THE RELATIONSHIP OF SINGLE NUCLEOTIDE POLYMORPHISMS AND INFLAMMATORY MARKERS OF CORONARY ARTERY DISEASE:
SIGNIFICANCE FOR NURSE PRACTITIONERS IN AN ACUTE CARE SETTING

by

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STATEMENT BY AUTHOR

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My Lord and Savior, Jesus Christ, without whom I would have never been admitted to the College of Nursing.

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ABSTRACT

The purpose of this paper is to elucidate the need for acute care nurse practitioners (ACNPs) to understand the significance of single-nucleotide polymorphisms (SNPs) and how they correlate with blood levels of certain inflammatory markers; an increase in blood levels of these markers may lead to coronary artery disease (CAD) and its sequelae. Genetic research regarding CAD is comparatively sparse. A comprehensive review of research articles describing the effects of three primary inflammatory markers and associated genetic polymorphisms on CAD and coronary sequelae was performed; findings revealed several key SNPs that have been shown to both increase inflammatory marker levels and increase clinical coronary-related events. ACNPs need to keep their practice up-to-date by synthesizing genetics research studying both inflammatory markers and SNPs. Appropriate management strategies include awareness of inflammatory marker levels and early pharmacological intervention.

Key Words

Single Nucleotide Polymorphisms, inflammation, C-reactive protein, fibrinogen, Interleukin-6.
Chapter I. Introduction

Introduction

CAD is the leading cause of morbidity and mortality in the U.S. Cardiovascular disease causes over 45% of deaths in the U.S. for men, and over 53% for women (American Heart Association [AHA], 2005). In 2005, Americans will pay well over $390 billion in health care costs related to CAD complications. About 70 million Americans suffer from some form of cardiovascular disease (AHA, 2005).

CAD is an inflammatory process (Plutzky, 2001). The inflammatory process is mediated by multiple inflammatory blood proteins. These inflammatory proteins, or markers, are in the plasma; therefore, their levels can be measured. The major inflammatory markers studied today include C-reactive protein (CR-P), interleukin-6 (IL-6), and fibrinogen (Pearson et al., 2003). Inflammatory marker levels have been postulated to be modulated by genetic variations called single-nucleotide polymorphisms (SNPs).

Etiology of CAD

CAD begins with coronary artery vessel endothelial damage (Cotran, 1999). CAD is the progressive formation of a fatty plaque that hardens and stiffens arteries, which may eventually rupture and subsequently form a thrombus. If left unchecked, CAD eventually leads to myocardial infarction (MI), or death of cardiac tissue. After the thrombus forms, the coronary artery is either completely or partially occluded. The tissue supplied by that vessel becomes ischemic, and will die if the thrombus is not dissolved or removed. When tissue death happens, an MI has occurred (Cotran, 1999). Most MIs
SNPs and NPs

have been found to occur after a long process of chronic inflammation, in which moderately stenosed vessels experience plaque rupture and subsequent thrombus formation (Plutzky, 2001).

**Traditional Genetic Risk Factors**

Traditional genetically linked risk factors for the development of CAD include hypertension, dyslipidemia, diabetes, and a family history of CAD (Pearson et al., 2003). Clearly, genetics plays a crucial role in the manifestation of CAD, yet many health care providers consider genetics a field that only applies to specialists (Wung, 2002).

The importance of genetics in CAD was first evidenced with a historic hallmark study that found first-degree relatives of patients with CAD have a 5-7 fold increased risk of death due to CAD (Slack & Nevin, 1968). A later study found there is a 4 fold higher risk of death for fraternal twins and an 8 fold increase in death risk for identical twins that have a sibling with CAD (Marengberg, Risch, Berkman, Floderus, & de Faire, 1994).

While traditional risk factors certainly are indicative of higher risk of MI, newer risk factors may be of assistance in determining the urgency of need for acute intervention, and in verifying the increased risk of MI.
Chapter II. Theoretical Framework

Novel risk factors

C-reactive protein

C-reactive protein (C-RP) has been called “an independent cardiovascular risk factor (Lagrand et al., 1999).” C-RP levels are indicative both of risk for MI and of outcome after MI (Lagrand, 1999), and there is a dose-response relationship between CR-P levels and risk of CAD (Pearson et al., 2003). There is also evidence that high C-RP levels during infections predispose an individual to CAD, and the protein can even be found localized in inflamed tissues such as infarcted myocardium (Lagrand, 1999). Indeed, it has been well established that C-RP levels are an independent risk factor for coronary events (Lagrand et al. [1999], Plutzky [2001], James et al. [2003], and Ichihara et al. [2002]).

Interleukin-6

Blood levels of C-RP in the acute stages of inflammation can be determined by levels of IL-6. These two markers have been identified as key markers in the inflammatory process (Pearson et al., 2003). The IL-6 cytokine stimulates the liver to release higher levels of CR-P, thus increasing the individual’s chance of developing CAD (Pearson et al. [2003] and Volankis [2001]). High IL-6 levels are also associated with an increased risk for future coronary events (Saadeddin et al. [2001] and Ridker et al. [1999]), and even death (Lindmark et al. [2001] and Luc et al. [2003]).

Fibrinogen
Fibrinogen, another clinical phenotype, also shows promise in determining an individual’s risk for developing MI. An article from the Center for Disease Control (CDC) and the AHA recently published an exhaustive review article describing inflammatory markers and their role in cardiovascular disease. This article specifically state that “the strongest association with prognosis has been with fibrinogen…(Pearson et al., 2003).” Fibrinogen levels have also been shown to be a good indicator of death rates in patients with unstable CAD (Lindhal et al. 2000) and of final cardiac infarct size (De Sutter et al., 2000).

In the respect of correlating CAD with inflammatory blood markers, research and evidence abounds. The most well-established of these are CR-P, IL-6 and fibrinogen (Pearson et al., 2003). Research is sparse and inconsistent, however, when it comes to correlating CR-P, IL-6, and fibrinogen-promoting SNPs with CAD and coronary events. In theory, genes specific for these phenotypes could be typed in an individual, thereby determining an individual’s level of risk for developing an MI.

