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Bβ-Fibrinogen Gene Promoter –455 G/A Polymorphism Associates with Severity of Coronary Artery Stenosis in Male Victims of Sudden Pre-Hospital Death

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Abstract

Background and Purpose: Elevated fibrinogen levels are associated with the risk of atherosclerotic disease and affected by smoking. In haplotype analyses, the A-allele of the -455 G/A promoter polymorphism of the Bβ-fibrinogen gene (FGB) was most strongly associated with elevated fibrinogen levels. The association of the FGB –455 G/A polymorphism with coronary artery disease (CAD) and its complications have not been studied at the vessel-wall level.

Methods: We measured coronary stenosis as well as coronary and aortic atherosclerotic areas in a prospective autopsy series of 300 middle-aged (33-69 years) men (the Helsinki Sudden Death Study). FGB -455 G/A genotype was determined by PCR.

Results: Genotype distributions were 69.9%, 24.9%, and 5.2% for GG, GA and AA, respectively. In a logistic regression model with age, hypertension, diabetes, body mass index (BMI) and smoking as confounders, there was a significant association between the A-allele of FGB -455 G/A and >50.0% stenosis in coronary arteries (44.0% vs. 25.3 %, OR=2.37, 95% CI 1.25 − 4.48, p=0.008), compared to GG homozygotes. There was no significant genotype-by-smoking interaction on the severity of coronary artery stenosis although the FGB -455 G/A A-allele had a more pronounced effect on stenosis severity. The FGB -455 G/A genotype was not linked with the extent of coronary or aortic atherosclerosis or with myocardial infarction (MI).

Conclusion: Carriers of the A-allele of the FGB –455 G/A polymorphism had more severe coronary artery stenosis but this genotype did not affect the extent of coronary or aortic atherosclerotic lesion areas.

Keywords: Fibrinogen; Polymorphism; Coagulation; Atherosclerosis; Coronary stenosis; Myocardial infarction

Introduction

Atherosclerosis is the primary cause of coronary artery disease (CAD), peripheral arterial disease (PAD) and stroke which are the leading causes of death in the Western world [1]. The known risk factors for atherosclerosis and CAD are the same as for sudden cardiac death (SCD), namely hypertension, diabetes, hypercholesterolemia, low high-density lipoprotein, smoking, male-sex and family history [2,3].

Fibrinogen is an acute phase protein synthesized by hepatic cells, and inflammation and smoking can increase fibrinogen levels [4,5]. During clot formation, fibrinogen acts as a substrate for platelet aggregation by binding to α_{IIb}/β_3 integrins on the adjacent platelet surfaces. Platelets also adhere to immobilized fibrinogen on endothelial cells and to vessel walls/subendothelial collagen [6-9]. Elevated fibrinogen levels are considered to be a risk factor for coronary heart disease (CHD) as fibrin is found in atheromatous plaques, and participates in the formation of occlusive thrombus [10-12].

The G/Avariability in the –455 locus of the Bβ-fibrinogen (FGB) promoter region have previously been shown to associate with elevated fibrinogen levels and a risk of cardiovascular diseases and stroke [13-16]. The A-allele of the FGB –455 G/A polymorphism is linked with an increase in liver fibrinogen synthesis [17,18]. In haplotype analyses of Aα, Bβ and γ fibrinogen genes, the FGB -455 G/A (rs1800790) was the single nucleotide (SNP) polymorphism that most strongly associated with fibrinogen levels, and was in complete linkage disequilibrium with other polymorphisms of the FGB gene family [19-21]. It has also been associated with atherothrombotic disease, although in clinical patients results are discordant for association with myocardial infarction [16,21].

