Published in final edited form as:

Anesthesiol Clin. 2008 September ; 26(3): 399–417. doi:10.1016/j.anclin.2008.04.002.

Anesthesiology Clinics: “Cardiac Anesthesia: Today and Tomorrow”

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Abstract

Coronary artery bypass graft (CABG) surgery is associated with several frequent postoperative adverse events. Outcome prediction is valued by patients and practitioners, in order to provide some measure of balancing risks and benefits, and to provide expensive or higher-risk therapies to individuals at highest risk. Surgeons and anesthesiologists have traditionally relied on demographic, preoperative, and intraoperative risk factors to predict outcomes after cardiac surgery. Yet such predictions often have poor positive and negative predictive value for the individual patient. Perioperative genetics attempts to determine the impact of an individual's genetic variation on the risk of developing adverse postoperative outcomes. In this review, we discuss emerging evidence that patients' genetic makeup predisposes them to adverse outcomes following cardiac surgery, specifically providing examples from perioperative bleeding, myocardial injury/infarction and atrial fibrillation (AF).

Keywords

Genetic; Perioperative complication; Heart Surgery; Risk; Atrial fibrillation; Myocardial Infarction; Hemorrhage

Introduction

Ischemic heart disease is the leading cause death in the United States annually¹. A proportion of patients with coronary artery disease (CAD) require coronary revascularization. While catheter-based revascularization is therapeutic for many patients, surgical revascularization is superior in patients with diffuse, multi-coronary vessel disease. Despite its superiority in this select patient population, CABG surgery is associated with several serious adverse events during the immediate postoperative period.

Postoperative bleeding, myocardial injury and AF are costly cardiac surgical complications, resulting in longer intensive care unit and hospital lengths of stay, decreased short and long-

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term survival, and increased healthcare resource utilization. To this end, clinicians have made efforts to predict these adverse outcomes using patients' demographic characteristics, coexisting disease profile and intraoperative events. While statistical models based on *environmental* (i.e. non-genetic) risk factors have proven moderately useful in assessing risk factors in populations, such predictions often have poor positive and negative predictive value for the individual patient. In addition, these risk factors seldom provide insight to the underlying biologic mechanisms and specific therapy directed towards mitigating these risk factors.

The emerging field of perioperative genetics has the potential to advance our understanding of the biologic mechanisms that result in adverse events after cardiac surgery. Considering the simplified paradigm, gene X is responsible for the expression of altered protein Y levels that, in turn, results in an adverse outcome following surgery; it is easy to imagine how perioperative genetics will likely clarify our understanding of the biologic mechanisms responsible for adverse surgical outcomes. In this review, we present emerging evidence for the important role of genes and gene variants in mediating adverse outcomes following cardiac surgery, specifically drawing examples from postoperative bleeding, myocardial injury and AF.

Genetic Variation

There are over 20,000 protein-coding genes in the human body. Structurally, each gene can be subdivided into a promotor region, introns and exons (Figure 1). The unique deoxyribonucleic acid (DNA) sequence of each gene is responsible for the protein product of that particular gene. It is not uncommon, however for DNA sequences to have variations known as single nucleotide polymorphisms (SNP). There are currently over thirteen million identified SNPs in the human genome, and depending on the exact location, SNPs result in altered serum protein level or protein structure. This phenomenon is the basis on which perioperative genetics is built.

SNPs can result in disease in one of several ways. Some SNPs located in the promotor region of a gene alter the binding of proteins that determine the amount of messenger ribonucleic acid (mRNA) transcribed from the DNA substrate. The greater the amount of mRNA made, the greater amount of protein made. In contrast, SNPs located in exonic protein-coding regions of a gene can sometimes code for a different amino acid from the triplet base-pair "codon". An altered amino acid sequence of a protein can sometimes result in altered protein structure and/or function. These simplistic descriptions do not describe the several other methods of altering protein production or function that are present; nevertheless they describe the fundamental changes that can arise from DNA variation at the single base pair level. Changes at the multiple base pair level, such as copy number variation, and at the DNA folding level will receive much more attention over the next few years.

