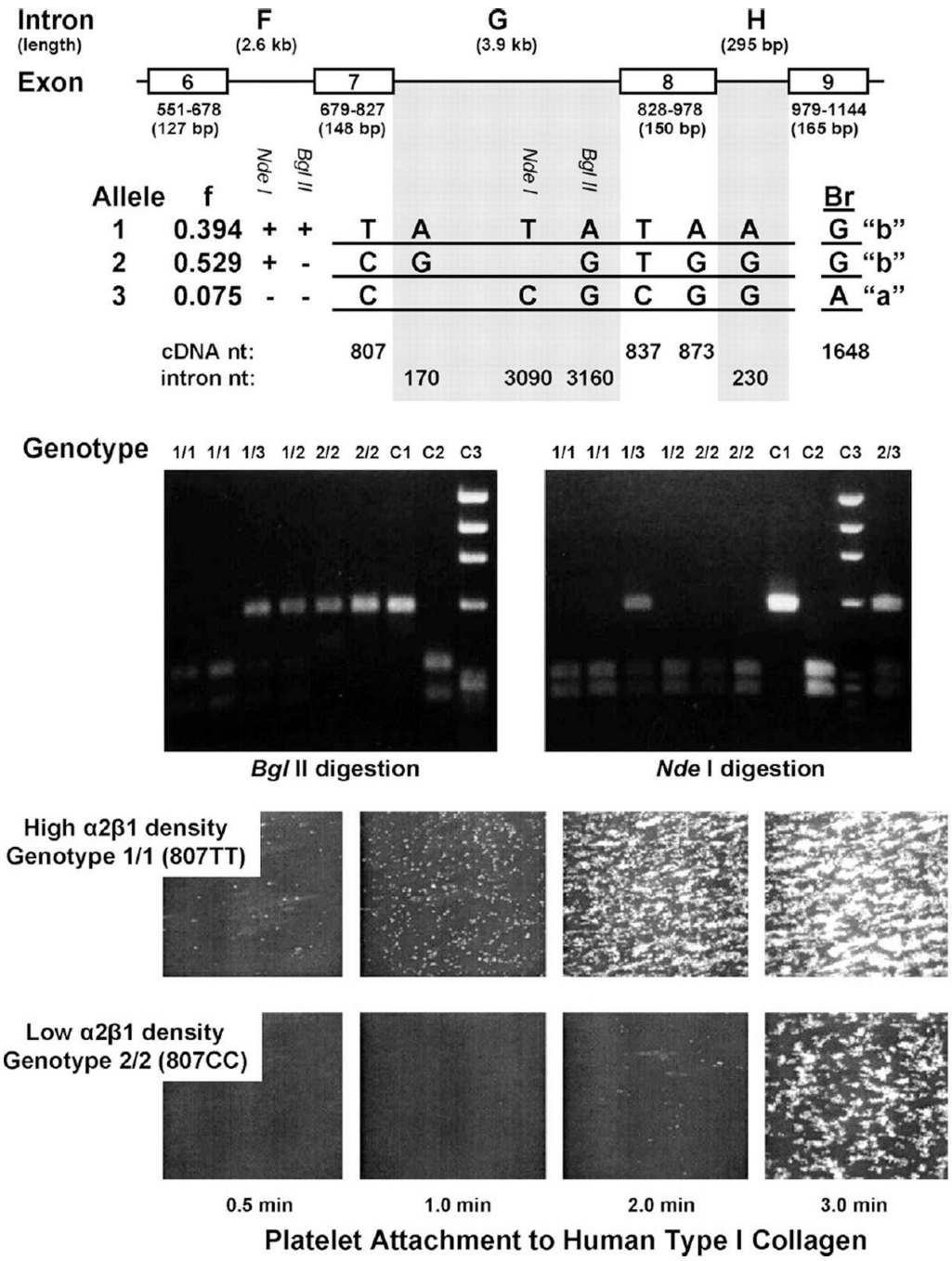

Figure 1. Relationship between α2β1 polymorphisms and collagen receptor density

Top, surrounding structure of the α2 gene at sites of the 807 and 873 polymorphisms, including 3 alleles defined by 8 nucleotide (nt) polymorphisms. Frequency of each allele (f) determined from a random pool of 85 individuals. "+" indicates ability of the allele to be cleaved by *Bgl* II or *Nde* I, and specific bp differences are shown affecting susceptibility to cleavage. ***Middle***, α2 allele genotyping using *Bgl* II/*Nde* I digestion and agarose gel electrophoresis. C1 indicates control sequence 807C/837C/873G; C2, control sequence 807T/837T/873A; C3 molecular weight λ*Hind* III/φX174*Hae* III. ***Bottom***, Real-time

epifluorescence video microscopy showing the time courses of platelet adhesion in whole blood under high shear to surface-bound solubilized human Type I collagen at 1,500/s for individuals homozygous for allele 1 (upper) and allele 2 (lower). Adapted from Kritzik et al[13] with permission.