We studied the association of the FGB -455 G/A promoter polymorphism with the severity of coronary stenosis (measured from silicone rubber casts of the coronary tree), morphometrically measured atherosclerosis (in the coronary arteries and abdominal aorta), and the risk of fatal autopsy-verified MI in a series of 300 middle-aged men who died suddenly, out-of-hospital (the Helsinki Sudden Death Study). We hypothesized that the FGB -455 A-allele might be associated with more severe CAD and that there may be a genotype-by-smoking interaction on the risk of CAD and adverse coronary events.

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Subjects and Methods

Prospective autopsy series of middle-aged men

The original study population comprised of a prospective consecutive series of 300 Caucasian white men aged 33 to 69, who were subjected to autopsy at the Department of Forensic Medicine, University of Helsinki from 1991 to 1992 (The Helsinki Sudden Death Study). This autopsy series covers 42% of all deaths under 65 years of age in one year for the area of Helsinki and its surroundings. Medico legal autopsy was performed due to unexpected and often unwitnessed sudden or violent death in non-hospitalized individuals. Fibrinogen polymorphism G/A -455 genotype data were available for 249 men. The cause of death was acute or old myocardial infarction in 23.6% (n=58), other cardiac causes for 15.4% (n=37), other diseases in 22.0% (n=54) and non-natural deaths (accidents and suicides) in 39.4% (n=97). CAD risk factors were obtained by a structured interview with the next of kin for the 135 deceased patients. This study was approved by the Ethics Committee of The Department of Forensic Medicine, University of Helsinki. More detailed descriptions of the study series and laboratory methods have been described elsewhere [22].

Measuring the percentage of stenosis in silicone rubber casts of coronary arteries

At autopsy, a coronary angiography was performed on 272 cases using vulcanizing liquid silicone rubber mixed with lead oxide as the contrast medium [22]. The proximal, middle, and distal stenosis of the main trunks of the left anterior descending coronary artery (LAD), left circumflex artery (LCX) and right coronary artery (RCA) were measured from the rubber cast model with a hand-held Mauser. The percentage of stenosis was obtained by dividing the diameter (millimetres) of the greatest stenosis with the diameter of the nearest proximal undamaged part of the model cast of the artery. Significant coronary artery disease was defined as over 50% stenosis in any coronary artery.

Measuring the area of atherosclerosis by computer-assisted morphometry of coronary arteries and the abdominal aorta

Coronary arteries and the abdominal aorta were fixed in 10% buffered formalin and stained for fat using the Sudan IV staining method [22]. The areas of fatty streaks, raised fibrous lesions, and complicated lesions (with fissures, hematoma or thrombosis) were measured by computer-assisted morphometry. The percentage area of these atherosclerotic changes was obtained by dividing the atherosclerotic area by the total vessel area, multiplied by 100. Similar measurements and morphometric methods were carried out for abdominal aortic autopsy samples.

Confirmation of myocardial infarction

At autopsy, the presence of MI was confirmed by macroscopic and histological examination of the myocardium. Coronary thrombosis was recorded whilst opening the coronary arteries, following angiography. Diagnostic studies of MI were done independently of cast or artery measurements. 29 men died of recent MI and an additional 29 had an old MI. Coronary thrombosis was observed in 16 men.

DNA procedures

DNA was isolated from frozen (-70°C) cardiac muscle samples using the standard phenol-chloroform method. The FGB –455 G/A polymorphism genotype was detected by PCR and restriction enzyme digestion followed by polyacrylamide gel electrophoresis. Primer sequences and the PCR protocol have been previously described in detail [23]. Genotyping was successful in 249 (83%) cases. There were 124 cases with complete data available including genotype, smoking status, BMI, diabetes, hypertension and coronary artery stenosis measurements.