In general, genetic disorders can be understood as being either *simple* or *complex*. Simple genetic disorders are typified by a single genetic variant, within a single individual, that results in a clinically obvious and predictable disorder or disease, also referred to as a *phenotype*. Examples of simple genetic disorders that result in predictable phenotypes include pseudocholinesterase deficiency and malignant hyperthermia. We know that several genetic variants within the same gene produce similar phenotypes, however, within a single individual only one of these variants is usually present and has an effect that has little modification by environmental influences. In contrast, complex genetic disorders are characterized by often multiple, interacting gene variants modified by several environmental factors, resulting in a disease phenotype that varies in severity and frequency between patients. Examples of complex genetic disorders include asthma, CAD, cancer and hypertension. Complex genetic disorders are more frequent than simple disorders and are often manifest at older age, after the environmental influences have been acting for several years. A simple example is the affect of

diet on CAD; we know of several genes that increase risk for CAD, yet there is a strong dietary influence and the onset of CAD is usually in the beyond the 5th decade of life.

Postoperative bleeding, myocardial injury and AF following CABG surgery are phenotypes that are the result of a complex interaction between gene variants and multiple environmental risk factors. Because of this complexity, identifying the responsible combination of gene variants and environmental risk factors requires large patient populations. While large population-based registries, such as the Framingham Heart Study, are pivotal in examining the association between gene variants and complex non-surgical phenotypes (asthma and CAD), it is only now that surgical registries have become large enough to examine associations between gene variants and complex post cardiac surgery phenotypes (bleeding, myocardial injury and AF).

Perioperative Bleeding

Perioperative bleeding is a complex genetic disorder with a wide range of phenotypic variation; influenced by environmental and genetic factors². From non-surgical patient populations, we know that there are several genetic disorders that result in a propensity to bleed. von Willebrand disease (vWD) and hemophilias A, B and C exhibit strong familial inheritance, making up over 95% of all inherited coagulation protein deficiencies³. These patients present early in life with either excessive bleeding and/or incidentally abnormal laboratory results. Patients with vWD and hemophilia undergo surgery with a well characterized and managed disease diagnosis and therefore usually avoid unexpected perioperative bleeding⁴⁻⁷.

There is strong heritability of levels of circulating coagulation proteins in non-surgical patient populations⁸⁻¹², notably of plasminogen activator inhibitor-1 (PAI-1), factor XIII, factor VII⁷, fibrinogen, tissue plasminogen activator (tPA) and vWF. Although levels of these proteins are genetically determined and probably had some evolutionarily-distant purpose, the significance of this variability is most likely unimportant in this sedentary world, except when an individual undergoes surgery or major trauma.

The only identified genetic association with bleeding in the *noncardiac* surgical population to date is the insertion/deletion (indel) polymorphism of the angiotensin-converting enzyme (ACE) gene. The level and activity of ACE is partly determined by this indel and has been associated with a wide range of cardiovascular diseases and non-cardiovascular characteristics¹³. The indel is an improbable causative polymorphism, as it has no identified functional significance despite considerable investigation, but is in strong linkage disequilibrium with several other more-likely candidate polymorphisms that alter ACE activity. Furthermore, ACE is an improbable biological cause of bleeding. Notwithstanding, homozygosity of the deletion genotype (DD) has been implicated as a risk factor for decreased bleeding by altering vascular tone and blood flow and is associated with higher ACE plasma activity^{14,15}.

Several variants in several genes have been associated with increased, or decreased risk of bleeding after cardiac surgery. PAI-1 is the primary inhibitor of t-PA. PAI-1 deficiency leads to increased levels of t-PA and increased risk of bleeding¹⁶⁻¹⁸. While altered PAI-1 levels are associated with lipid profile¹⁹⁻²² and PAI-1 has an acute-phase response to cardiopulmonary bypass^{23,24}, recent evidence suggests a PAI-1 genetic variant strongly influences circulating PAI-1 levels. A single guanine base pair deletion located in the promoter region of the PAI-1 gene results in reduced binding of a protein that represses transcription of PAI-1 mRNA. Thus the deletion variant results in increased PAI-1 transcription. In essence, the deletion variant results in increased PAI-1 levels, which in turn decreases the effect of t-PA, the principal activator of fibrinolysis, and results in decreased blood loss²⁵. Among patients undergoing

cardiac surgery, individuals *without* the deletion exhibit lower PAI-1 mRNA production, lower circulating PAI-1 levels, and increased transfusion of coagulation factors²⁶.

