Glycoprotein Ia 807TT/873AA genotype is not associated with myocardial infarction

Glikoprotein Ia 807TT/873AA genotipi, miyokard infarktüsü ile ilişkili değildir

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ABSTRACT

Objective: The glycoprotein Ia/IIa complex is a major platelet collagen receptor. Its surface expression is influenced by two linked single nucleotide polymorphisms (C807T and G873A) in the glycoprotein Ia (GPIa) gene. In this study we aimed to determine the frequency of GPIa C807T/G873A genotype in patients with myocardial infarction (MI) and healthy controls in Turkish population and association between these dimorphisms and risk factors of MI.

Methods: We examined GPIa (C807T/G873A) genotypes in 158 patients with MI and 145 healthy controls. Distributions of the C807T and G873A dimorphisms were investigated by genotyping DNA using multiplexed allele-specific PCR.

Results: There was no association between GPIa genotypes and MI. We further analysed each group for all known risk factors such as plasma lipid levels, cigarette smoking, diabetes, hypertension, gender, age, MI history and body mass index. When compared with other two genotypes for glycoprotein Ia (GT/GA and CC/GG), TT/AA showed an association with higher high-density lipoprotein (HDL) -cholesterol levels in the healthy control group, but none in the group with MI.

Conclusion: The 807TT/873AA genotype of the GPIa gene alone or in combination with risk factors had no major effect on MI, however, it appears to be associated with higher HDL-cholesterol levels in healthy subjects. *(Anadolu Kardiyol Derg 2005; 5: 182-6)*

Key words: Glycoprotein Ia, myocardial infarction, dimorphism

ÖZET

Amaç: Trombosit adhezyonunda kollajen reseptörü olarak görev yapan glikopotein Ia/IIa kompleksinin trombosit yüzeyindeki ekspresyonunda, glikoprotein Ia (GPIa) genindeki birbiriyle bağlantılı 2 polimorfizmin (C807T ve G873A) etkili oldukları belirlenmiştir. Bu çalışmada, miyokard infarktüslü (Mİ) hastalarda ve Türk populasyonundan seçilmiş sağlıklı kontrollerde GP Ia'nın C807T/G873A genotip sıklıkları ve miyokard infarktüsüne neden olan risk faktörleri ile bu dimorfizmler arasındaki ilişkinin belirlenmesi amaçlanmıştır.

Yöntemler: Miyokard infarktüslü 158 hasta ve 145 sağlıklı bireyin GPIa C807T/G873A genotipleri araştırılmıştır. C807T ve G873A dimorfizmlerinin dağılımları, multipleks allel-spesifik PCR kullanarak izole edilmiş olan DNA'nın genotiplenmesi ile belirlenmiştir.

Bulgular: GPIa genotipleri ile Mİ arasında ilişki bulunamamıştır. Ayrıca her grubun, plazma lipid seviyeleri, sigara kullanımı, diyabet, hipertansiyon, cinsiyet, yaş, aile hikayesi ve vücut kitle indeksi gibi bilinen risk faktörleri ile analizleri yapılmıştır. GPIa'nın diğer iki genotipi (GT/GA ve CC/GG) ile karşılaştırıldığında TT/AA genotipinin, kontrollerde yüksek HDL-kolesterol seviyeleri ile ilişkili olduğu gösterilmiştir.