Figure 1. The major inflammatory cytokines.
SNPs: the Genetic Link

Genetic screening for specific polymorphisms is a process in need of further development. Genetic screening could include genotyping an individual, or analyzing blood samples for clinical phenotypes (Wung, 2002). Phenotypes are the clinical manifestation of a genetic variation or mutation. CAD is a complex disease that may potentially involve hundreds of genetic polymorphisms, called SNPs (See Figure 2). An SNP (pronounced "snip"), is a “small genetic change, or variation, that can occur within a person's deoxyribonucleic acid (DNA) sequence. The genetic code is specified by the four nucleotides A (adenine), C (cytosine), T (thymine), and G (guanine). SNP variation occurs when a single nucleotide, such as an A, replaces one of the other three nucleotide letters—C, G, or T (NCBI, 2005).”

These polymorphisms may predispose an individual to be more susceptible to plaque formation, high lipid levels, and thrombus formation (Wung, 2002). This review and critique will attempt to reinforce the mechanism by which the inflammatory process may begin—with the expression of certain SNPs, which initiate a rise in blood levels of notorious inflammatory markers such as C-RP, IL-6, and fibrinogen (See Figure 3). This review will specifically examine one CR-P SNP, six IL-6 SNPs, and five fibrinogen SNPs in their role in the inflammatory process and in CAD development. These SNPs were selected because they were the most frequently studied in relationship to CR-P, IL-6, and the fibrinogen inflammatory markers.
The pathophysiology of CAD is essentially a chronic inflammatory process (Plutzky [2001], Schonbek & Libby [2004], and Willerson & Ridker [2004]). The inflammatory process is perhaps the most damaging process in the body for those susceptible to CAD development (Pearson et al., 2003). Willerson & Ridker (2004) indicate that the inflammatory process appears to begin with pro-inflammatory risk factors, such as infectious agents, oxidized low density lipoproteins, or a vascular injury. The inner lining of the artery, or endothelium, then promotes the migration of leukocytes. Leukocytes adhere to the endothelium via adhesion molecules, and their presence attracts more leukocytes and monocytes through the release of additional cytokines (Cotran,
SNPs and NPs

1999). The white cells then begin to consolidate into the endothelium, decreasing endothelial function and increasing matrix degeneration (Schonbeck & Libby, 2004). The monocytes become macrophages, take up LDLs, and proliferate (Willerson & Ridker, 2004). The resulting fatty streaks build up over time and increase the lesion size. A fibrous cap forms over the fatty streak from surrounding vascular smooth muscle cell production of collagen (Cotran, 1999). This cap is fragile and is eventually dissolved by the leukocytes through metalloproteinases (Willerson & Ridker, 2004). Throughout the process, leukocytes and macrophages are releasing proinflammatory modulators, of which IL-6 is the principal procoagulant cytokine, which in turn increases both CR-P and fibrinogen levels (Willerson & Ridker, 2004). Fibrinogen and CR-P amplify inflammatory and coagulopathic responses; CR-P also causes cellular adhesion molecules to be expressed (Willerson & Ridker, 2004). CR-P is also implicated in directly reducing nitric oxide (NO) bioavailability. Endothelium-derived NO is a molecule which enhances vasodilation, inhibits platelet aggregation, reduces leukocyte adherence, and suppresses smooth muscle cell proliferation (Willerson & Ridker, 2004). As NO levels gradually decline while inflammatory marker levels increase, the probability of rupture and thrombosis formation increases (Willerson & Ridker, 2004).

It has been proposed (Jenny et al., [2002], Vickers et al., [2002], Elghannam et al., [2000], Basso et al., [2002], Burzotta et al., [2001], Brull et al., [2001], Georges et al., [2001], Humphries et al., [2001], Losito et al., [2003], Gaudino et al., [2003], De Maat et al. [1997], Weng, X., Cloutier, G., & Genest, J. Jr. [1999], Van ‘t Hooft et al. [1999], Folsom et al. [2001], and Margaglione et al., [2000]) that SNPs are responsible for high
levels of inflammatory cytokines, and thus exacerbate the inflammatory process through increasing inflammatory mediators such as IL-6, CR-P, and fibrinogen in the mid to latter stages of atherosclerosis. While SNPs influencing inflammatory marker levels has yet to be proven, this paper will attempt to elucidate the significance of single-nucleotide polymorphisms (SNPs) and how they correlate with blood levels of CR-P, IL-6, and fibrinogen.

Figure 3. SNPs and the inflammatory response cascade.
Literature Review of Single Nucleotide Polymorphisms

Introduction to Literature Review

The literature search was performed online using Medline. Keywords used were CAD, MI, and SNP. The most popular SNPs were used for keywords as well. These SNPs were the C substitution for the G allele at the 174th nucleotide in the promoter region of the IL-6 gene, an A substitution for the G allele at the 455th nucleotide in the promoter region of the beta-fibrinogen gene, and a C substitution for the G allele at the 1059th nucleotide in the promoter region of the CR-P gene. There was a much larger volume of literature found that studied the relationship of SNPs in other inflammatory conditions such as rheumatoid arthritis (RA), but these were not included because they were not specific to CAD, MI, or its sequelae.

Articles reviewed had several different ways of describing nucleotide substitutions and homozygous (two same) or heterozygous (two different) alleles. The different forms these alleles were described in the body of text of the articles will be the way they will be described in the literature review. Most described substitutions with a “/” between the “normal” allele and the substituted allele. For example, if an allele was normally homozygous with two guanines (GG), a guanine (G) substituted with a cytosine (C) would be G/C. This was the most popular form of describing the polymorphisms. Homozygotes are always described without a slash, such as GG. Heterozygotes, such as the C substitution described above, might also be described with just the “C”, with the G allele being implied. All of these nomenclatures follow the locus of the polymorphism; that is, where the polymorphism appears on the gene. Most popular locations studied are
described in the previous paragraph as -174 for IL-6, -1059 for CR-P, and -455 for fibrinogen.

* C-RP Promoting SNPs

A C allele substitution for the G allele on the 1059 nucleotide of the CR-P gene was first discovered by Cao and Hegele in 2000. The study stated the discovery of the CR-P G1059C polymorphism; no comparisons or experiments were attempted. The authors proposed that this polymorphism may contribute to high levels of CR-P in atherosclerotic lesions, leading to MI (Cao & Hegele, 2000). Although this was not a review article, number of subjects and method of sampling, as well as design of the study, were not mentioned; as a result, no comments can be made regarding the author’s conclusions.