Table 1

Correlation Between the Presence of Platelet Glycoprotein $\alpha_2\beta_1$ Variant 807T and Risk for Adverse Outcomes in Various Thrombotic Disorders

Positive Studies				Negative Studies		
Study	**Year**	**Cohort**	**O.R.**	**Study**	**Year**	**Cohort**
Acute Coronary Syndromes						
Moshfegh[16]	1999	177 MI pts	3.3	Croft[22]	1999	546 white MI pts
Santoso[17]	1999	2237 men with CAD*	2.6	Anvari[23]	2000	94 survivors of SCD
Roest[18]	2000	480 women with CV death*	2.2	Roest[18]	2000	480 women with CV death
Cassorelli[19]	2001	157 pts with ACS	2.9	Morita[24]	2001	210 Japanese MI pts
Zhao[20]	2003	137 pts with MI	2.14	Rosenberg[25]	2002	100 young men with MI
Zhao[21]	2004	75 pts with ACS	3.47	ATVB[26]	2003	1210 young pts with first MI
Cerebrovascular Disease/Stroke						
Carlsson[27]	1999	45 young stroke pts	3.0	Carlsson[27]	1999	182 stroke pts >50 years old
Sacchi[28]	1999	45 young stroke pts	2.95	Corral[31]	1999	104 pts with CVD
Reiner[29]	2000	36 young women with stroke	2.24	Iniesta[32]	2003	141 pts with primary ICH
Cervera[30]	2007	82 stroke pts	9.6	Iniesta[33]	2004	103 pts with subarachnoid bleed
Coronary Artery Disease/Arterial Thrombosis						
Jiménez[34]	2008	131 pts with APS	3.59	Santoso[17]	1999	2237 men with CAD
Pellitero[35]	2010	229 pts with Type 2 diabetes	2.86	Corral[31]	1999	101 pts with CAD
				Streifler[36]	2001	153 pts with 50% carotid stenosis
				Ajzenberg[37]	2005	171 pts with CAD undergoing CABG
				Jiménez[34]	2008	102 pts with SLE
Venous Thromboembolism						
				Carlsson[38]	1999	pts with DVT
				Corral[31]	1999	97 pts with DVT
				Hessner[39]	1999	233 factor V (Leiden) carriers
				Dinauer[40]	1999	331 white American VTE pts
MACE After Stenting						
				Von Beckerath[41]	1999	1797 pts undergoing stenting

*Subgroup analysis. Cohort lists numbers of case patients; entries in italics indicate a protective association. Data are tabulated as of October 2010. Adapted from Kunicki,[15] with permission.

ACS = acute coronary syndromes; APS = antiphospholipid syndrome; CABG = coronary artery bypass surgery; CAD = coronary artery disease; CT = coronary thrombosis; CV = cardiovascular; CVD = cerebrovascular disease; DVT = deep vein thrombosis; GP = glycoprotein; ICH = intracranial hemorrhage; MACE = major adverse cardiac events; MI = myocardial infarction; O.R. = odds ratio; pts = patients; SCD = sudden cardiac death; SLE = systemic lupus erythematosus; UA = unstable angina; VTE = venous thromboembolism

Arterioscler Thromb Vasc Biol. Author manuscript; available in PMC 2014 August 01.

Table 2

Correlation Between Presence of Platelet Glycoprotein Ibα VNTR-B or B/C Variants and Risk for Adverse Outcomes in Various Thrombotic Disorders