Sonuç: GPIa geni 807TT/873AA genotipinin yalnız veya risk faktörleri ile birlikteyken miyokard infarktüsünden sorumlu olmadığı, ancak kontrollerde yüksek HDL-kolesterol seviyeleri ile ilişkili olduğu tespit edilmiştir. *(Anadolu Kardiyol Derg 2005; 5: 182-6)*

Anahtar kelimeler: Glikoprotein Ia, miyokard infarktüsü, dimorfizm

Introduction

The platelet membrane glycoprotein Ia-IIa (GPIa-IIa) complex (also known as the integrin $\alpha 2\beta 1$) is a receptor for collagen that plays a fundamental role in the adhesion of blood platelets to the extracellular matrix (1). The GPIa-IIa is expressed on a wide variety of cell types, including megakaryocytes, platelets, fibroblasts, endothelial cells, and epithelial cells (1, 2). The allelic differences in the glycoprotein Ia (GPIa) gene are associated with expression levels of the GPIa-IIa on the platelet surface. Several nucleotide sequence variations of GPIa gene have been described. Recently, linked silent dimorphisms in the coding region of GPIa gene at nucleotides 807 (C or T) and 873 (G or A) were identified. Although these dimorphisms do not change the amino acid sequence of GPIa, a significant correlation between these dimorphisms and expression levels of GPIa-IIa on the platelet surface was found (1). These two dimorphisms, C807T (Phe224) and G873A (Thr246) within the GPIa gene, which have been correlated with low receptor densities are homozygous for the 807C/873G allele; whereas individuals homozygous for the

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807T/873A allele have high receptor densities (1, 3) and associated with vascular disease (4).

There are several environmental risk factors, which are known to be causative in the development of myocardial infarction, such as hyperlipidemia, hypertension, diabetes mellitus, obesity, cigarette smoking. Additionally, there are some genetic markers whose roles are still poorly determined (5). The high-density allele 807T/873A has been found to be associated with increased risk of myocardial infarction in two independent studies. Moshfagh et al (1999) (3) determined the prevalence of the homozygous 807T/873A genotype to be 2.9 times higher among myocardial infarction patients than among controls (16.4% v 5.4%; p=0.022). This was an association between patients homozygous for the 807T/873A allele and myocardial infarction (OR 3.3 (95% CI 1.2-8.8)), which was the strongest in the smoker's subgroup. In the other study Santoso et al (1999) (6) reported an association of the 807T/873A allele with nonfatal myocardial infarction in younger patients (<49 years; OR 2.61; p=0.009). Additionally, Carlson et al. (1999) (7) found the 807T/873A allele to be the only over-represented variable among stroke patients ≤50 years of age (OR 3.02; p=0.023). Based on these findings we did a case-control study to see whether there is an association between the 807T/873A allele and myocardial infarction in a subgroup of Turkish population. We aimed to determine the frequency of GPIa C807T/G873A genotype in patients with myocardial infarction and healthy controls and a possible association between these dimorphisms and risk factors for MI. Furthermore, we analyzed the genotype-phenotype correlation of healthy control subjects for the known risk factors of myocardial infarction.

Methods

Population

The study included 158 patients (72 female and 80 male) with myocardial infarction. The diagnosis of myocardial infarction was based on chest pain symptoms, typical electrocardiographic changes and serum enzymes elevation. The patients group of 158 myocardial infarction comprised with a mean age of 57.25±13.36 years. The study also included 145 control subjects (84 female and 61male). These 145 healthy blood donors were introduced in the study to reflect the GPIa C807T/G873A genotype distribution in a Turkish population. Their mean age was 36.23± 13.63 years.

Risk Factors

Baseline examination included a questionnaire involving gender, age, familial predisposition to MI, and smoking. In addition, plasma total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, height (m), and body weight (kg) were measured. Hypertension was defined by history of several measurements of elevated blood pressure (> 140/90 mmHg). Diabetes mellitus was defined by elevated blood fasting glucose levels (> 7.8 mmol/liter-140 mg/dl) or 2h after 75g of oral glucose loading (> 11.1 mmol/liter-200 mg/dl). Hypercholesterolemia was defined by elevated total plasma cholesterol levels (> 200 mg/dl). Individuals were classified as smokers if they reported themselves to be current smokers. Body mass index (BMI, kg/m^2) was calculated as weight (kg) divided by height squared (m^2).