Zee and Ridker (2002) found that high plasma CR-P levels are associated with the “C” allele of the 1059 polymorphism of the CR-P gene, while patients with homozygous GG allele had lower concentrations. Authors sampled 14, 916 men prospectively over 8.6 years and matched subjects who subsequently developed arterial thrombosis to controls for a total of 726 case-control pairs. However, there was no significant association between arterial thrombosis risk and high CR-P levels in all groups (CC, GC, & GG). The findings of this study indicate a genetic link between high CR-P levels and the G1059C SNP, but yet appear to contradict a majority of research in showing that high CR-P levels are not associated with arterial thrombosis risk in this study (Pearson et al. [2003], Lagrand et al. [1999], Plutzky [2001], James et al. [2003], and Ichihara et al. [2002]).
The authors stated, “While increased concentrations of C-reactive protein (CRP) are associated with increased vascular risk, little information is available describing genetic determinants of this effect (Zee & Ridker, 2002).” Therefore, additional research is warranted.

**CR-P Promoting SNP Summary**

Cao and Hegele (2000) discovered the CRP G1059C polymorphism; they did not study its effects on subjects. As a result, no definite conclusions can be drawn from this study. Zee and Ridker (2002), studying the same polymorphism, discovered that there were significantly higher levels of CR-P in the C carriers of the CRP G1059C polymorphism, but were not able to correlate the higher CR-P levels with an increased risk of arterial thrombosis. It is unclear why this is; it has been well established that higher CR-P levels correlate with higher risk for MI, which is precipitated by arterial thrombus formation (Cotran, [1999], Pearson et al., [2003], Lagrand et al., [1999]). See Table 1 on page 44 for a brief synopsis of proposed CR-P promoting SNP articles reviewed and their findings.

**IL-6 Promoting SNPs**

One of the main polymorphisms investigated for IL-6 expression is the C substitution for the G allele on the 174 nucleotide of the IL-6 gene. The IL-6 G-174C SNP is implicated in the development of CVD in a cross-sectional, nonexperimental study conducted by Jenny et al. (2002). The group with a minor C allele had higher blood levels of CR-P, fibrinogen, and IL-6 when compared to the group with a G allele. The group with a minor C allele was also at greater risk of developing acute MI. The
researchers suggested that the minor C allele combined with high IL-6 levels is a predisposition to atherosclerosis (Jenny et al., 2002). The strengths of this study included a large sample size of 5201, which included all allele groups and MI/non MI subjects. Although the findings show a trend toward an increase in IL-6 levels in patients with C allele than those with G allele, the difference did not show statistical significance.

Vickers and coworkers (2002) found that elevated baseline levels of CR-P are associated with the IL-6 G174C polymorphism in 588 members of nuclear British Caucasian families. The authors used a nonexperimental, cross-sectional design. This article brings forth the argument that acute and chronic CR-P levels brought on by inflammation may not be the primary impetus for MI development. Carriers of the C allele of the IL-6 G174C polymorphism may predispose an individual to elevated CR-P levels and, therefore, acute MI.

In a study by Elghannam et al. (2000), there was an association between baseline minimum lumen diameter of coronary arteries and the -174G/C genotype in 375 subjects 35-75 years of age with one or more stenotic (30-75%) coronary lesion and high (110-190 mg/dl) LDL levels randomized to fluvastatin treatment or placebo control groups. Fluvastatin was found to be effective in reducing lipoprotein (a) in the cohorts with the CC allele when compared with the GG or GC alleles. The researchers suggested an association between the GG allele and an increase in high-density lipoprotein (HDL) levels (p=0.054). Baseline demographic characteristics such as age, gender, ethnic background, height, weight, body mass index, systolic and diastolic blood pressure, waist/hip ratio, and history of MI, diabetes, and smoking did not show statistically
significant relationships with the IL-6 genotypes. Although it is well known that these characteristics influence a client’s risk of MI (Cotran, 1999), the statistically significant findings in this study of an increased lumen diameter, increased response to fluvastatin, and decrease in HDL levels with the CC allele show a genetic influence on MI risk factors. Single polymorphisms may only influence one aspect (i.e., lumen diameter) of a client’s physiologic characteristics; multiple polymorphisms in a population might need to be studied in order to correlate baseline characteristics with a client’s genetic makeup.

Basso et al. (2001) studied the IL-6 -174G/C polymorphism, and a polymorphism involving a C substitution of the G allele in the 572 locus of the IL-6 gene. A sample of 6595 moderately hypercholesterolemic men ages 45-64 with no prior MI history and no renal or hepatic dysfunction were randomized to placebo or pravastatin treatment, and 498 cases and 1109 apparently healthy, case-matched controls were selected. The cases included those experiencing MI, angioplasty, or coronary artery bypass grafting (CABG) within 4.8 years of follow-up. Participants were genotyped for the above mentioned polymorphisms, and blood levels of fibrinogen, C-RP, and IL-6 were measured. There was no significant evidence of higher risk for CAD when the GG, CC, or GC alleles of the IL-6 -174G/C polymorphism. However, the -174CC genotype had a twofold higher baseline levels of fibrinogen, CR-P, and IL-6, although the difference did not reach statistical significance. The -174CC genotype also had the lowest risk of CAD after pravastatin treatment. Results of this study indicated the individuals with the CC allele had higher baseline levels of inflammatory markers and the greatest change in CAD risk
after pravastatin treatment, showing the benefit of research into the IL-6 -174G/C promoter gene, CAD, and its sequelae.

Higher levels of IL-6 and longer hospital stays were associated with the -174GG polymorphism of the IL-6 gene in the study conducted by Burzotta et al. (2001). One hundred eleven patients undergoing elective CABG at one hospital were screened and then prospectively studied over 16 months using a non-experimental design. Burzotta found that CABG patients with the GG genotype had higher levels of IL-6 and were in the ICU longer than C carriers. However, C-RP and fibrinogen level did not differ significantly among the C carrier and homozygous GG allele groups. Interestingly, the results from this study differ from results found from previous four studies (Jenny et al. [2002], Vickers et al. [2002], Elghannam et al. [2000], and Basso et al. [2001]), where the minor C allele was associated with higher levels of IL-6, fibrinogen, C-RP, and artery lumen diameter; Burzotta and coworkers found the homozygous GG allele to be associated with higher levels of IL-6. Although the results show a positive correlation between the GG allele and IL-6 levels, there was no correlation indicating a relationship between the GG homozygous allele and the severity of CAD or higher frequency of MI than the C carriers. This is yet another indication for further research, as both C and GG alleles have been identified as the culprits for increased IL-6 levels.