Positive Studies				Negative Studies		
Study	**Year**	**Cohort**	**O.R.**	**Study**	**Year**	**Cohort**
Acute Coronary Syndromes						
Mikkelson[63]	2001	80 men with MI	2.0	Kenny[51]	2002	1014 pts with ACS
Ozelo (VNTR-CD)[50]	2004	180 survivors of MI	2.36	Rosenberg[25]	2002	100 young men with MI
				Douglas[52]	2002	88 pts with MI
				Ni[53]	2004	69 Chinese pts with UA
Cerebrovascular Disease/Stroke						
Gonzalez-Conejero[54]	1998	104 pts with CVD	2.83	Baker[57]	2001	219 pts with ischemic stroke
Lozano[55]	*2001*	*104 pts with CVD*	*2.1*	Streifler[36]	2001	153 pts 50% carotid stenosis
Zhang ($^{VNTR-D}$)[56]	2007	119 pts with stroke	1.6	Iniesta[32]	2003	141 pts with primary ICH
				Iniesta[33]	2004	103 pts with subarachnoid bleed
				Cervera[30]	2007	82 pts with stroke followed 5 y
Coronary Artery Disease/Arterial Thrombosis						
Gonzalez-Conejero[54]	1998	101 pts with CAD	2.84	Carter[58]	1998	125 diabetic pts
Mikkelson[63]	2001	65 men with CT	2.6	Carter[59]	1998	609 pts with stroke
				Ito[60]	1999	158 Japanese pts with CAD
				Ishida[61]	2000	156 Japanese pts with CAD
				Lozano[55]	2001	101 pts with CAD
				Jiménez[34]	2008	102 pts with SLE
				Jiménez[34]	2008	131 pts with APS
				Pellitero[35]	2010	209 pts with Type 2 diabetes
Venous Thromboembolism						
				Gonzalez-Conejero[54]	1998	95 pts with DVT
				Lozano[55]	2001	150 pts with DVT
In-Stent Restenosis						
				Ozben[62]	2007	87 pts with restenosis

Data and abbreviations as in Table 1. Data are tabulated as of October 2010.

Table 3

Correlation Between Presence of Platelet Glycoprotein Ibα Variants HPA-2^{b} and HPA-2^{Met} and Risk for Adverse Outcomes in Various Thrombotic Disorders.

Positive Studies				Negative Studies		
Study	**Year**	**Cohort**	**O.R.**	**Study**	**Year**	**Cohort**
Acute Coronary Syndromes						
Mikkelsson[63]	2001	80 men with MI	2.0	Chen[64]	2000	95 Chinese pts with MI
				Rosenberg[25]	2002	100 young men with MI
				Ozelo[50]	2004	180 survivors of MI
				Candore[65]	2006	105 young Sicilians with MI
Cerebrovascular Disease/Stroke						
Gonzalez-Conejero[54]	1998	104 pts with CVD	2.4	Carlsson[68]	1997	218 pts with stroke
Sonoda[66]	2001	235 pts with CVD	2.0	Reiner[29]	2000	36 young women with ischemic stroke
Ishii[67]	2004	200 pts w/ischemic CVD		Chen[64]	2000	188 Chinese pts with stroke
				Baker[57]	2001	219 pts with ischemic stroke
				Streifler[36]	2001	153 pts with ≥50% carotid stenosis
				Iniesta[32]	2003	103 pts with subarachnoid bleed
				Gao[69]	2005	100 pts with ischemic stroke
				Cervera[30]	2007	82 pts with stroke followed 5 yrs
Coronary Artery Disease/Arterial Thrombosis						
Mikkelsson[63]	2001	65 men with CT	2.6	Ito[64]	1999	158 Japanese pts with CAD
ARIC[70]	2004	349 pts with CAD	5.6	ARIC[70]	2004	80 black pts with CAD*
Pellitero[35]	2010	209 diabetic pts	2.03	Jiménez[34]	2008	102 pts with SLE
				Jiménez[34]	2008	131 pts with APS
				Aleksić[71]	2008	402 pts with CAD
Venous Thromboembolism						
				Gonzalez-Conejero[54]	1998	95 pts with DVT

Data and abbreviations as in Table 1. Data are tabulated as of October 2010.

Table 4

Correlation Between Presence of Platelet Glycoprotein IIb/IIIa Variant Pl^{A2} and Risk for Adverse Outcomes in Various Thrombotic Disorders