Genotyping

Leukocyte DNA was isolated from whole blood using standard procedures (8). The silent dimorphisms, C807T and G873A within the GPIa gene have been identified to introns, and the sequences of this region have been extracted from the GenBank (Accession No: AF035968) (2).

GPIa genotyping was conducted by allele-specific (AS) PCR so that the 807T and 873G amplicons were multiplexed in one reaction and the 807C and 873A amplicons were multiplexed in a second reaction (4). Reactions were prepared in 25 μl volume as follows: 1xPCR Buffer (10 mM Tris-HCL, pH: 8.8, 50 mM KCl, 0.8% Nonidet P40), 2 mM $MgCl_2$, 0.2 mM dNTP, 0.6 mM intron G reverse primer (5'-GATTTAACTTTCCCAGCTGCCTTC-3'), 0.72 μM Exon 8 reverse primer (5'-CTCAGTATATTGTCATGGTTGCATTG-3'), 0.5 U Taq polymerase, and 100 ng of genomic DNA. Allele-specific primers in the first reaction were 0.6 μM 807T forward primer (5'-ATGGTGGGGACCTCACAAACACATAT-3') and 0.72 μM 873G forward primer (5'-GGTGGGCGACGAAGTGCTAGG-3'). Allele-specific primers in the second reaction were 0.52 μM 807C forward primer (5'-GTGGGGACCTCACAAACACATGC-3') and 0.72 μM 873A forward primer (5'-GGTGGGCGACGAAGTGCTAGA-3') (4). After initial denaturation at 94°C for 2 minutes, 35 cycles of amplification were performed (94°C for 1 minutes, 55 °C for 1 minutes, and 72 °C for 1 minutes). A first denaturation step at 94 oC for 2 minute was followed by 35 cycles of 94 °C for 1 minute, 62 °C for 1 min and 72 °C for 1 minute. 20 ml of each PCR product was loaded onto 2 % agarose gels and stained with ethidium bromide. Determination of each genotype was performed as described earlier (9).

Data Analysis

Statistical analysis was performed using the SPSS software (Version 7.0; SPSS Inc., Chicago, IL, USA). The X2 test was used to compare the distributions of GPIa C807T/G873A genotypes, allele frequencies and qualitative risk factors between patients and controls. Sample means of quantitative risk factors were compared using analysis of variance. Median and range or proportions for baseline risk factors were calculated for patients and controls. Odds ratios were calculated as estimates of the relative risk of MI associated with carrier ship of the GPIa 807T/873A allele, with 95% confidence limits determined. Adjustment was made for the dichotomized risk factors: gender (male/female), history of cardiovascular disease (yes/no), hypertension (yes/no), diabetes (yes/no), smoking (yes/no), and for the continuous risk factors: age, BMI, total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride. Statistical significance was assumed for P-values <0.05.

Results

A total of 303 subjects, 158 patients and 145 controls were studied for a possible correlation of the GPIa C807T/G873A genotypes and MI. There were no differences between patients and healthy blood donors in GPIa C807T/G873A allele frequencies (0.665 807C/873G, 0.335 807T/873A v 0.655 807C/873G, 0.345 807T/873A, respectively) and genotype distributions (Table 1). There was no association between C807T/G873A genotypes limited to subgroups aged 45 years and 50 years as shown in Table 1.

Furthermore, all genotypes (807CC/873GG, 807CT/873GA and 807TT/873AA) were examined for their probable association with each of the known risk factors for MI, such as age, gender, cigarette smoking, serum lipid levels, BMI, and MI history. The-

re appeared to be a relationship between patients with TT/AA genotype and subgroups (yes/no) of diabetes and hypertension (Table 2). We compared the GPIa frequencies of the three genotypes in patients and the healthy control population, subgrouping them according to their possession of one or more of the known risk factors.