Nauck et al. (2002) found no correlation between the -174G/C polymorphism and IL-6 levels, MI, and CAD in 2559 patients with documented CAD with (n=1365) and without (n=1194) MI, and 729 non-random controls (no CAD) at a heart center in Germany. Sampling was done over a 3 year period; the study was called the
Ludwigshafen Risk and Cardiovascular Health study (LURIC). All CC, GC, and GG allele subgroups were studied, and none of the groups correlated significantly with IL-6 levels, MI, and CAD. However, IL-6 and CR-P levels were higher in the GC allele. These findings need to be weighed against other previous study results, since most other studies reviewed have found a correlation between the IL-6-174C SNP, IL-6 levels, and acute coronary events (Jenny et al. [2002], Vickers et al. [2002], Elghannam et al. [2000], and Basso et al. [2001]). Some explanations for the differences in results might include the possibility that there is more than one SNP that influences IL-6 levels. There is also a question as to whether the IL-6 -174G/C polymorphism plays more of a role in chronic or acute IL-6 levels. Additional research needs to be conducted, including IL-6 promoter polymorphisms at different genetic sites and at different time frames after acute MI before a conclusion can be reached regarding an association between genotype and susceptibility to MI and CAD.

After adjusting for age, smoking history, and sex, the -174G/C and -572G/C polymorphisms of the IL-6 gene were found to be strong predictors of IL-6 levels after CABG in the study by Brull et al. (2001). One hundred twenty seven patients undergoing CABG were selected at Middlesex Hospital in England. The study used a nonexperiemntal design, with no control group, intervention, or randomization. The -597G/A allele was also studied, but no statistically significant results between genotype and baseline IL-6 levels were found. The -572G/C allele had significantly higher IL-6 levels than the -572GG group 6 hours after surgery. The -174CC group also had higher IL-6 levels when compared with the -174G carriers. These results support the studies by
Jenny et al. (2002), Vickers et al. (2002), Elghannam et al. (2000), and Basso et al. (2001), who found a significant difference between the C allele and IL-6 levels. It may be beneficial to perform genetic tests on multiple polymorphic sites for each clinical phenotype; for example, testing the IL-6 -174G/C, -572G/C, and -597G/A SNPs in a single study; this exemplifies the necessity for continued research in this area.

A study by Georges et al. (2001) found a correlation between the -174G/C, -572G/C, and -596G/C polymorphisms of the IL-6 gene and susceptibility to MI using a cross-sectional design. The SNPs were studied to determine effect of genetic variation on number of stenosed (>50%) coronary vessels. Over a two year period, 640 clients suffering an acute MI were recruited from health monitoring registers in several European countries, and 719 age-matched randomly sampled controls. Of note, the -174G/C and -596G/A polymorphisms were closely associated with one another, having the highest correlation with three stenosed coronary arteries. The -174C allele was associated with a higher risk of MI, although this allele was correlated with two or fewer stenosed vessels, indicating a need to separate the extent of CAD and the susceptibility to MI as two separate entities. Certain alleles may cause an individual to be more susceptible to more extensive, yet stable CAD, but not necessarily increase their risk for MI.

A multivariate analysis showed that the GG genotype of the IL-6 -174G/C polymorphism was “the only independent predictor of postoperative atrial fibrillation (AF)” in a prospective correlational study conducted by Gaudino et al. (2003) in 110 subjects undergoing coronary artery bypass grafting (CABG) at a Catholic hospital in
Patients with the GG and the CC genotype were compared. A multivariate analysis showed that IL-6 and fibrinogen levels were elevated in the GG genotype when compared to the CC group (p<0.001). In addition, postoperative AF was increased in the GG allele over the GC and CC alleles (10.4% vs. 33.9%) to within a 95% confidence interval (CI). This is the only study found that found an increase in IL-6 levels with the homozygous GG alleles instead of C carriers or the CC homozygote. Most other studies found the C carriers and the CC homozygote to have increased levels of IL-6 or increased risk for acute MI (Jenny et al. [2002], Vickers et al. [2002], Elghannam et al. [2000], Basso et al. [2001], Brull et al. [2001], and Georges et al. [2001]). Brull et al. (2001) conducted a similar study on postoperative CABG patients and found IL-6 levels to be elevated in CC alleles as opposed to the GG alleles. Results should therefore be reviewed with caution; selection methods were not random, no controls were used, and sample size was small (110). In addition, “isolated CABG patients” were the only subjects used. However, these are similar parameters used by Brull et al. (2001). It is otherwise unclear why Gaudino and colleagues found the GG allele to have higher levels of IL-6, fibrinogen, and postoperative AF than the -174 CC and C alleles.

Losito et al. (2003) examined 161 dialysis patients with the -174CC and GC allele of the IL-6 polymorphism in a cross-sectional study, and found that hypertension (p=0.008) and left ventricular hypertrophy (LVH) were both increased (p=0.026) in both alleles. Hemodialysis patients in a single unnamed hospital unit were age and gender-matched to healthy controls. The authors did not study CAD, inflammatory marker levels and their relationship to the IL-6 -174C allele; they were correlating a risk factor
(hypertension) and a result of peripheral vascular disease (LVH) to the allele. The findings by Losito and colleagues nevertheless shows an association with a majority of the research by indicating a relationship between the C allele of the -174 polymorphism and risk factors for acute MI (Jenny et al. [2002], Vickers et al. [2002], Elghannam et al. [2000], Basso et al. [2001], Brull et al. [2001], and Georges et al. [2001]).

Nakajima et al. (1999) used a case-control design to study 143 normotensive and 150 hypertensive Japanese women recruited from volunteers living in a Japanese prefecture and found little correlation between hypertension and three new polymorphisms of the IL-6 gene, the -4391G/A, -634C/G, and -447A/T polymorphisms. Polymorphisms were similar in frequency in both the normotensive and the hypertensive groups. No randomization was performed, and no experimental intervention was involved. The authors concluded that the newly discovered SNPs played a minimal role, if any, in the genetic etiology of hypertension.

Systolic blood pressure, CR-P, and fibrinogen levels were found to be elevated in a sample of 2751 healthy, middle-aged U. K. men with the IL-6 -174G/C or CC allele when compared to the GG allele in a prospective study by Humphries et al. (2001). There was also no significant effect between blood pressure, fibrinogen, or risk of CAD and the -572G/C polymorphism. Findings from this study reinforce the majority of other articles (Jenny et al. [2002], Vickers et al. [2002], Elghannam et al. [2000], Basso et al. [2001], Brull et al. [2001], Georges et al. [2001, and Losito et al. [2003]) stating the C allele of the -174G/C polymorphism is the culprit for promoting CAD and its sequelae.