Statistical analysis

The data was analyzed by PASW Statistics (version 18.0, SPSS INC., Chicago, Illinois, USA) software. The Mann-Whitney U-test was used to analyze the association between the FGB -455 G/A A-allele carrier genotype and coronary artery stenosis, and coronary and aortic atherosclerotic lesion areas, because these values were not normally distributed. The association of the FGB –455 G/A A-allele carrier genotype with >50% stenosis of coronary arteries, AMI and coronary thrombosis were analyzed by Pearson`s Chi-square test. The results were confirmed using the MANOVA model, and logistic regression analysis with age, hypertension, smoking, diabetes and BMI included as confounding factors. Individuals with a non-coronary cause of death served as controls for analyses. For interaction analyses, a combination term was formed from the genotype and smoking data, assuming an increased risk profile: 1) never smoker with GG-genotype, 2) smoker with GG-genotype, 3) never smoker with A+ genotype and 4) smoker with A+ genotype. Smokers were considered as current or ex-smokers, whilst `non-smokers` had never smoked.

Results

Prevalence of FGB –455 G/A alleles

Genotype distributions in our study were 69.9%, 24.9%, and 5.2% for GG, GA and AA, respectively. Allele distributions were in Hardy-Weinberg equilibrium. The frequency of the FGB -455 G/A A-allele in our series (17.7%) is similar (17.9%) to that reported by Humphries et al. [23]. Demographic properties according to genotype data are shown in (Table 1). Carriers of the FGB -455 G/A A-allele were slightly older (p=0.03) and more often non-smokers (p=0.03), compared to the common GG-homozygotes.

Severity of atherosclerosis and the FGB -455 G/A polymorphism

Analyses with the Mann-Whitney U-test showed that there were no significant associations between the FGB -455 G/A A-allele and atherosclerosis lesion types in coronary arteries or the abdominal aorta

Factor	FGB -455G/A genotype		
	G/G n=174	G/A + A/A n=75	Chi-square p-value
Mean age, years	51.3 (SD 9.62)	54.3 (SD 9.21)	0.03*
Mean BMI kg/m²	25.2 (SD 5.18)	24.5 (SD 4.46)	0.27*
Smoking status			0.03
Never smoker	11 (6.3%)	14 (18.7%)	
Ex-smoker	12 (6.9%)	1 (1.3%)	
Smoker	68 (39.1%)	29 (38.7%)	
Not known	83 (47.7%)	31 (41.3%)	
Hypertension	3 (1.7%)	1 (1.3%)	0.82
Diabetes	6 (3.4%)	0 (0.0%)	0.10
Cause of Death			
Cardiac Disease	65 (37.4%)	29 (38.7%)	0.87
Other Disease	42 (24.1%)	13 (17.3%)	0.27
Non-natural Cause	67 (38.5%)	33 (44.0%)	0.83

BMI indicates body mass index
*Students *t*-test

Table 1: Demographic Properties of HSDS Study Population According to FGB -455G/A Genotype.

(Table 2). These results were confirmed using the MANOVA model. Analyses were done separately for younger (<53 years, mean age 43.8, SD 4.79) and older (>53 years, mean age 60.4, SD 4.79) age groups.

Coronary artery stenosis and the FGB –455 G/A polymorphism

The median stenosis percentage for LAD, LCX and RCA was 24.2%, 18.8% and 25.6%, respectively. In 32.9% (n=77) of the cases, the severity of coronary artery stenosis was 50% or more of the coronary diameter, in at least one major coronary artery (LAD, LCX, RCA).

In Mann-Whitney U-test analyses, the A-allele associated with the most severe stenosis in any coronary artery (p=0.005). Similarly, in Pearson`s Chi-square test analyses, the FGB -455 G/A A-allele was more frequently (44.0% vs. 25.3%, p=0.002) seen in men with >50.0% stenosis of at least one coronary artery when compared to GG homozygotes (Table 3). This association of the FGB -455 G/A A-allele with coronary stenosis was seen in LAD (24.0% vs. 10.9%, p=0.008), but not in LCX or RCA (Table 3).

In logistic regression analyses (enter model), the significant association between FGB -455 G/A A-allele and >50% stenosis in any coronary artery remained (OR=2.37, 95% CI 1.25 – 4.480, p=0.008) even with age, hypertension, smoking, diabetes and BMI as confounders (Table 3). This association was significant with >50% LAD stenosis (OR=2.53, 95% CI 1.18 – 5.44, p=0.02) but did not reach significance for RCA or LCX.