E-selectin, part of the family of cell adhesion molecules, is present only on the endothelial cell surface and binds to a class of carbohydrates present on leukocytes, thus mediating the adhesion of leukocytes to vascular endothelium at sites of inflammation. It may seem strange that a leukocyte adhesion molecule only present on endothelium should alter the risk of bleeding; however, there is considerable evidence for a role of leukocytes in augmenting the platelet plug and cellular hemostasis. Within the 5' untranslated region (UTR) of the E-selectin gene a frequent variant (so-called 98G/T) was associated with increased bleeding in a cardiac surgical population²⁷. The exact biological mechanism for this effect is not apparent. We can speculate that this variant has a promoter role and alters the expression of E-selectin on the endothelial surface, thus affecting leukocyte adhesion; however evidence for this is lacking.

The well-known platelet glycoprotein (GP) IIb/IIIa complex is a receptor for fibrinogen, vWF, and fibronectin and is a mediator of platelet aggregation, the final common pathway in platelet plug formation. To avoid excessive receptor activation to normal levels of circulating fibrinogen, the GP IIb/IIIa receptor complex is only expressed on the platelet surface after the platelet is activated by other pathways. The functional significance in surgical populations of a well known GPIIIa coding polymorphism (Leu33Pro), known as the human platelet antigen (HPA)-1, or as P1^{A1}/A² has been recently elucidated²⁸. This relatively common variant (20% in Caucasians) results in a structural alteration of the IIIa subunit of the GPIIb/IIIa receptor that leads to an increase in platelet reactivity and activation, stimulates α -granule release, enhances fibrinogen cross-linking and has been associated with thrombus formation in "healthy" individuals²⁹⁻³³. Adding a level of complexity to the effect of this SNP is the variation in the response to anticoagulant medications commonly used in cardiovascular disease, such as aspirin, warfarin, the GPIIb/IIIa inhibitors, and other platelet inhibitors³⁴⁻³⁹. Without aspirin, Pro33 (P1^{A2}) carriers have *decreased* blood loss after CABG surgery. In contrast, in the presence of aspirin, Pro33 (P1^{A2}) carriers have *increased* bleeding compared with Leu33 (P1^{A1}) homozygotes⁴⁰. It is speculated that the increased affinity of fibrinogen to the GPIIb/IIIa receptor in Pro33 (P1^{A2}) patients is a result of changes at the GPIIb/IIIa receptor and the fibrinogen binding site, but the exact mechanism has not been elucidated⁴¹.

In one of the few studies that have examined the effect of genetic variation upon bleeding after *cardiac* surgery, Duke researchers found that the deletion allele of the ACE polymorphism was associated with *decreased* bleeding⁴². This confirms the results of the study in *noncardiac* surgical patients, though both lack proof of functional significance. Apart from the ACE indel polymorphism, six other polymorphisms showed an association with increased bleeding. These included the GPIaIIa ($\alpha 2\beta 1$ integrin) -52C/T and 807C/T polymorphisms, the GPIIb 524C/T polymorphism, the tissue factor -603A/G polymorphism, the prothrombin 20210G/A polymorphism and the tissue factor pathway inhibitor (TFPI) -399C/T polymorphism. In a multivariable model in interaction with each other, they accounted for 9% of the variability of chest tube drainage ($P < 0.01$). Though the exact biological mechanisms for the association between these variants and increased bleeding are not known, we can speculate that since these genetic variants modulate thrombin generation, platelet surface receptor density, clotting factor and platelet consumption on CPB, they each contribute a small additive risk for perioperative coagulopathy. As such, the combined effect of several clinical variables and several genetic polymorphisms typifies a genetically-complex disease.