Summary of IL-6 Promoting SNPs
The majority of research reported a correlation between the minor C allele at the 174th nucleotide of the IL-6 gene and increased IL-6 levels (Jenny et al., [2002], Vickers et al., [2002], Elghannam et al., [2000], Basso et al., [2002], Brull et al., [2001], Georges et al., [2001], Humphries et al., [2001], and Losito et al., [2003]), except one by Nauck et al. (2002). Nauck et al. (2002) found none of the CC, GC, or GG alleles of the -174G/C polymorphism was correlated positively with IL-6 levels, MI, and CAD. It is frankly unclear as to why this study by Nauck et al. was unable to replicate findings of others. It is possible that the -174G/C and CC alleles studied do not significantly alter translation and transcription of proteins and thus affect inflammatory marker levels in some patients. There may be more than one SNP that influences IL-6 levels, such as the -596GA polymorphism found by Brull et al. (2001). There needs to be more research conducted to determine whether the IL-6 -174G/C polymorphism plays more of a role in chronic or acute IL-6 levels. In short, additional research needs to be conducted with IL-6 promoter polymorphisms at different genetic sites and at different time frames after acute MI before a conclusion can be reached regarding an association between the -174G/C genotype, IL-6 levels, and susceptibility to acute MI. See Table 2 on page 45 for a brief synopsis of proposed IL-6 promoting SNP articles reviewed and their findings.

**Fibrinogen-promoting SNPs**

A correlation between CAD and the beta-fibrinogen -455G/A SNP was reported by de Maat et al. (1998). Using a true double-blind, placebo-controlled experimental design, authors recruited 885 male clients undergoing catheterization at multiple
hospitals. Intervention groups received pravastatin, and controls received placebo. The -455A/A genotype was especially implicated in significantly higher levels of fibrinogen; in addition, the 2-year follow up revealed an increased progression of CAD determined by minimum obstruction diameter (MOD) and mean segment diameter (MSD) for the placebo group of the same genotype. Pravastatin therapy was given to the treatment group, and appeared to offset the effect of the A/A genotype in the treatment group after a 2-year follow-up. The authors propose that clients could be genotyped to determine who would benefit from early statin treatment, or have other pre-CAD cardioprotective measures instituted. The study is somewhat old, but employs a strong design to demonstrate a correlation between CAD and the -455G/A SNP.

Weng, Cloutier, and Genest (1999) discovered an increase in erythrocyte aggregation related to the beta-fibrinogen -455G/A polymorphism. Study participants consisted of 135 French Canadians with documented CAD, recruited from a Cardiology clinic with no controls or intervention. Authors used a cross-sectional, nonexperimental design. Blood levels were drawn once, 3 months after percutaneous intervention, CABG, or AMI. Aggregation was measured by laser reflectometry. All three SNP subtypes were studied; -455GA, -455AA, and -455GG. The -455AA allele had the strongest association with aggregation, although it was the rarest SNP. The researchers concluded that this relationship may be explained by a change in the concentration or by the function of the fibrinogen molecule itself. Since fibrinogen can be associated with the more acute stages of MI, i.e., thrombosis formation, this study may lend clues into using the beta-fibrinogen
-455G/A SNP as more of an acute marker, rather than a chronic, lifetime-developing CAD marker.

Folsom et al. (2001) studied 398 incident coronary heart disease patients over 5.3 years of follow-ups and compared them to an identical number of participants who were randomly selected from the same cohort, and found a significantly higher plasma fibrinogen concentration in those with homozygous AA allele of the -455G/A polymorphism when compared to the G allele cohort. No association was found between the A allele carriers and diagnosis of CHD. Although results of this study indicate minimal correlation of the -455/AA polymorphism to CHD, there is still a correlation of the -455/AA SNP with increased fibrinogen levels. It is well established that increased fibrinogen levels correlate with increased CHD risk (Pearson et al., [2003], Lindhal et al., [2000], De Sutter et al., [2000]). In addition, all of the studies that find no correlation between SNP groups used nonexperimental designs; the 2 employing randomized, interventional, placebo-controlled studies with large cohorts do find statistically significant differences in SNP groups (Elghannam et al., 2000, and De Maat, 1998).

Margaglione and colleagues (2000) investigated the relationship between several different serum markers, including fibrinogen, and genetic polymorphisms, such as fibrinogen G-455A, and a family history of MI in 1048 individuals of variable ethnicity without clinical evidence of atherosclerosis. They found that the individuals who were beta-fibrinogen -455A carriers had a trend toward having a first degree relative suffer an MI than those with GG allele (p=0.08), but found no associations between the allele and fibrinogen levels. Although fibrinogen levels were raised in individuals who had a first-
degree relative suffer an MI, there was no statistical significance found in this study linking the -455A carriers with fibrinogen levels. Authors conjectured this may be due to a difference in genetic background from those sampled. Additionally, the results “only reflect the association between a set of variables and a family history of MI (Margaglione et al. (2000).” In other words, authors did not study the risk of MI in subjects recruited.

In a study conducted by Van ‘t Hooft et al. (1999), the –455A and -854A alleles were associated with higher transcription rates of fibrinogen than their -455G and -854G counterparts, and together explained approximately 11% of the variation in plasma fibrinogen concentrations in 210 men randomly recruited from a register of permanent residents in Stockholm County, Sweden. No control groups were used, and there was no randomization or experimental intervention in this cross-sectional study. Authors concluded that the A allele of the -455G/A and -854G/A polymorphisms are “physiologically relevant” and have a “significant impact” on the plasma fibrinogen concentration. Other common polymorphisms in the beta-fibrinogen gene, -148C/T, -249C/T, and 993C/T, did not show statistically significant relationship with the fibrinogen levels. This is the only study investigating any polymorphisms associated with inflammatory marker levels and CAD and polymorphisms in the fibrinogen gene other than the -455G/A SNP. Findings from this study support the significance of the -455A polymorphism to high fibrinogen levels and risk for future MI, which is similar to results found by others (Maitland, 2002, De Maat, 1997, Weng, 1999, Margaglione, 2000).