Factors	–455 G/A Genotype		Mann-Whitney	ANOVA
	GG n=89	GA/AA n=44	p-value	p-value
LAD atherosclerosis % (mean areas, SD)				
Fatty	6.52 (6.97)	6.43 (5.65)	0.54	0.72
Fibrous	4.61 (5.84)	3.60 (3.46)	0.75	0.32
Complicated	1.52 (4.10)	0.98 (2.78)	0.36	0.35
Calcification	4.20 (7.99)	3.43 (5.12)	0.67	0.51
Abdominal Aorta Atherosclerosis (mean areas, SD)	GG n=135	GA/AA n=55		
Fatty	13.7 (8.95)	15.6 (13.2)	0.41	0.29
Fibrous	7.37 (4.81)	7.25 (5.61)	0.89	0.18
Complicated	8.21 (10.3)	8.74 (12.9)	0.76	0.99
Calcification	5.47 (6.73)	4.42 (5.05)	0.75	0.59

Table 2: Association of the FGB –455 G/A genotypes with atherosclerotic changes of the LAD and abdominal aorta. Calculations based on the Mann-Whitney U-test and on the general ANOVA model with age, BMI, hypertension, diabetes and smoking as confounders.

Factors	–455 G/A Genotype		Chi-Square	Logistic regression	
	GG n=174	GA/AA n=75	p-value	OR (95% CI)	p-value
Coronary artery (stenosis >50%) Any Coronary	25.3% (44)	44.0% (33)	0.002	2.37 (1.25 - 4.48)	0.008
LAD	10.9% (19)	24.0% (18)	0.008	2.53 (1.18 - 5.44)	0.02
LCX	12.6% (22)	14.7% (11)	0.67	0.91 (0.40 - 2.05)	0.80
RCA	17.2% (30)	22.7.% (17)	0.32	1.14 (0.55 - 2.37)	0.72
All MI (old + acute)	23.0% (40)	24.0% (18)	0.56	0.87 (0.40 - 1.65)	0.56
All acute MI	12.1% (21)	10.7% (8)	0.75	0.78 (0.32 - 1.89)	0.58
AMI + Coronary Thrombosis	4.6% (8)	10.7% (8)	0.07	2.43 (0.81 - 7.27)	0.11

Table 3: Association of the FGB –455 G/A genotypes with Coronary Artery Stenosis (>50%), MI (old and/or acute) and Coronary Thrombosis.

Cause of death, myocardial infarction, coronary thrombosis and the FGB –455 G/A polymorphism

The FGB -455 G/A A-allele did not relate to cardiac, other diseases or non-natural causes of death in uni- or multivariate analyses. Smoking history associated with cardiac causes of death (83.5% vs. 16.5%, p=0.06), when compared to non-smokers in univariate analyses, although this was not replicated in logistic regression analyses (OR 1.20, 95% CI 0.47-3.08, p=0.70).

The FGB -455 G/A A-allele tended to be more frequent (10.7% vs. 4.6%, OR 2.43, p=0.11) among men with AMI, most likely due to coronary thrombosis, compared to controls (Table 3). However, the frequencies of the FGB -455 G/A A-alleles among men who died of old or acute MI were similar to controls who died of other diseases or non-natural causes.

Genotype-by-smoking interactions on atherosclerosis

Men with the FGB -455 G/A A-allele and a history of smoking (smokers and ex-smokers) more often had over 50% stenosis in univariate test analyses (p=0.03), compared to non-smokers. This association was lost in multivariate analyses (p=0.29). When ex-smokers were excluded, there was no significant difference in the degree of coronary artery stenosis with FGB -455 G/A genotype (p=0.14).