Perioperative Myocardial Injury

Annually, about 1 million individuals suffer cardiac death or nonfatal myocardial infarction (MI) during the perioperative period, worldwide⁴³. Patients suffering a perioperative

myocardial infarction (PMI) after non-cardiac surgery have a hospital mortality rate of 15%-25% with an average prolonged hospital stay of 11 days. Additionally, non-fatal PMI is an independent risk factor for cardiovascular death and further non-fatal MI in the 6 months following surgery^{44,45}.

A relatively large number of genes have been associated with CAD and MI in ambulatory populations. Many of these reside in lipid-controlling pathways, underscoring the importance of lipid control in ambulatory populations and the role of long-term exposure of elevated lipid levels in development of atherosclerotic plaque. However, these variants don't provide clear insight to the mechanistic role of genetic variants in perioperative myocardial infarction (PMI). In general, we believe that surgery, with its associated trauma, is a pro-inflammatory environment. Anesthesia, fasting, pain, hypothermia, bleeding, anemia, and hyperglycemia additionally contribute to initiate and perpetuate a proinflammatory, hypercoagulable state. Thus the spectrum of "candidate" genes is expanded to inflammatory mediators, amongst others.

There are several environmental factors that can contribute to PMI during or after cardiac surgery. Suboptimal coronary graft anastomoses, graft thrombosis during the immediate postoperative period, traditional cardiology caveats of hypotension and tachycardia, and suboptimal myocardial protection during cardiopulmonary bypass can result in myocardial injury.

Platelets and Myocardial Injury

Traditionally, the hallmark event in the development of an MI is thrombotic occlusion of a coronary artery at the site of a ruptured or eroded atherosclerotic plaque, with subsequent microembolization of platelet-rich atherothrombotic load, platelet-mediated vasoconstriction, enhanced thrombus formation, and finally platelet-mediated inflammatory process in the now ischemic myocardium⁴⁶. It is likely, although unproven, that the nidus of thrombus development in PMI need not be the macroscopically ruptured or eroded atherosclerotic plaque. Platelets or leukocytes, "primed" by the pro-inflammatory surgical environment, may require only microscopic endothelial injury for thrombus propagation. Furthermore, platelet function extends greatly beyond simple clot formation (Figure 2). There is now evidence to suggest that genetic variants predispose patients to platelet and inflammation-mediated myocardial injury during and after cardiac surgery, and there is marked variation in the human platelet genome that directly determines platelet reactivity^{2,47}. Platelet reactivity is a significant predictor of cardiac outcomes after MI^{31,48}.

Variation in platelet genetic structure alters platelet function

Platelet polymorphisms alter platelet function and are associated with PMI^{30,32,49,50} (Table 1). To date, research has focused on the platelet glycoprotein receptors which are involved in platelet adhesion, activation, aggregation and ultimately stable clot formation. Importantly, many of these receptors are also expressed on other cell types, principally endothelium and leukocytes.

During initial clot formation, the vWF receptor interacts with the platelet receptor glycoprotein GPIb-V-IX to establish contact with the lesion on the vessel wall⁵¹. The GPIb-V-IX complex is composed of four polypeptide subunits: GPIb α , GPIb β , GPV and GPIX. Binding of vWF and GPIb-V-IX that occurs at the GPIb α subunit, and tethers platelets to the endothelium at high shear rates, is insufficient for stable adhesion and is rapidly reversible. In non-surgical patients, the Thr145Met and T-5C polymorphisms on the GPIb gene have been associated with ischemic cerebrovascular disease and an increased stroke risk in the young^{52,53}. Similarly, the Thr145Met polymorphism has been associated with coronary artery disease in a vascular

surgery population^{31,52,53}. These were both small studies purely showing an association, without experimental biological data; moreover, conflicting data has been published^{54,55}.

