

Identification of single-nucleotide polymorphisms of the ITGA2 integrin gene and their association with platelets in patients with arterial hypertension

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Abstract

Arterial hypertension (AH) is one of the most socially significant pathologies associated with human nuclear genome mutations. The aim was to study the polymorphisms of the ITGA2B gene and its association with platelet parameters among Azerbaijanis with AH.

Methods. The study included 76 patients with AH (main group) and 24 patients without this pathology (control group). The main group was divided into 3 subgroups: group I — 29 patients with AH, group II — 23 patients with AH and coronary heart disease (CHD), group III — 24 patients with AH, CHD and type 2 diabetes mellitus (DM). The analysis of platelets was carried out using hematologic analyzer, the polymorphism of ITGA2 gene — using mass spectrometry (MALDI-TOF).

Results. The prevalence of C/C, T/C and T/T genotypes of the ITGA2 gene was 69.0%, 17.2% and 13.8% in patients with AH; 65.2%, 21.7% and 13.0% in patients with AH and CHD, respectively; 62.5%, 29.2% and 8.3% in patients with AH, CHD and type 2 DM. The prevalence of the T allele among patients with AH was 31.0%, among patients with AH and CHD — 34.8%, and among patients with AH, CHD, and type 2 DM — 37.5%. The highest level of platelet count (PLT), platelet distribution width (PDW) and platelet-large cell ratio (P-LCR) were determined in group III, and the highest level of mean platelet volume (MPV) was seen in group II. The highest PLT was observed in T/T genotype carriers from group III; MPV in T/T genotype carriers from group I; PDW in T/T genotype carriers from group III; PCT in T/T genotype carriers from group III; P-LCR in T/T genotype carriers from group I.

Conclusions. According to the results obtained, the highest level of PLT, PDW and P-LCR were detected in patients with AH, CHD and DM-2, and MPV—in patients with AH and CHD. Marked changes in platelet parameters were noted in carriers of T/T and T/C genotypes. The prevalence of the C/C, T/C, and T/T genotypes of the ITGA2 gene was 69.0%, 17.2%, and 13.8% in patients with AH; 65.2%, 21.7%, and 13.0% in patients with AH and CHD; and 62.5%, 29.2%, and 8.3% in patients with AH, CHD, and DM-2, respectively. Studies with larger samples are needed to confirm the results.

Keywords: arterial hypertension, ITGA2 gene, genotypes, allele, platelet parameters.

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Introduction

Arterial hypertension (AH) is the leading preventable risk factor for cardiovascular diseases (CVD) and all-cause mortality worldwide [1–3]. A joint press release of the the World Health Organization (WHO) and Imperial College London noted that according to the first comprehensive global analysis of AH prevalence, the number of adults aged 30–79 years with AH has increased from 650 million to 1.28 billion over the past thirty years [4].

AH is caused by a complex interaction of environmental and pathophysiological factors, as well as genetic predisposition. Evidence of the genetic basis of AH provides valuable information on the regulation of blood pressure (BP). Over 100 single nucleotide polymorphisms (SNP — Single Nucleotide Polymorphism) associated with BP phenotypes have been identified based on genome-wide association studies (GWAS) [5]. AH is one of the most socially significant pathologies associated with mutations in the human nuclear genome. Identification of genes associated with this disease will provide a mechanism for classification of hypertensive phenotypes, will allow the creation of diagnostic markers for individual patients and families who are at highest risk of complications such as atherosclerosis, stroke, coronary heart disease (CHD), myocardial infarction. Platelet aggregation plays the main role in the pathogenesis of acute thrombosis in patients with CHD, stroke and peripheral arterial disease [3].

Integrin alfa-2 gene (ITGA2B) is a receptor for fibronectin, fibrinogen, plasminogen, prothrombin, thrombospondin and vitronectin and participates in

platelet activation [5, 6]. Platelets are key components of blood that play a physiological role in the initiation of endogenous hemostasis and effective endothelial repair after vascular damage. The key functions of platelets, such as adhesion, activation, aggregation and interaction with clotting factors, work in the context of a complex and balanced interaction of receptors and mediators that provide control of this process and its targeted effect on sites of vascular damage [7].

