Clinical Symptoms of Acute Coronary Insufficiency Correlate with GP-IIIa Genotype of Integrin β-Subunit

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Studies of the clinical course of acute coronary insufficiency (progressive angina and myocardial infarction) in patients carrying a mutant allele of the Pl-A(II) gene encoding integrin GPIIIa β-subunit revealed significant differences in the incidence of some clinical signs in comparison with patients homozygous for the normal Pl-A(I) allele.

Key Words: *integrin; GP-IIIa gene; acute coronary insufficiency*

Integrins are a group of cell surface receptors determining cell adhesion to extracellular matrix by binding to its components (fibronectin, laminin, *etc.*) or to other cells by binding surface molecules of the immunoglobulin superfamily. Integrin receptors consist of α and β subunits, each of these subunits is presented by several variants encoded by a group of related genes. Moreover, each variant exists in different allelic forms. For instance, β-subunit type III subtype a, referred to as glycoprotein IIIa (GPIIIa) exists in two allelic forms Pl-A(I) and Pl-A(II) [4].

GPIIIa subunit usually forms a dimer with α-subunit type IIb. The surface IIb/IIIa integrin receptor expressed in platelets, megakaryocytes, and some other cells binds to fibrinogen, Willebrand factor, fibronectin, vitronectin, thrombospondin, *etc.* [3-5].

It was hypothesized that the product of the GP-IIIa gene is involved in the regulation of venous and arterial thromboses and can be a genetic risk factor of cardiovascular diseases. For example, a correlation was found between Pl-A(II) allele and the risk of acute coronary insufficiency (ACI) in subjects below 60 years [6]. This hypothesis is consistent with the results of independent studies; however, the existence this correlation was questioned in further studies [6].

Here we report the data on the prevalence of alleles Pl-A(I) and Pl-A(II) in the Moscow urban macropopulation and the relationship of these alleles with ACI.

MATERIALS AND METHODS

Clinical course of ACI was analyzed in 20 patients admitted to the coronary-care unit of Moscow Municipal Hospital No. 36 with suspected acute myocardial infarction. On the basis of clinical findings and laboratory tests, progressive angina was diagnosed in 2 patients and acute myocardial infarction was diagnosed in 18 patients. The patients were divided into two groups: group 1 patients (n=13) were homozygous for Pl-A(I), and group 2 patients (n=7) were hetero- or homozygous for Pl-A(II).

The control group consisted of healthy donors.

The fraction of partially purified DNA was isolated from peripheral blood cells by the following procedure: 100 μl stabilized blood was mixed with 400 μl 0.15 M NaCl; the mixture was centrifuged at 5000g for 5 min, resuspended in 500 μl 10 mM Tris-HCl buffer (pH 7.5) containing 0.2% Triton X-100, and incubated for 20 min at room temperature. The samples were then centrifuged at 10,000g for 10 min,

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the pellet was resuspended in 500 μl 10 mM Tris-HCl, and NaCl was added to a final concentration of 1 M. The material was precipitated with ethanol (1:2, v/v), dissolved in 200 μl water and used for PCR.

PCR was performed with oligonucleotide primers described previously [6]. The PCR program consisted of 30 cycles: 30 sec at 96°C, 1 min at 55°C, and 2 min at 72°C. DNA fragments were analyzed by PAGE [2]; the gel was stained with silver. Cleavage of the amplified 266-bp fragment of the GP-IIIa gene with Msp-1 restrictase yielded a 221-bp fragment corresponding to Pl-A(I) and a 177-bp fragment corresponding to Pl-A(II) [8].

The data were processed statistically using Fisher's angular transformation with the argument of normal distribution. The significance level (p) for qualitative parameters was determined from the tables for one-tailed test [1].

RESULTS

The prevalence of Pl-A(II) in control healthy donors was 14% (Table 1), which is consistent with the data obtained from analysis of the general European population (15%) [7]. The prevalence of this allele in male patients with ACI was normal, but in females it considerably surpassed the population mean.

TABLE 1. Prevalence (%) of Pl-A Alleles in Healthy Donors and ACI Patients

Allele	Healthy donors	ACI patients		
		males	females	total
Pl-A(I)	86	85	72	81
Pl-A(II)	14	15	28	19

The analysis of the genotype distribution for the locus Pl-A (Table 2) and the prevalence of clinical signs of the disease in patients with different genotypes yielded a more complex picture (Table 3).

The whole group displayed no deviations from the population norm (Table 2). However the analysis of subgroups with different clinical courses of ACI revealed the following features: patients homozygous for Pl-A(II) and heterozygous Pl-A(I)/Pl-A(II) were characterized by higher prevalence of myocardial infarction and permanent atrial fibrillation (from medical history), higher probability of ACI regress and evolution to functional class III angina, higher incidence of

TABLE 2. Distribution (%) of Pl-A Genotypes in Helathy Donors and ACI Patients

Genotype	Healthy donors	ACI patients		
		males	females	total
Pl-A(I) homozygous	62	77	43	65
Pl-A(II) homozygous and heterozygous	38	23	57	35

TABLE 3. Incidence of Clinical Signs in ACI Patients with Different Pl-A Genotypes

Clinical sign	Pl-A(I) homozygous		Pl-A(II) homozygous and heterozygous	
	abs.	%+	abs.	%+
Q-wave AMI	13	100	4**	57
History of:				
angina	5	39	5	71
myocardial infarction	2	15	4**	57
essential hypertension	10	77	4	57
progressive angina	5	39	4	57
Atrial fibrillation (permanent)	2	15	4**	57
Recurrent pain	3	23	6*	85
ACI regress	0	0	2*	29
Uncomplicated course	4	31	2	29

Note: *$p<0.01$, **$p<0.05$ compared to Pl-A(I) homozygotes; +of total number of patients with this genotype.

recurrent pain and lower incidence of *Q*-wave acute myocardial infarction (Table 3).

There were no significant differences in the severity of the disease between groups.

Thus, only in female patients the presence of Pl-A (II) allele was associated with increased risk of ACI. A significant correlation between the presence of Pl-A(II) and the incidence of some clinical signs of the disease is characteristic of both male and female patients.

These data suggest that identification of the genotype for the Pl-A locus of the Gp-IIIa gene in ACI patients is important for predicting the course of the disease and choosing appropriate therapy. Further studies of the role of integrins in the pathogenesis of ACI will provide new insight in the molecular and biological mechanisms of this condition.

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