The patients and healthy controls were divided into two subgroups, according to their GPIa genotypes. The groups possessing 807T/873A genotype were subdivided further into groups, depending on the medians of known risk factors. Restriction of the statistical analysis was done according to the plasma lipid level, BMI, smoking or an age, comparing the genotypes. The individuals less than the median for each group, failed to show an increased risk of MI associated with the GPIa 807T/873A allele (Table 3). There was also no association between the GPIa 807T/873A allele and risk of MI when the analysis was limited to subgroups rather than the median for patients. In healthy group, however, the risk ratio for plasma HDL-cholesterol levels between 807TT/873AA homozygotes and 807CC/873GG wild types was 3.82 (95% CI 1.15 to 12.67) (Table 3), indicating an association with high HDL-cholesterol levels in healthy subjects.

Table 1. Age-related distribution of genotype frequencies for GPIa C807T/G873A in patients and controls

Genotype	Patients, n=158	Controls, n=145	X^2	p
CC/GG	42.4% (67)	42.1% (61)		
TT/AA	9.5% (15)	11% (16)	0.201	0.905
CT/GA	48.1% (76)	46.9% (68)		
Age <50 years, n=161				
CC/GG	23.8% (10)	44.5% (53)		
TT/AA	14.3% (6)	8.4% (10)	5.833	0.054
CT/GA	61.9% (26)	47.1% (56)		
Age ≥50 years, n=130				
CC/GG	49.1% (53)	31.8% (7)		
TT/AA	7.4% (8)	22.7% (5)	5.484	0.064
CT/GA	43.5% (47)	45.5% (10)		
Age <45 years, n=136				
CC/GG	23.4% (7)	47.2% (50)		
TT/AA	16.6% (5)	9.4% (10)	5.649	0.059
CT/GA	60% (18)	43.4% (46)		
Age ≥45 years, n=155				
CC/GG	46.7% (56)	25.7% (9)		
TT/AA	7.5% (9)	14.3% (5)	5.327	0.070
CT/GA	45.8% (55)	60% (21)		

Number of subjects (% within group) and genotype frequencies are shown. Result (p-values) of X^2 test was calculated for genotypes frequencies. Significance was accepted at a level of $p<0.05$.

Discussion

The C807T and G873A dimorphisms of the GPIa gene were examined for their probable association with each of the known risk factors for MI, such as age, gender, cigarette smoking, serum lipid levels, BMI, diabetes, hypertension and MI history. Our results in this case-controlled study indicate that GPIa C807T/G873A genotype is not associated with an increased risk of myocardial infarction, suggesting that variation in GPIa/GPIIa receptor density and differences in adhesiveness of platelets to fibrillar collagens – as previously shown to be associated with this dimorphism - do not contribute to an increased risk of cardiovascular disease (1). Prevalence studies from various populations indicate that approximately 4.8-28% of the healthy subjects carry the 807TT/873AA genotype. The Native American (n= 93) and Hispanic (n= 92) groups had the highest 807TT/873AA genotype frequency (28% and 27%, respectively) (4), whereas the Italian (n= 302) (10) and Swiss (n= 89) (3) groups had the lowest 807TT/873AA genotype frequency (4.8% and 5.6%, respec-