The genotype-by-smoking interaction on severity of coronary artery stenosis was not statistically significant. The FGB -455 G/A A-allele had a pronounced effect on the severity of coronary artery stenosis, regardless of smoking status (Figure 1). In addition, a genotype-by-smoking interaction was not observed on AMI or coronary thrombosis, or on coronary or abdominal aortic atherosclerotic lesion areas.

Discussion

We found the A-allele of the FGB -455 G/A polymorphism to associate with >50% coronary artery stenosis but not with the area of coronary and aortic atherosclerotic plaques in a population consisting of middle-aged men who died suddenly out-of-hospital. The FGB -455 G/A polymorphism did not associate with autopsy-verified MI, although a trend was seen for the FGB -455 G/A A-allele and coronary thrombosis (Table 3). In univariate analyses there was a genotype-by-smoking interaction on the severity of coronary artery stenosis, although significance was lost in multivariate analyses. Furthermore, the FGB -455 G/A A-allele seems to have a pronounced effect on coronary artery stenosis severity, despite smoking status (Figure 1).

The A-allele of the FGB -455 G/A polymorphism has previously been found to associate with risk of peripheral artery disease (PAD) and elevated fibrinogen levels, but not with severity of CAD [24,25]. In a recent large scale association analysis comprising 111 candidate genes for premature coronary heart disease, the FGB -455 G/A polymorphism was identified as one of the SNPs influencing CAD [26]. This is in accordance with our findings that the FGB -455 G/A A-allele predicts more severe coronary stenosis in middle aged men. Green et al. reported in their review that the FGB -455 G/A polymorphism is associated with plasma fibrinogen levels and atherothrombotic disease [16]. According to a recent study on fibrinogen haplotypes and MI, the FGB -455 G/A polymorphism associated with elevated fibrinogen concentrations and was the only SNP to differentiate between fibrinogen concentrations [19].

The FGB -455 G/A A-allele genotype increases fibrinogen synthesis in the liver and therefore causes circulating fibrinogen levels to elevate, possibly contributing to the atherosclerotic process

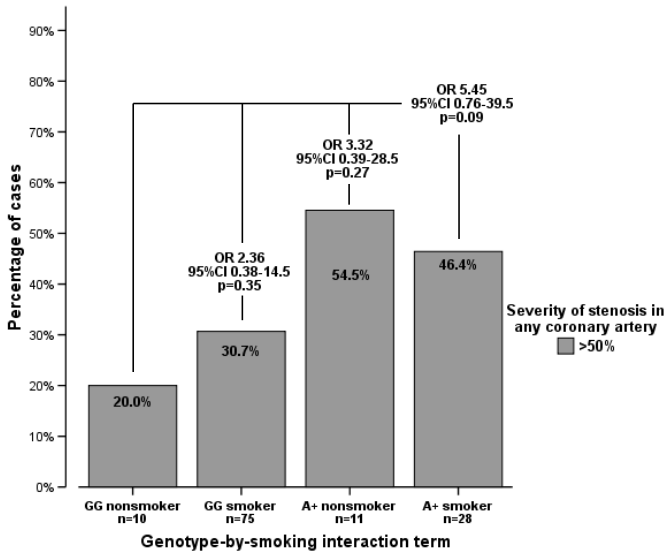

Figure 1: Genotype-by-smoking interaction on the severity of stenosis in coronary arteries (n=124). Logistic regression analysis was used with age, hypertension, diabetes and BMI as confounders.

by accelerating plaque growth in coronary arteries [18]. Another suggested pathophysiological link is that fibrinogen enhances leukocyte adhesion to endothelial cells, and supports transendothelial monocyte migration [27]. The FGB -455 G/A A-allele may be involved early in the process of clinically silent platelet adhesion/fibrin deposition in coronary artery lesions, leading to progressive narrowing, and later with the development of a larger thrombus. Our findings indicate that the FGB -455 G/A A-allele genotype is involved in more severe coronary stenosis and may act as a risk factor for coronary thrombosis. However, fibrinogen may have a dual role in the progression of atherosclerosis, partly increasing the risk for CAD and partly reflecting the inflammatory process in the vessel-wall.