Current data suggest that several genetic polymorphisms of ITGA2B are associated with wide range of clinical events, including stroke and antiplatelet drugs resistance [8, 9]. In addition, various mutations of this gene have been found to result in loss of aggregation ability and immune response production.

The aim of this study was to investigate the polymorphisms of the ITGA2B gene and its association with platelet parameters in Azerbaijan residents with AH.

Materials

The study included 76 patients with AH (main group) and 24 patients without this pathology (control group).

Inclusion criteria: age from 32 to 77 years; patients of both sexes; patients with AH, CHD, and type 2 diabetes mellitus (type 2 DM).

Exclusion criteria: patients younger than 20 years and older than 80 years, pregnancy, congenital heart disease, congenital and acquired bleeding disorders, patients with cancer, patients receiving chemotherapy, and patients with mental disorders.

Patients who took part in the study were informed about the purpose of the study and signed written in-

Table 1. Demographical characteristics of the study groups

Parameters	I group (n = 29)	II group (n = 23)	III group (n = 24)	Control group (n = 24)	p
Mean age, years	50,62 ± 8,55	58,30 ± 7,59	59,21 ± 4,62	45,87 ± 8,35	> 0,05
Male, n (%)	19 (65,5)	17 (73,9)	15 (62,5)	15 (62,5)	> 0,05
Female, n (%)	10 (34,5)	6 (26,1)	9 (37,5)	9 (37,5)	> 0,05
BMI, kg/m ²	30,49 ± 3,72	29,66 ± 3,80	31,44 ± 3,33	28,08 ± 2,76	> 0,05
SBP, mmHg	148,97 ± 14,86	139,78 ± 15,48	144,88 ± 18,45	119,58 ± 6,42	> 0,05
DBP, mmHg	93,08 ± 11,06	85,65 ± 11,98	85,46 ± 13,0	76,75 ± 5,21	> 0,05

Note. p — statistical significance of differences between study groups.

formed consent in order to participate in the study. The study procedure followed the principles of the Helsinki Declaration. The examination of patients was performed according to the practice guidelines of the International Society of Hypertension 2020. [10]. The study was approved by the Ethics Committee of the Azerbaijan State Institute of Advanced Medical Education named after A.Aliyev on 5th of May, 2019, protocol № 4.

The main group and the control group included patients aged 32 to 77 years and 26 to 61 years, respectively. The main group was divided into 3 clinical groups depending on the presence of CHD and DM: Group I included 29 patients with AH, Group II included 23 patients with AH and CHD, and Group III included 24 patients with a combination of AH with CHD and DM-2. The control group consisted of patients without these diseases.

All patients underwent complete blood count, blood pressure measurement (systolic BP/diastolic BP), body mass index (BMI) was calculated according to the following formula:

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height (m}^2\text{)}}$$

Platelets were examined using the Quintus hematology analyzer (Sweden) and Swelab Alfa Standard (Sweden) using control and calibration reagents. The venous blood sample placed in the tube containing anticoagulant K-EDTA. Blood test was performed on an empty stomach. The following platelet parameters were determined using hematology analyzer: PLT (10⁹/L) — platelet count (impedance method), PDW (%) — platelet distribution width, MPV (fl-femtoliters) — mean platelet volume, P-LCR — platelet-large cell (over 12 fl) to total platelet volume ratio, PCT (%) — plateletcrit. ITGA2 gene polymorphism was determined by mass spectrometry (MALDI-TOF) using Seguenon mass spectrometer (USA). The material for the study was whole blood.

Statistical processing of the results and construction of tables and graphs was performed using Microsoft Office Excel, Statistica 16.0 software using standard methods of variation statistics. The mean value and mean deviation were calculated. Frequency of individual genotypes was determined as the percentage of individuals to the total number of those examined. Differences between qualitative parameters were determined by the χ^2 test, and differences between quantitative parameters were determined by the T-criterion. The level of significance for all tests was set as $p < 0.05$.

Results

Groups did not differ significantly by age and gender (Table 1).

Table 1 demonstrates that the BMI was slightly higher in the control group compared with other groups. SBP and DBP were 19.7 % and 17.5 %, 14.4 % and 10.4 %, 17.5 % and 10.2 % higher in groups I, II and III, respectively, compared to the control group.