Summary of Fibrinogen-promoting SNPs
Results from studies examining the beta-fibrinogen-455G/A polymorphism showed a positive correlation between the SNP and increased serum fibrinogen levels and/or increased risk for coronary events (De Maat et al., [1998], Weng et al., [1999], Folsom et al., [2001], Margaglione et al., [2000], Maitland-van der Zee et al., [2002], Van’t Hooft et al., [1999]). The only study examining other polymorphisms was Van’t Hooft (1999), who studied five polymorphisms of the beta-fibrinogen gene, -455G/A, -854G/A, -148C/T, -249C/T, and -993C/T, and found that only two (-455A and -854A) increased the plasma fibrinogen concentration. The fact that the other SNPs did not appear to increase serum fibrinogen levels to a statistically significant degree may indicate that the substitutions produce no significant effect on translation and subsequent transcription of the fibrinogen protein. Further research using large sample sizes, a higher degree of randomization and control, and meta-analysis of all known SNPs affecting CR-P, IL-6, and fibrinogen levels is warranted to confirm this hypothesis. See Table 3 on page 46 for a brief synopsis of proposed fibrinogen promoting SNP articles and their findings.
Chapter III. Present Study

Summary

There are very few well-established genetic markers in modern research implicated in the proliferation of proinflammatory markers, or CAD initiation and progression (Winkelmann & Hager, 2000). Although CR-P, IL-6 and fibrinogen are implicated in the inflammatory process leading to CAD and MI, the genetic link has yet to be established. The genetic literature available correlating SNPs and coronary events or inflammatory marker levels is not extensive in relation to strictly inflammatory marker studies, and results from some studies are contradictory. Sample sizes have a high degree of variation, from hundreds to thousands. Therefore, further research employing randomized, placebo-controlled, blinded trials with large sample size and studying multiple SNP markers, such as in the De Maat et al. (1998) study, is warranted to determine whether there is a high correlation between SNPs, blood levels of inflammatory markers, and MI incidence.

The most studied polymorphism in the literature currently is the IL-6/-174G/C polymorphism. Only two studies reported that the -174G allele to be more highly associated with IL-6 levels (Burzotta et al. [2001], and Gaudino et al. [2003]). The majority of the articles found the -174C allele has the strongest association with IL-6 levels, CAD, and coronary events (Jenny et al., [2002], Vickers et al., [2002], Elghannam et al., [2000], Basso et al., [2002], Brull et al., [2001], Georges et al., [2001], Humphries et al., [2001], and Losito et al., [2003]. Among these studies, only Basso et al. (2002) and Elghannam et al. (2000) used therapies to improve outcomes; Elghannam et al.
(2000) found that fluvastatin decreased mean lumen diameter of coronary arteries in CC homozygotes, while Basso found pravastatin was the most effective in lowering risk of CHD in CC homozygotes. In future research, determining which allele is the most problematic would be most beneficial; this could be accomplished by researching multiple polymorphisms in relation to CVD. More true experimental designs with therapies for patients to improve outcomes would also be beneficial.

Besides IL-6 levels, the IL-6 -174C/G SNP is also purported to affect C-RP levels according to Jenny et al. (2002) and Vickers et al. (2002).

The homozygous and C carriers of the CRP-1059 and IL-6 -572 polymorphisms, along with the A carrier of the IL-6 -596G/A polymorphism have been implicated in the increased production of their respective inflammatory markers in several studies (Zee and Ridker [2002], Brull et al. [2001], Georges et al. [2001], Humphries et al. [2001]). The IL-6 -597A SNP, studied only in the Brull et al. article (2001), was not correlated with high levels of IL-6 after CABG. Three other IL-6 SNPs including -4391A, -634G, and -447T were examined in only one study by Nakajima et al. (1999), in which authors found no correlation between these polymorphisms and hypertension. However, theses polymorphisms are implicated in raised inflammatory marker levels and subsequent cardiac events require further investigation. Most other studies did not measure hypertension; they measured serum inflammatory marker levels or risk for acute coronary events.

Data from five studies showed that the -455AA allele of the beta-fibrinogen gene is associated with higher fibrinogen levels and subsequent heart-related sequellae than the
SNPs and NPs

G allele (De Maat et al. [1997], Weng, X., Cloutier, G., & Genest, J. Jr. [1999], Van ‘t Hooft et al. [1999], Folsom et al. [2001], Margaglione et al., [2000]). The Margaglione (2000) study also found marginal statistical significance ($p=0.08$) between the AA allele of the beta-fibrinogen -455 gene, when comparing allele frequency of first degree relatives suffering an MI. This discrepancy, while small, may be a result of the indirect nature of the measurement; comparing allele frequency with actual subjects who had suffered an MI, rather than first degree relatives. The evidence is therefore strong that this allele is associated with higher fibrinogen levels, and therefore heart-related sequelae.

Several other SNPs of the fibrinogen gene have been proposed to have implications in the increasing of fibrinogen levels and its possible cardiac effects. The study by Van ‘t Hooft et al. (1999) found that of the –455A, -854A, -148T, -249T, and 993T SNPs studied, only the -854G/A SNP was positively associated, along with the -455AA SNP, with a higher rate of fibrinogen production. The -854G/A SNP might be an important genetic marker for fibrinogen level and thus cardiac consequence.

Discussion: Implications for Practice & Management

Nurse Practitioner Implications: Focus on genetics

So, why should NPs care about genetics? As a professional nurse practitioner, it is important to know the physiological processes behind the inflammatory process, right down to the genetic level; this is readily apparent when the results of current reviewed articles regarding genetics and their correlation with inflammatory blood markers and coronary sequelae are taken into account. It becomes clear that the savvy NP will rely on
more than just family history to determine a client’s susceptibility to future coronary events. Inflammatory marker levels increase during coronary events and decrease afterward; a client’s genetic makeup remains constant (Pearson et al., 2003). Knowing a client’s susceptibility to coronary events through genotyping will improve the client’s plan of care. In the future, ensuring patients are genetically screened for CR-P, IL-6, and fibrinogen SNPs prior to and as a follow-up to intervention would likely decrease the client’s chances for a future coronary event. Perhaps most important, coronary sequelae while in the hospital after intervention could be reduced by early pharmacologic intervention and knowledge of a client’s specific genetic predisposition to sequelae. On a practical level, if a client in the ER is known to be genetically susceptible to coronary events, early pharmacological interventions that decrease CR-P, fibrinogen, and IL-6 levels could be initiated. CR-P is considered an independent risk factor for MI, and the probability that CR-P levels are genetically linked cannot be overlooked. Furthermore, CR-P and other inflammatory marker levels may fluctuate between chronic baseline levels and acute levels. This could be part of the reason for some of the variability in the literature reviewed. The genetic link may be helpful when determining a client’s susceptibility for MI.