Table 2. Population characteristics according to GPIa C807T/G873A genotypes

Population Characteristics		Patients				Controls			
		CC/GG	TT/AA	CT/GA	p	CC/GG	TT/AA	CT/GA	p
Individuals, n (% of total)		67 (42.4)	15 (9.5)	76 (48.1)		61 (42.1)	16 (11.0)	68 (46.9)	
History of MI	Yes, n (%)	28 (34.1)	7 (10.8)	30 (46.2)	0.773	13 (46.4)	1 (3.6)	14 (50)	0.421
	No, n (%)	35 (40.7)	7 (8.1)	44 (51.2)		28 (43.1)	7 (10.8)	30 (46.2)	
Gender	Female, n (%)	32 (44.4)	8 (11.2)	32 (44.4)	0.544	35 (41.7)	11 (13.1)	38 (45.2)	0.640
	Male, n (%)	32 (40)	6 (7.5)	42 (52.5)		26 (42.6)	5 (8.2)	30 (49.2)	
Hypertension	Yes, n (%)	9 (53)	4 (23.5)	4 (23.5)	0.026	2 (33.3)	1 (16.7)	3 (50)	0.983
	No, n (%)	30 (47.6)	3 (4.8)	30 (47.6)		19 (36.5)	9 (17.3)	24 (46.2)	
Diabetes	Yes, n (%)	23 (65.7)	0 (0)	12 (34.3)	0,003	1 (20)	2 (40)	2 (40)	0.043
	No, n (%)	41 (35.7)	14 (12.2)	60 (52.1)		47 (44.3)	8 (7.5)	51 (48.2)	
Smokers	Yes, n (%)	42 (38.9)	12 (11.1)	54 (50)	0.285	23 (46)	5 (10)	22 (44)	0.921
	No, n (%)	22 (50)	2 (4.5)	20 (45.5)		35 (42.7)	8 (9.8)	39 (47.5)	
Mean age , years		60.73± 12.06	52.43± 14.73	55.18± 13.62	0.064	34.20± 12.52	38.47± 17.40	37.53± 13.63	0.557
Total Cholesterol, mg/dl		192.65± 46.16	200.21± 35.69	199.85± 49.82	0.202	168.05± 32.68	162.67 ± 31.03	166.89± 35.92	0.711
HDL-Cholesterol, mg/dl		39.59± 11.69	38.79± 10.96	39.63± 10.42	0.424	41.71± 12.24	49.19± 9.83	44.34± 13.25	0.055
LDL-Cholesterol, mg/dl		118.59± 41.52	137.00± 34.82	128.42± 44.40	0.148	104.60± 46.70	92.45± 31.79	98.75± 41.70	0.256
Triglyceride, mg/dl		168.08± 82.86	147.00± 54.69	179.95± 91.46	0.769	135.67± 54.92	107.40± 59.11	131.37± 79.94	0.138
BMI, kg/m^2		24.84± 3.03	25.20± 2.76	25.44± 3.55	0.719	24.42± 4.04	24.60± 2.78	24.32± 4.28	0.488

Values are mean± SD or frequencies, which are presented as absolute number with percentage in parentheses. Significance was accepted at a level of $p<0.05$.BMI - body mass index; HDL – high-density lipoprotein; LDL – low-density lipoprotein; MI - myocardial infarction;

Table 3. Odds ratios for risk of myocardial infarction for GPIa 807TT/873AA and 807CT/873GA genotypes compared with 807CC/873GG genotype for various categories of subjects

	Patients				Controls			
	Median	CC/GG	TT/AA	CT/GA	Median	CC/GG	TT/AA	CT/GA
Total cholesterol	199	1	0.17 (0.02-1.46)	0.93 (0.44-1.95)	166.50	1	0.64 (0.20-2.04)	1.03 (0.50-2.10)
HDL- cholesterol	39	1	1.92 (0.59-6.21)	1.44 (0.72-2.87)	42	1	3.82 (1.15-12.67)	1.86 (0.86-3.99)
LDL- cholesterol	126	1	2.59 (0.77-8.66)	1.75 (0.87-3.56)	93	1	0.44 (0.11-1.68)	0.58 (0.27-1.23)
Triglyceride	52	1	0.82 (0.25-2.65)	1.19 (0.60-2.34)	117	1	0.35 (0.10-1.16)	0.58 (0.28-1.19)
BMI	24.97	1	0.92 (0.25-3.36)	1.31 (0.63-2.7)	24.22	1	1.25 (0.35-4.37)	1.56 (0.75-3.24)
Smokers	-	1	3.14 (0.64-15.31)	1.41 (0.68-2.92)	-	1	0.95 (0.26-3.27)	0.85 (0.40-1.80)
Age	60	1	0.28 (0.07-0.99)	0.54 (0.27-1.08)	35	1	0.63 (0.19-2.08)	1.19 (0.59-2.41)