Platelet collagen receptor GPIIb/IIIa expression varies significantly in non-surgical patients,⁵⁶ and the rate of platelet attachment to collagen under conditions of high shear is highly correlated to the expression of GPIIb/IIIa receptors⁵⁷. GPIIb/IIIa receptor expression in turn is associated with hereditary variation and has a direct impact on coagulation. The -92C/G promoter variant of GPIIb/IIIa (ITGA2) is strongly associated with expression of the GPIIb/IIIa receptor⁵⁸. Platelet expression of GPIIb/IIIa and genetic variation that modifies such expression have been strongly associated with retinal vein thrombosis, but less well associated with non-surgical MI⁵⁹⁻⁶².

The previously mentioned Pro33 polymorphism of the GPIIIa subunit of the GP IIb/IIIa receptor has been associated with MI in ambulatory populations. Homozygosity for Pro33 has been associated with a threefold increase in ischemic cardiovascular disease and a fourfold increase in incidence of MI⁶³. Several studies have shown an association between the Pro33 polymorphism and either acute coronary thrombosis or sudden cardiac death in persons less than 60 years of age^{33,63-65}. In the perioperative setting, Pro33 is an independent predictor of myocardial ischemic outcomes in major vascular surgery³¹, increased levels of circulating Troponin I after CPB³², and cardiac events or death within 12 months after cardiac surgery⁶⁶; conversely, in a non-surgical population, this polymorphism did not lead to altered platelet function assessed by platelet aggregometry in African Americans⁶⁷. Accordingly, we have several lines of evidence favoring a genetic role, but an absence of proof.

The principal collagen-binding receptor, GPVI, is required for stable adhesion of platelets to the subendothelium⁶⁸. In the absence of this GP receptor, other surface receptors are inadequate for platelet adhesion⁵¹. In two small non-surgical studies in, the Ser219Pro polymorphism has been associated with coronary thrombosis and an increased risk of MI in older individuals, likely due to an increased tendency of platelets to adhere to coronary plaques under high shear stress^{50,69}.

The Complement System and Perioperative Myocardial Injury

The complement system is part of the innate immune system activated in response to both infectious and non-infectious pathogens. The complement system is comprised of three pathways; classical, lectin and alternative pathways. Activation of one or all of these pathways activates the effector complement pathway; the terminal pathway (Figure 3). During CABG surgery, complement is activated primarily by 1) the obligatory myocardial reperfusion that occurs following coronary revascularization and removal of the aortic cross-clamp and, 2) exposure of circulating blood to the extracorporeal synthetic material of the cardiopulmonary bypass (CPB) circuit⁷⁰⁻⁷³. The pro-inflammatory effects of the activated complement system contribute to myocardial injury and necrosis seen during cardiac surgery. Complement gene variants have been associated with varying degrees of complement protein expression, prompting investigators to hypothesize whether or not these variants are associated with varying degrees of myocardial injury following cardiac surgery. To date, mannose-binding lectin (*MBL*) and complement factor H (*CfH*) genes have received attention.

Mannose-binding Lectin (MBL)—Human MBL is an activator of the lectin complement pathway (LCP). As a pattern recognition molecule, MBL recognizes carbohydrate structures (or innate molecules mimicking carbohydrate structures) expressed on myocardium following oxidative stress or reperfusion^{74,75}. Binding of MBL to post-ischemic myocardium and subsequent activation of the LCP has been shown in animal studies to mediate myocardial injury⁷⁶⁻⁷⁸. Also, reduced myocardial infarct size in the absence of serum MBL supports its role as a regulator of myocardial reperfusion injury^{77,78}.

We recently demonstrated a significant association between *MBL2* gene variants and the incidence of perioperative myocardial injury in cardiac surgical patients⁷⁹. Specifically, the incidence of myocardial injury in Caucasians (n = 843) co-expressing the combined *MBL2* 5' LYQA secretor haplotype (CGTCGG) and 3' haplotype (CGGGT) was significantly higher than in Caucasians not expressing the haplotype (38% vs. 10%; $P < 0.007$). Although serum MBL levels were not measured, and therefore a causal relationship could not be determined, these results lend credence to the notion that complex phenotypic traits such as perioperative myocardial injury may be explained by genetic variation.