*More genetics research.*

Genetics may explain the high blood levels of inflammatory marker proteins, since proteins are manufactured genetically. Current genetic research displays a lack of investigating multiple SNPs, with large sample sizes. An experimental design to increase power of the results would be preferable, although admittedly not always
feasible. All but two (Elghannam, [2000], & De Maat, [1998]) of the studies use a nonexperimental design; control groups are occasionally used. Many are comparative by nature regardless, so an experimental design would not necessarily be relevant. There is not enough genetic research involving SNPs, their relationship to inflammatory marker levels, and coronary sequelae when comparing the volume of research involving inflammatory marker levels only. Replicated studies testing multiple suspected IL-6, CR-P, and fibrinogen SNPs need to be tested with experimental designs if possible, and larger sample sizes.

*Genetic markers guiding acute care therapy.*

Genotyping an individual for genetic markers specific to IL-6, CR-P, and fibrinogen before therapy may eventually enable better anticipation of outcomes after acute care intervention. It could potentially be an excellent indicator of a patient’s susceptibility to a certain disease process. Certain individuals may possess SNPs that promote higher blood levels of inflammatory markers, thus making the host more susceptible to acute cardiac events. Genotyping can potentially assist nurse practitioners caring for acutely ill clients in the diagnosis and treatment of specific illnesses, such as acute coronary syndromes, and custom-tailor treatment based on individual genotype. For example, a client may have the AA allele of the beta-fibrinogen -455 SNP, and could be given anti-inflammatory medications before and after acute care intervention, and/or be placed on chronic treatment to decrease their chance for future coronary events. Genetic testing specific for IL-6, CR-P, and fibrinogen-promoting SNPs is not ready for widespread clinical use yet. Although there have been many studies on clinical
phenotypes of SNPs, i.e., C-RP and IL-6 levels, only limited studies discussed in this paper have looked at the genetic makeup of the individuals. Genotypes can potentially augment existing phenotyping blood tests, as well as encourage lifestyle changes through helping to explain to an individual that they are especially susceptible to acute coronary events (Pearson et al., 2003).

*Pharmacotherapeutics.*

There were only three studies that described treatment based on genotype susceptibility to high inflammatory marker levels and/or future acute coronary events (Elghannam et al., [2000], Basso et al., [2002] and De Maat et al., [1997]). These three studies used pharmacotherapeutics to offset the effects of the offending SNP. Elghannam (2000) found fluvastatin to be more effective for IL-6-174CC polymorphic cohorts in reducing lipoprotein (a) in when compared with -174GG or GC alleles. Basso (2001) indicated that the IL-6-174CC group had higher baseline levels of inflammatory markers and the greatest change in CAD risk after pravastatin treatment. De Maat (1998) used pravastatin to decrease fibrinogen levels and decrease risk of a future acute coronary event. In each study, statins were shown to be beneficial in reducing inflammatory marker levels and/or risk for acute coronary events. These results indicate pharmacogenomics might be applied for individualized therapeutics in lowering risk for MI in genetically susceptible individuals. Therefore, awareness of pharmacogenetic research can have significant applications for advanced practicing nurses, especially nurse practitioners who are prescribing medications in individuals with cardiovascular risks and diseases.
Management Strategies

Statins have been shown by multiple studies to lower C-RP levels (Kereiakes, [2003], Karaca et al., [2003]). However, they also may decrease both IL-6 (Basso et al., 2002) and fibrinogen levels (De Maat et al., 1998). In fact, a recent review article in the Circulation journal by Schonbeck and Libby (2004) found that the benefits clients received from statins were above and beyond what they should have received from lipid-lowering alone. Authors also indicated that statins reduced proinflammatory serum marker levels, while enhancing the expression of anti-inflammatory markers, thus accounting for the additional benefit (Schonbek & Libby, 2004). Inflammatory mediators such as IL-6 and CR-P levels were reduced by statins and thrombotic mediators such as fibrinogen were also reduced (Schonbek & Libby, 2004).

ACE inhibitors have been reported in some studies to lower CR-P levels (Uehara, 2003) as well as IL-6 levels (Gage, 2004) and even fibrinogen levels (Fogari et al, [1998], Gibbs et al, [2001]). ASA plays its own well-known role in reducing platelet aggregation and reducing inflammation/CRP levels (Kereiakes, 2003). Therefore, a known genetic predisposition to increased blood levels of CR-P, IL-6 and fibrinogen should prompt the clinician to begin pharmacotherapy with statins, ASA, and ACE inhibitors.
Conclusion

Current literature shows a genetic link between CR-P, IL-6, and fibrinogen levels and acute coronary events, but the correlation remains to be confirmed. The association between the CRP 1059C, IL-6-174C and beta-fibrinogen -455A SNPs, inflammatory markers and acute coronary sequelae should be replicated in future studies. There is good evidence that the IL-6-174C and beta-fibrinogen -455A SNPs increase inflammatory marker levels and/or increase risk for acute coronary events (Jenny et al., [2002], Vickers et al., [2002], Elghannam et al., [2000], Basso et al., [2002], Brull et al., [2001], Georges et al., [2001], Humphries et al., [2001], Losito et al., [2003], and De Maat et al. [1997], Weng, X., Cloutier, G., & Genest, J. Jr. [1999], Van ‘t Hooft et al. [1999], Folsom et al. [2001], Margaglione et al., [2000]). The association between other SNPs such as the CRP-1059C, IL-6-572C, IL-6-596A, and beta-fibrinogen-854A alleles and an increase in serum CR-P, IL-6, and fibrinogen levels has not been established (Zee and Ridker [2002], Brull et al. [2001], Georges et al. [2001], Humphries et al. [2001], Van’t Hooft et al. [1999]). The IL-6/-4391A, -634G, and -447T SNPs show no correlation with hypertension (Nakajima et al. 1999). The beta-fibrinogen-148T, -249T, and 993T SNPs show no correlation with inflammatory marker levels or an increased risk for acute coronary events (Van’t Hooft et al. 1999). In the future, genetic testing may allow more precise treatment through gene-specific drug therapy (Elghannam et al., [2000], Basso et al., [2002], and De Maat et al., [1998]). NPs may improve client outcomes and prevent future coronary events by instituting early pharmacological
intervention with ASA, ACE-Is, and statins with clients who are at risk for, or have a suspected coronary event.
References


Table 1. Proposed CR-P promoting SNPs.