In our study, the FGB-455 A-allele associated with >50% stenosis in coronary arteries, especially in LAD. For hemodynamic reasons, the proximal part of the LAD is the predilection site of coronary atherosclerosis. Significant coronary stenoses (>50%), especially in the LAD, have an important role in victims of sudden death as they are considered to be proarrhythmic causing fatal arrhythmias (ventricular tachycardia, ventricular fibrillation) during hypoxemic/ischemic periods [28, 29]. LAD stenosis, rather than total LAD occlusion or evident infarction, has been shown to associate with a high frequency of sudden death in the swine model. This implies that hibernating myocardia increase vulnerability to fatal arrhythmias and sudden death [28,29]. In our studies, the association between the FGB -455 G/A A-allele and >50% coronary stenosis was significant, although we did not find any connections between the A-allele and sudden pre-hospital cardiac death. This may be due to the fact that the risk of SCD could be simultaneously affected by several other genetic loci that act in concert with traditional risk factors.

Previous studies have failed to find an association between the FGB-455 G/A A-allele and MI [21,30]. Similarly, we did not find any association when all types (thrombotic and non-thrombotic) of MI were analyzed together. However, the FGB -455 G/A A-allele genotype tended to associate with thrombotic MI. The small number of cases with coronary thrombosis limits the value of this finding. Our study population does not represent a cross-section of a normal western population due to the high proportion of unnatural deaths. However, the present series comprises practically all sudden prehospital SCD cases in the Helsinki city during the one year study period. SCD in turn represents 50-75% of the CAD mortality in general. An important limitation of our study is the lack data on fibrinogen levels. This is due to the nature of the series: comprising men of whom many had not visited a doctor or hospital during their life. The FGB -455 G/A A-allele is linked functionally with increased fibrinogen production and elevated plasma levels [18]. Our results may thus be explained by a participation of fibrinogen in silent platelet adherence to the erosion site of vulnerable coronary plaques. Nevertheless, fibrinogen may act as a prothrombotic factor especially in small vessels such as cerebral arteries [15]. We did not find an association between the FGB -455 G/A A-allele and atherosclerotic changes in the abdominal aorta (Table 2). Rupture of lipid-rich plaques with consequent thrombosis and fibrin deposition would cause no substantial lumen occlusion in the abdominal aorta, compared with coronary arteries where occlusive ischemic events evolve more easily.

We have earlier described an interaction between the FGB -455 G/A A-allele and smoking on multiple lacunar strokes [15]. In the present study, there was a genotype-by-smoking interaction on the severity of coronary artery stenosis in univariate analyses but was lost in multivariate analyses. The small size of our series may limit the value of this interaction analysis as smoking is one of the environmental factors known to elevate circulating fibrinogen levels [4,5].

The search for possible interactions between prothrombotic polymorphisms and environmental/lifestyle factors may contribute to more effective preventive measures of major adverse cardiovascular events in different patient populations (e.g. more efficient antithrombotic therapy by novel thrombin inhibitors). In addition, the decision for proper revascularization method (percutaneous, surgical or hybrid) could be supported by genetic information suggesting accelerated stent or graft occlusion. Nevertheless, our findings support the role of the FGB -455 G/A A-allele in the clinically silent progression from coronary plaques to significant stenosis in middle aged men. Genetic and environmental determinants of fibrinogen production together with other CAD risk factors might provide the medical community with a tool for risk stratification, disease prevention and even treatment selection in atherosclerosis-prone individuals.

Conclusion

The A-allele of the FGB -455 G/A polymorphism is associated with more severe coronary artery stenosis, but not the extent of coronary or aortic atherosclerosis. There was no genotype-by-smoking interaction on the severity of coronary artery stenosis.

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