Complement factor H—The complement factor H (*CfH*) gene encodes for complement inhibitor protein (CfH). CfH inhibits the alternative complement pathway by binding and inhibiting C3 convertase, in turn limiting downstream activation of the terminal complement pathway responsible for direct cell lysis and further amplification of complement activity^{80, 81}. Gene polymorphisms that result in altered protein structure or function (non-synonymous coding polymorphisms) may render the CfH protein unable to bind C3, potentially predisposing patients to complement-mediated injury. The *Tyr402His* variant⁸² has been associated with age-related macular degeneration (AMD), most likely mediated through increased complement activation because of decreased CfH activity⁸³⁻⁸⁵. More recently, this polymorphism has been associated with myocardial infarction in non-surgical patients with no prior history of CAD⁸⁶. While the association is biologically plausible, there are no functional studies confirming the causal relationship between the *Tyr402His* variant and myocardial injury. To date, there is no published data reporting the association between *CfH* gene variants and postoperative myocardial injury in the surgical patient population.

In sum, there is evidence to suggest that complement gene variants contribute to the observed variability in complement levels, function, and myocardial injury. Further elucidating the role of these genes, and others in the complement system, will not only increase our understanding of complement-mediated myocardial injury during cardiac surgery, but may also lead to the identification of novel therapeutic targets for limiting post-CABG myocardial injury.

Atrial Fibrillation

Postoperative atrial fibrillation (PoAF) is the most common complication following cardiac surgery with an incidence of ~30%⁸⁷⁻⁹¹. Advanced age, history of AF or COPD, valve surgery, and withdrawal of β -blockers or ACE inhibitors are independent risk factors for developing PoAF⁸⁹. PoAF after cardiac surgery is associated with significantly longer intensive care unit (ICU) and hospital lengths of stay and a higher incidence of postoperative cognitive and renal dysfunction, infection and death. While there is strong evidence to support genetic susceptibility for familial AF^{92,93}, there are a very limited number of poorly-powered studies that have examined the association between gene variants and PoAF.

The inflammatory response to cardiac surgery is a known risk factor for developing PoAF⁹⁴⁻⁹⁶. Interleukin (IL)-6 is a proinflammatory cytokine that is significantly elevated following cardiac surgery^{97,98} and has been found to be associated with a higher incidence of adverse postoperative cardiovascular events, including AF^{99,100}. The -174G/C polymorphism on the IL-6 gene has been associated with elevated serum IL-6 levels following cardiac surgery and in ambulatory population. Perhaps surprisingly, given the low power of the study, the -174 G/C variant was associated with AF after cardiac surgery (hazard ratio 3.25, 95%CI 1.23 to 8.62)¹⁰¹. The association between the IL-6 gene and PoAF was subsequently confirmed in a larger study that identified a single locus effect of the -174 polymorphism able to predict PoAF with 58.8% accuracy¹⁰².

A recently published genome-wide analysis has identified a region on the long arm of chromosome 4 (4q25) associated with an increased risk of AF in several ambulatory populations¹⁰³. However, the variants in this region that best predict AF are not located in a gene that could explain this association from a biologic standpoint. Interestingly, the paired-like homeodomain transcription factor 2 (*PITX2*) gene is located in a block immediately adjacent to this region. This gene has been shown to effect left-right determination of the cardiac atria¹⁰⁴, and left atrial sinoatrial node formation during embryologic development¹⁰⁵. Until functional studies become available, we can only speculate as to the causal relationship between these variants and AF, and whether or not the *PITX2* gene has a biological role. Currently, there is no study examining the association between polymorphisms in the area of 4q25, including the *PITX2* gene and postoperative AF in patients undergoing cardiac surgery.