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Findings</th>
<th>Implicated Allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cao and Hegele</td>
<td>(None described)</td>
<td>discovered C substitution for G at the 1059th nucleotide in the promoter of the CR-P gene</td>
<td>C</td>
</tr>
<tr>
<td>(2000)</td>
<td></td>
<td></td>
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<tr>
<td>Zee and Ridker</td>
<td>14, 916 men prospectively sampled over 8.6 years and matched subjects who developed arterial thrombosis to controls for a total of 726 case-control pairs</td>
<td>C carriers of the CRP 1059 gene had higher CR-P levels than GG allele</td>
<td>C</td>
</tr>
<tr>
<td>(2002)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jenny et al. (2002)</td>
<td>5201 adults &gt;65 y.o. sampled, those who developed cardiovascular disease were case-control matched</td>
<td>C substitution of G allele in -174 region of IL-6 gene higher blood levels of CR-P, fibrinogen, and IL-6 than in GG</td>
<td>C</td>
</tr>
<tr>
<td>Vickers et al. (2002)</td>
<td>588 members of nuclear British Caucasian families</td>
<td>Elevated baseline levels of CR-P assoc. with C substitution at -174 locus of IL-6 gene</td>
<td>C</td>
</tr>
</tbody>
</table>
Table 2. Proposed IL-6 promoting SNPs.

<table>
<thead>
<tr>
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<th>Findings</th>
<th>Implicated Allele</th>
</tr>
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<td>C</td>
</tr>
<tr>
<td>Vickers et al. (2002)</td>
<td>588 members of nuclear British Caucasian families</td>
<td>Elevated baseline levels of CR-P assoc. with C substitution at -174 locus of IL-6 gene</td>
<td>C</td>
</tr>
<tr>
<td>Elghannam et al. (2000)</td>
<td>375 subjects 35-75 years of age with one or more stenotic (30-75%) coronary lesion and high (110-190 mg/dl) LDL levels randomized to fluvastatin treatment or placebo control groups</td>
<td>Association between baseline minimum lumen diameter of coronary arteries and -174CC genotype</td>
<td>CC</td>
</tr>
<tr>
<td>Basso et al., (2002)</td>
<td>6595 hypercholesterolemic men 45-64 y.o. w/no MI hx randomized to placebo or pravastatin treatment 498 cases &amp; 1109 healthy, case-matched controls selected Cases = MI, angioplasty, or CABG within 4.8 years of follow-up</td>
<td>-174CC genotype 2x higher (but statistically insignificant) baseline levels of fibrinogen, CR-P, and IL-6</td>
<td>CC</td>
</tr>
<tr>
<td>Burzotta et al. (2001)</td>
<td>111 patients undergoing elective CABG at one hospital screened and then prospectively studied over 16 months</td>
<td>Higher levels of IL-6 and longer hospital stays associated with -174GG polymorphism</td>
<td>GG</td>
</tr>
<tr>
<td>Brull et al. (2001)</td>
<td>127 patients undergoing CABG were selected at Middlesex Hospital in England</td>
<td>-174G/C and -572G/C polymorphisms of the IL-6 gene found to be strong predictors of IL-6 levels after CABG</td>
<td>C</td>
</tr>
<tr>
<td>Georges et al. (2001)</td>
<td>640 clients suffering an acute MI were recruited over 2 years from health monitoring registers in several European countries; 719 age-matched randomly sampled controls selected</td>
<td>correlation between IL-6 -174G/C, -572G/C, and -596G/C polymorphisms and susceptibility to MI</td>
<td>C</td>
</tr>
<tr>
<td>Humphries et al. (2001)</td>
<td>2751 healthy, middle-aged U. K. men</td>
<td>systolic blood pressure, CR-P, and fibrinogen levels found elevated in -174GC and CC polymorphisms</td>
<td>C, CC</td>
</tr>
</tbody>
</table>
Table 2. Proposed IL-6 promoting SNPs (continued).

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Findings</th>
<th>Implicated Allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losito et al. (2003)</td>
<td>161 dialysis patients</td>
<td>-174CC and GC allele both w/increased hypertension and LVH when compared to GG allele</td>
<td>C CC</td>
</tr>
<tr>
<td>Gaudino et al. (2003)</td>
<td>110 subjects undergoing CABG at a Catholic hospital in Rome</td>
<td>-174GG genotype w/increased post-op (CABG) AF and IL-6 levels</td>
<td>GG</td>
</tr>
<tr>
<td>Nauck et al. (2002)</td>
<td>2559 patients with documented CAD with (n=1365) and without (n=1194) MI, and 729 non-random controls (no CAD) at a heart center in Germany</td>
<td>no correlation between the -174G/C polymorphism and IL-6 levels, MI, and CAD</td>
<td>___</td>
</tr>
<tr>
<td>Nakajima et al. (1999)</td>
<td>143 normotensive and 150 hypertensive Japanese women recruited from volunteers living in a Japanese prefecture</td>
<td>no correlation between hypertension and IL-6 -4391G/A, -634C/G, and -447A/T polymorphisms</td>
<td>___</td>
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</table>

Table 3. Proposed fibrinogen promoting SNPs.

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Findings</th>
<th>Implicated Allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Maat et al. (1997)</td>
<td>885 male clients undergoing catheterization at multiple hospitals</td>
<td>-455A/A genotype implicated in higher levels of fibrinogen and progression of CAD Pravastatin therapy given to treatment group offset the effect of the A/A genotype</td>
<td>AA</td>
</tr>
<tr>
<td>Weng, X., Cloutier, G., &amp; Genest, J. Jr. (1999)</td>
<td>135 French Canadians with documented CAD, recruited from a Cardiology clinic</td>
<td>increase in erythrocyte aggregation with beta-fibrinogen -455G/A polymorphism</td>
<td>A</td>
</tr>
<tr>
<td>Van 't Hooft et al. (1999)</td>
<td>210 men randomly recruited from a register of permanent residents in Stockholm County, Sweden</td>
<td>-455A and -854A alleles associated with higher transcription rates of fibrinogen than -455G and -854G counterparts</td>
<td>A</td>
</tr>
<tr>
<td>Folsom et al. (2001)</td>
<td>398 CAD patients over 5.3 years of follow-ups compared to identical number of participants randomly selected from the same cohort</td>
<td>higher plasma fibrinogen concentration with homozygous AA allele of -455G/A polymorphism</td>
<td>AA</td>
</tr>
<tr>
<td>Margaglione et al. (2000)</td>
<td>1048 individuals of variable ethnicity without clinical evidence of atherosclerosis</td>
<td>beta-fibrinogen -455A carriers trend toward having a first degree relative suffer MI than those with GG allele</td>
<td>A</td>
</tr>
</tbody>
</table>