Positive Studies				Negative Studies		
Study	**Year**	**Cohort**	**O.R.**	**Study**	**Year**	**Cohort**
Acute Coronary Syndromes						
Ardissino[77]	1999	200 young MI survivors	1.84	Ridker[78]	1997	374 men with MI
				Gardeman[79]	1998	2252 men with CAD
				Joven[80]	1998	250 young men with MI
				Anderson[81]	1999	225 pts with MI
				Cenarro[82]	1999	40 pts with hypercholesterolemia
				Hooper[83]	1999	110 black MI pts
				Rosenberg[25]	2002	100 young men with MI
				Bojesen[84]	2003	316 men with MI
				Bojesen[84]	2003	165 women with MI
Cerebrovascular Disease/Stroke						
Streifler[36]	2001	153 pts with carotid stenosis	3.4	Carlsson[68]	1997	218 pts with stroke
Iniesta[32]	*2003*	*103 pts with SAH*		Ridker[78]	1997	209 men with stroke
Szolnoki[85]	2003	168 pts with large-vessel stroke	2.9	Wagner[86]	1998	65 pts with ischemic stroke
				Van Goor[87]	2002	45 young stroke pts
				Iniesta[33]	2004	141 pts with primary ICH
Coronary Artery Disease/Arterial Thrombosis						
Weiss[88]	1996	71 white pts with ACS	2.8	Carter[58]	1998	125 diabetic pts
Carter[58]	1998	609 pts with stroke	2.37	Gardeman[78]	1998	2252 men with CAD
Garcia-Ribes[89]	1998	pts undergoing PCI	3.9	Anderson[81]	1999	791 pts undergoing angiography
Bojesen[84]	2003	689 men with CAD	1.5	Bojesen[84]	2003	496 women with CAD
Mikkelson[90]	2001	700 men with SCD	2.9	Jiménez[34]	2008	102 pts with SLE
				Jiménez[34]	2008	131 pts with APS
Venous Thromboembolism						
				Ridker[78]	1997	121 pts with VTE
				Hooper[83]	1999	91 black pts with VTE

Positive Studies				Negative Studies		
Study	**Year**	**Cohort**	**O.R.**	**Study**	**Year**	**Cohort**
			Restenosis			
Kastrati[91]	1999	1150 pts with stents	1.42			

PCI = percutaneous coronary intervention; SAH = subarachnoid hemorrhage.

Other data and abbreviations as in Table 1. Data are tabulated as of October 2010.

Table 5

Genome-Wide Association Studies Related to Platelet Aggregation

Study	population	Variable of interest	Location of Linkage	Candidate gene(s)
Evans 2004[99]	327 monozygotic, 418 dizygotic twin pairs	Platelet count	chromosome 19, q13.13-13.31	*GP VI*
Yang 2007[100]	1000 FHS participants from 310 families	ADP-induced PA	rs10493895, chromosome 1	*BC064027; DPYD*
			rs10484128, chromosome 14	
		Collagen-induced PA	rs848523, chromosome 2	*CRIM1*
			rs565229, chromosome 11	
			rs10506458, chromosome 12	
		Epinephrine-induced PA	rs6811964, chromosome 4	*PDGFC*
			rs1958208, chromosome 14	
			rs10502583, 18	*RNF138; MEP1B*
Danik 2009[101]	17,686 Women's Genome Health Study participants	Serum fibrinogen level	rs1016988, chromosome 5 rs10479002, chromosome 5 rs10512597, chromosome 5	*SLC22A5, SLC22A4, IRF1*
			rs1037170, chromosome 17	*CD300LF, SLC9A3R1 NAT9*
Trégouët 2009[102]	2176 French VTE cases, 2636 French controls	VTE	rs1613662	*GP VI*
			rs13146272	*CYP4V2*
			rs1208134 and rs2420371, chromosome 1	*Factor V*
			rs657152, rs505922, rs630014, chromosome 9	*ABO*
Meisinger 2009[103]	10,048 subjects, 3 cohorts	Mean platelet volume	rs7961894, chromosome 12	*WDR66*
			rs12485738, chromosome 3	*ARHGEF*
			rs2138852, chromosome 17	*TAOK1*
Soranzo 2009[104]	8586 subjects, 5 cohorts	Mean platelet volume, platelet annexin and fibrinogen binding, P-selectin expression	rs342293, chromosome 7	*PIK3CG*
Johnson 2010[105]	2,753 FHS participants* 1238 GeneSTAR participants*	PA	7 loci	*GP VI, PEAR1 ADRA2A, PIK3CG JMJD1C, MRVI1, SHH*
	840 black GeneSTAR participants		6 loci	
Mathias 2010[106]	1231 healthy European Americans, 846 healthy black Americans with family history of premature CAD	Epinephrine-, collagen-, ADP-, arachidonic-acid-nduced PA; urinary thromboxane B_2 level; PFA-100; fibrinogen level; vWF level†	9 loci	*MME, PIP3-E, GLIS3 LDHAL6A*

*Of European ancestry.

†Before and after 14 days of aspirin treatment.

CAD = coronary artery disease; FHS = Framingham Heart Study; GeneSTAR = Genetic STudy of Aspirin Responsiveness; KORA = Kooperative Gesundheitsforschung in der Region Augsburg; PA = platelet aggregation; PFA = Platelet Function Analyzer; vWF = von Willebrand factor.