Analysis of the polymorphism of the integrin ITGA2 gene indicated the prevalence of the normal homozygous C/C genotype in all study groups (Fig. 1).

As follows from figure 1, the distribution of the C/C genotypes of the ITGA2 integrin polymorphism did not differ significantly between the clinical groups despite prevalence of normal homozygous C/C genotype in all study groups. There was no significant difference between the frequency of C/C genotype in patients from group I ($\chi^2 = 1.974$, $p = 0.160$), group II ($\chi^2 = 1.113$, $p = 0.292$) and group III ($\chi^2 = 0.752$, $p = 0.383$) and the control group. There was also no significant difference in the frequency of this genotype between clinical groups ($p > 0.05$).

There were no significant differences in the frequency of heterozygous mutant genotype T/C and homozygous mutant genotype T/T genotypes between patients from groups I, II, and III and controls, as well as between clinical groups ($p > 0.05$). The prevalence

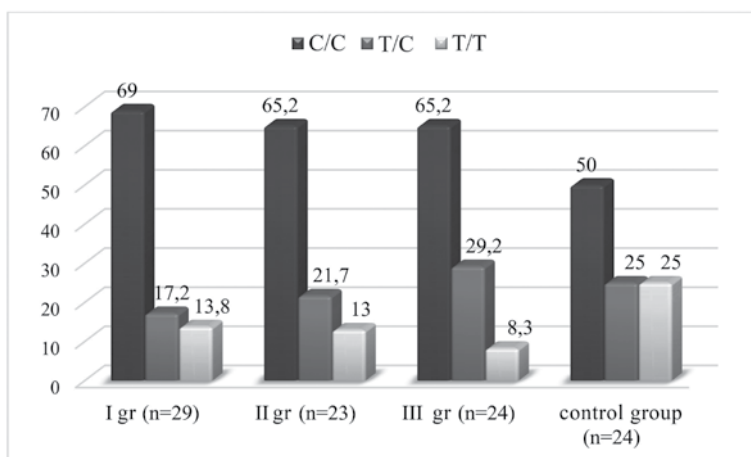


Fig. 1. Distribution of ITGA2 gene genotypes between study groups

of the T allele in group I was 31.0%, and in groups II and III — 34.8% and 37.5%, respectively.

The platelet parameters of the clinical groups are shown in Table 2.

Platelet parameters did not differ significantly between the clinical groups and the control group, as well as between the clinical groups. The data in Table 2 show that the highest platelet count (PLT), platelet distribution width (PDW) and platelet-large cell ratio (P-LCR) were determined in group III, the mean platelet volume (MPV) — in group II patients.

When determining the platelet parameters in patients with different genotypes, the highest PLT was

observed in the carriers of homozygous mutant T/T genotype in group III ($t = 1,05$, $p > 0,05$ compared with the control group), the lowest — in the carriers of heterozygous mutant T/C genotype in group II ($t = 0,99$, $p > 0,05$ compared with the control group) and in the carriers of homozygous mutant T/T genotype in group I ($t = 1,74$, $p > 0,05$ compared with the control group) (Table 3).

Table 3 shows that the highest MPV (mean platelet volume) was in the homozygous mutant T/T genotype carriers in group I ($t = 1,03$, $p > 0,05$ compared with the control group), the lowest MPV was in group III patients with this genotype ($t = 0,32$, $p > 0,05$ com-

Table 2. Platelet parameters in the study groups

Parameter	I group (n = 29)	II group (n = 23)	III group (n = 24)	Control group (n = 24)	p
PLT, 10 ⁹ /l	188,95 ± 35,52	205,09 ± 45,41	213,42 ± 39,21	201,71 ± 29,66	> 0,05
MPV, fl	8,38 ± 0,71	8,44 ± 0,65	7,94 ± 1,23	8,14 ± 1,28	> 0,05
PDWsd, fl	12,22 ± 2,97	11,54 ± 2,05	12,65 ± 2,61	11,46 ± 1,74	> 0,05
PCT, %	0,15 ± 0,03	0,16 ± 0,04	0,16 ± 0,04	0,16 ± 0,03	> 0,05
P-LCR	18,71 ± 5,30	17,79 ± 4,60	19,56 ± 4,79	18,16 ± 4,62	> 0,05