The figures in parentheses are 95% confidence intervals. The value after each odds ratio is the p-value derived by comparison with the 807CC/873GG genotype (reference group). BMI - body mass index; HDL – high-density lipoprotein; LDL – low-density lipoprotein;

tively). Knowledge about the frequency of GPIa (C807T/G873A) genotypes in various populations is important for the estimation of risk factor for MI and coronary artery disease. Our results indicate that there was not an association between this genotype and MI in Turkish population. The association of the C807T and G873A dimorphisms with MI is supported by findings of two independent case-controlled studies, which reported an increased risk of nonfatal MI in men with the 807T allele as opposed to 807C allele. The strongest relationship was found in smokers (3) and in younger patients (<49 years; OR 2.61; p=0.009) (6). In opposite to these two studies, no association between 807TT/873AA genotype, age subgroups and smokers was detected in our study. Another report concluded that carriers of the 807T allele of the GPIa gene among patients suffering a first acute coronary syndrome episode had an increased risk of recurrent acute coronary syndromes (11). Additionally, two other groups reported that the 807T/873A allele was associated with an increased risk of acute coronary syndrome (OR 2.9 (95% CI 1.4-5.8)) (10) and cardiovascular mortality in women who smoked or had indications of compromised endothelium, such as diabetes and microalbuminuria (OR 14.1 (95% CI 5.0-39.9)) (12). However, others have reported that inherited dimorphisms of platelet GPIa were not associated with an increased risk of myocardial infarction (5, 13), coronary artery disease (13) and with malignant arrhythmia in coronary artery disease patients (14). As with other candidate genes, GPIa polymorphisms have been shown to be a risk factor in only a part of the previously published studies. Our findings on the statistically significant higher frequency of the GPIa 807TT/873AA genotype in the high HDL-cholesterol subgroup of healthy controls had , support the theory of additive effect of two or more factors contributing to MI development. This leads us to hypothesize, that GPIa 807TT/873AA genotype might have a protective effect, either through direct or indirect association with higher HDL-cholesterol levels. Epidemiological studies have identified that plasma concentrations of LDL- cholesterol, HDL-cholesterol and triglycerides are important predictors for MI risk (15, 16). The unique lipid and lipoprotein profile of Turkish population is characterized primarily by very low plasma levels of HDL-cholesterol. Despite their relatively low plasma total cholesterol levels, Turks have extremely low HDL-cholesterol resulting in very high total cholesterol/HDL-cholesterol ratios that predict increased risk for coronary heart diseases (17-19). Primarily, this study was undertaken to explore a possible association between glycoprotein Ia C807T/G873A genotypes and myocardial infarction. We did not observe statistical differences between the healthy control and the MI group with respect to GPIa genotypes, however, further we have explored differences in the subgroups. There appeared to be a relationship between the TT/AA genotype and HDL-cholesterol levels. This secondary observation of our study deserves further attention, in order to find a molecular explanation.

Myocardial infarction most often occurs as a result of a thrombotic coronary occlusion at the site of a ruptured or erosive atherosclerotic plaque. It is well known that acquired secondary factors associated with genetic factors contribute in concert to development of infarction in myocardium, thus it is probable that the combination of 807T/873A allele and high HDL-cholesterol might be a predictor for protection from MI.

To explore this further, a study with selected cases with higher HDL-cholesterol levels should be performed and followed up for several years. Or one might choose as healthy control group elderly people and look for a possible correlation with several genes, assuming that if genetically predisposed, MI should have occurred at an earlier age.

Conclusion

We conclude that the 807TT/873AA genotype of the GPIa gene appears to be associated with higher HDL-cholesterol levels in healthy control subjects, rather than having a direct effect on myocardial infarction alone or in combination with known risk factors.

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