Conclusion

In this review, we have described a number of genetic polymorphisms that have been associated with increased bleeding, myocardial injury and atrial fibrillation during the perioperative period, specifically in cardiac surgery. These polymorphisms are complex genetic disorders, explaining some, but not all of the variability of each disease. An individual does not need to have the polymorphism to have the disease, and not every person with the disease has the polymorphism. Furthermore, the overall genetic effect is usually the sum of numerous small genetic effects, modified by non-genetic factors. To date, preoperative surgical and anesthetic risk assessment and perioperative management decisions have been made based on known environmental determinants, but there remains considerable inter-individual variability in both incidence and severity of adverse outcomes following cardiac surgery.

But where does this litany of, sometimes conflicting, studies associating genetic variants with adverse outcomes leave us in terms of patient management? As we do not have the ability to routinely test for these variants yet and most studies suffer from small sample sizes, it would be not be sensible to make management recommendations to the practitioner - yet. With larger patient registries, better phenotyping, and most importantly validation of the results with other populations prior to publication, we will hopefully be able to find true biologically-proven associations that will have an impact on clinical care.

Acknowledgments

Work supported by a K30 RR022292 (TEP) and a K23 HL68774 (SCB) from the National Institutes of Health, and a Bayer Fellowship in Blood Conservation (JDM)

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Major Allele

The majority of individuals have a given sequence of alleles that code for normal protein structure and function.

Minor Allele

Compared with the Major Allele, a single base pair change (**bold**) is referred to as a single nucleotide polymorphism (SNP), and can result in altered protein structure and/or function that, in turn may result in disease.

A gene is comprised of a promotor region, exon and introns, and surrounded by 5' and 3' untranslated regions (UTR), respectively. Within each gene, nucleotides with their respective bases (**A**denine, **T**hymine, **G**uanine **C**ytosine) make up the individuals' unique genomic sequence that regulate the genes expression of protein.

Figure 1.

A schematic of typical gene structure

Figure 2.
The role of platelets in perioperative myocardial infarction

Figure 3.
Complement system activation during cardiac surgery

Table 1
Summary of genetic variation in platelet receptors

Gene	Polymorphisms	Mechanism	Phenotype	Ref
Platelet membrane glycoproteins				
GPIIb/IIIa, ($\alpha_2\beta_1$ integrin)	-92, -52, C807T, G873A, A1648G	Variable binding of platelets under high shear	Integrin α_2 receptor density leads to clinical thrombosis or bleeding	57
GPIb-IX-V	-5 (Kozak), T145M (HPA-2), 1285 VNTR	Variable surface receptor expression		
		↑ Surface receptor expression	↑ Risk of coronary artery disease	31-53
		Changes in high shear rate properties	↑ Stroke risk in the young	
			↑ Ischemic outcome in vascular surgery patients	
GP IIIa (β_3 integrin)	Leu33Pro (HPA-1, PIA1, A2)	↑ Sensitivity to activation	Associated with acute coronary syndrome in patients younger than 60yrs.	31-32-63-33-106-107-108
		Lower threshold for platelet activation		
		α - granule release	↑ Risk of coronary stent thrombosis	
		GP IIb/IIIa activation	↑ Restenosis after stent placement	
		Fibrinogen binding	3-fold ↑ of ischemic cardiovascular disease, 4-fold risk of MI in young men.	
			↑ Troponin I concentrations following CPB	
			↑ Risk of cardiac events or death in the 2-12 months after cardiac surgery	
GPVI	Ser219Pro, Q317L	Unknown	Associated with coronary thrombosis	50-69
			↑ Area of complicated coronary lesions	
			↑ Risk of MI in older individuals	
Selectins				
E-Selectin	Ser128Arg	Altered leukocyte binding and soluble	Implicated in inflammatory injury after cardiac surgery with CPB	109-110-111
			E-selectin release	
			Risk factor for premature/severe coronary artery disease	
			↑ risk for early severe atherosclerosis	
P-Selectin	Thr715Pro	Unknown	↓ Risk of MI	112
Purinergic Receptors				

Gene	Polymorphisms	Mechanism	Phenotype	Ref
P2RX1, P2RY1, P2RY12		↑ ADP platelet aggregation	↑ Risk of atherothrombosis and/or a ↓ Clinical response to drugs inhibiting platelet function	113