Table 3. Platelet parameters in study groups with various ITGA2 polymorphisms

ITGA2 genotype	Groups	PLT, 10 ⁹ /l	MPV, fl	PDWsd, fl	PCT, %	P-LCR
C/C	I (n = 20)	190,72 ± 29,60	8,19 ± 0,61	11,73 ± 2,59	0,15 ± 0,03	16,64 ± 4,67
	II (n = 15)	224,47 ± 48,83	8,37 ± 0,78	12,17 ± 2,61	0,17 ± 0,04	18,59 ± 5,52
	III (n = 15)	211,87 ± 38,81	8,07 ± 1,18	12,66 ± 2,47	0,17 ± 0,04	20,03 ± 5,02
	Control group (n = 12)	204,83 ± 38,44	8,0 ± 1,68	12,2 ± 1,88	0,16 ± 0,05	19,95 ± 4,81
T/C	I (n = 5)	205,0 ± 66,4	8,56 ± 0,68	14,92 ± 4,86	0,16 ± 0,04	23,97 ± 5,72
	II (n = 5)	159,4 ± 22,08	8,54 ± 0,17	10,36 ± 0,25	0,13 ± 0,02	16,52 ± 0,94
	III (n = 7)	205,86 ± 41,31	7,77 ± 1,43	12,26 ± 2,46	0,15 ± 0,04	18,39 ± 3,62
	Control group (n = 6)	185,17 ± 15,17	8,53 ± 0,49	10,12 ± 0,65	0,15 ± 0,01	15,88 ± 3,39
T/T	I (n = 4)	160,0 ± 17,0	9,28 ± 0,32	11,3 ± 0,55	0,14 ± 0,01	21,92 ± 2,22
	II (n = 3)	184,33 ± 18,22	8,57 ± 0,82	10,37 ± 1,15	0,16 ± 0,03	16,13 ± 5,84
	III (n = 2)	251,5 ± 28,5	7,55 ± 0,95	13,95 ± 3,95	0,18 ± 0,01	20,10 ± 5,20
	Control group (n = 6)	212,0 ± 24,67	8,03 ± 1,17	11,32 ± 1,88	0,17 ± 0,03	16,85 ± 5,29

pared with the control group) and heterozygous mutant T/C genotype carriers ($t = 0.50$, $p > 0.05$ compared with the control group). The maximum level of platelet distribution width (PDW) was determined in the carriers of homozygous mutant T/T genotype in group III ($t = 0.60$, $p > 0.05$ compared with the control group), the minimum level was in the patients carrying heterozygous mutant T/C genotype ($t = 0.34$, $p > 0.05$ compared with the control index) and homozygous genotype T/T in group II ($t = 0.43$, $p > 0.05$). The highest value of plateletcrit (PCT) among homozygous T/T genotype carriers was observed in group III ($t = 0.32$, $p > 0.05$ compared with the control group), the lowest value was observed among heterozygous T/C genotype carriers in group II ($t = 0.89$, $p > 0.05$ compared with the control group). The highest platelet large cell ratio (P-LCR) was detected in heterozygous T/C genotype carriers in group I ($t = 1.22$, $p > 0.05$ versus control group), the lowest P-LCR was detected in homozygous T/T genotype carriers in group II ($t = 0.09$, $p > 0.05$ versus control group).

Discussion

In recent decades, the genomics of cardiovascular diseases (CVDs) has attracted increasing interest: it has become possible to identify polymorphic genes responsible for predisposition to CVDs, including CHD. It is known that integrins are adhesion molecules that promote platelet aggregation, leading to clot formation [11]. Discovery of integrins has been going on for a long time, and the knowledge in this field is constantly expanding.

We genotyped ITGA2 in patients with AH (group I), patients with AH and CHD (group II) and patients with AH, CHD and DM-2 (group III). According to the results obtained, carriers of the normal homozygous C/C genotype and carriers of the mutant homozygous T/T genotype were more frequent in all groups. Our results slightly differ from those of Shishkina E.A. et al. [11], who identified heterozygous mutant C/T genotype and homozygous mutant T/T, carriage of the T allele of the ITGA2 gene, among patients with AH in 61.7% of cases.

The T allele of the C807T polymorphic marker of the ITGA2 gene (rs 1126643) is associated with increased expression of platelet GPIa-receptors and increased platelet adhesion to collagen [12]. Adhesion molecules are glycoproteins that can mediate interactions between cells or between cells and the extra-

cellular matrix. These proteins can help leukocytes and platelets to adhere to the vascular endothelium, thus contributing to the formation of cerebral atherosclerotic plaques [12]. The literature presents data on the association of the T allele with increased platelet adhesion rate [13].

It is known that platelets are cytoplasmic fragments of bone marrow megakaryocytes 3–5 μm in diameter and 4.5–11 femtoliters in volume. We determined platelet parameters in patients carrying ITGA2 genotypes. Platelet indices can be considered as promising diagnostic and prognostic markers for thrombotic complications [14]. The measurements were: platelet count (PLT — platelet count); mean platelet volume (MPV); platelet distribution width (PDW); plateletcrit (PCT); platelets large cell ratio (P-LCR). Platelet parameters in patients in the clinical groups differed from those in the control group, but the changes were statistically insignificant ($p > 0.05$).

Platelets with high hemostatic activity play a pivotal role in the pathophysiology of CHD, and mean platelet volume (MPV) has been proposed as an indicator of platelet reactivity. There are data on the association of high MPV with CHD [15]. According to our data, the maximum MPV level was detected in patients with AH, carriers of mutant homozygous T/T genotype. Patients with AH and CHD had the maximum elevated MPV compared with other clinical groups and the controls. It has been reported that platelet volume parameters (PVP), such as mean platelet volume (MPV), platelet distribution width (PDW) and platelet-to-large cell ratio (P-LCR), may be elevated in patients with acute coronary syndrome, which may be due to larger platelets containing more proaggregating mediators and representing more expanded functions [16]. Researchers suggest that platelets are not only involved in coronary artery thrombosis, but also contribute to atherosclerosis and endothelial damage by secreting mediators during CHD development [17, 18]. It is also noteworthy that platelet parameters, markers of platelet activation, are parameters obtained daily as part of automatic blood analysis.

PDW, also known as an indicator of platelet diversity, increases in CVD as a result of platelet activation [19]. The results of comparative analysis presented in the literature are confirmed by the revealed positive correlation between the presence of CHD and PLT and negative correlation with PDW and P-LCR [20].

Our results indicated an increased level of PLT in mutant homozygous T/T genotype carriers suffering from AH combined with CHD and type 2 diabetes mellitus.

The data studied in the present study are the subject for research due to the key role of platelets in hemostasis, inflammation, protection against pathogens, wound healing and angiogenesis.

Conclusion

According to the results obtained, elevated PLT, PDW, and P-LCR parameters were detected in patients with AH, CHD, and type 2 diabetes mellitus, and a high MPV level was found in patients with AH and CHD.

The prevalence of the normal homozygous C/C, mutant heterozygous T/C, and mutant homozygous T/T genotypes of the ITGA2 gene was 69.0%, 17.2%, and 13.8% in AH patients; 65.2%, 21.7%, and 13.0%

in patients with AH and CHD; and 62.5%, 29.2%, and 8.3% in those with AH, CHD, and type 2 DM, respectively. The prevalence of the T allele among patients with AH was 31.0%, among patients with AH and CHD—34.8%, and among patients with AH, CHD, and type 2 diabetes—37.5%. Platelet parameters, PLT, PDW, and PCT in particular, tended to be higher among patients with AH, CHD, and type 2 DM and mutant homozygous T/T genotype carriers ($p > 0.05$). relatively high MPV level was observed among mutant homozygous T/T genotype carriers with AH ($p > 0.05$), P-LCR—among mutant heterozygous T/C genotype carriers with AH. However, differences were not statistically significant ($p > 0.05$). Studies with larger samples are needed to confirm the results.

Conflict of interest. None declared.

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- 16 Nazirova V.B. et al.
Identification of single-nucleotide polymorphisms of the ITGA2 integrin gene...
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