# МЕДИЦИНСКИЕ НАУКИ

***Karpenko O.O.***
*Postgraduate Student*
*Bogomolets National Medical University*
*ORCID 0000-0002-6530-7543*
***Netiazhenko V.Z.***
*Corresponding Member of NAMS of Ukraine, professor*
*Bogomolets National Medical University*
***Plenova O.M.***
*Associate professor*
*Bogomolets National Medical University*

## ITGB3 GENE POLYMORPHISM AND ITS RELATION TO PLATELET PHASE OF HEMOSTASIS ACTIVITY IN PATIENTS WITH CORONARY ARTERY DISEASE COMBINED WITH TYPE 2 DIABETES

**Summary.** One of the urgent problems of modern health care is the elucidation of the molecular-genetic basis of the development of cardiovascular diseases. One of the effective approach to studying the role of genetic mechanisms of pathogenesis is associated with the selection of genes that have the greatest contribution to the regulation of primary hemostasis, ensuring the adequacy of the platelet response. The GP IIb/IIIa receptor is the major platelet receptor whose molecular defects can lead to platelet hyperaggregation. The ITGB3 gene (GPIIIa) encodes a protein component of the platelet fibrinogen receptor, which provides the interaction of platelets with blood plasma fibrinogen, resulting in platelet aggregation and thrombus formation. The main goal of the study is to assess platelet aggregation activity in patients with various forms of coronary artery disease in combination with type 2 diabetes and different polymorphism of ITGB3 gene.

*Key words: platelets, gene polymorphism, thrombus, diabetes, aggregation.*

**Introduction.** In recent years, genetic risk factors for coronary artery disease (CAD) have been extensively studied in connection with the development of molecular genetics methods. The main area of genetic research is the study of associations of candidate genes with the risk of developing the disease. First of all, these are genes whose products are operated in the blood coagulation system or affect the physiology of the vessel wall. The development of CAD are based on two main processes - atherosclerosis and thrombosis [7]. Attention should be paid to the fact that atherosclerotic vascular changes are more typical for the elderly. In young patients the greater contribution to the formation of pathology is made by disorders in the coagulation system that lead to increased thrombus formation [5]. Based on the above, it should be emphasized that the polymorphism of genes of the hemostasis system plays an essential role in the etiology of CAD. Detection of genetic markers of thrombophilic conditions can significantly increase the possibility of adequate pathogenetic treatment and prevention of acute circulatory disorders, especially in young working age, which is important for medical and social matter.

The study of the genetic aspects of thrombosis testifies to the prevalence of the latter in people with "unfavorable" alleles of proteins participating in the hemostatic cascade [4].

Platelet glycoprotein receptors play a significant role in platelet adhesion and aggregation during thrombus formation, allowing them to be considered as candidate genes for association with acute coronary syndrome and other cardiovascular diseases. Thus, the polymorphism of the genes that regulate the expression or activity of these receptors can influence the course and consequences of any disease that is involved in the pathogenesis of the hemostasis system. According to M.J. Quinn, E.J. Topol [9 - 11], the contribution of genetic factors to the variability of platelet reactivity is about 30%. In O'Donnell et al. [2] has shown that hereditary factors make significant adjustments (20-30%) in the state of platelet aggregation, while the proportion of different clinical parameters account for from 4 to 7%.

The most important feature in platelet activation is the modification of the IIb/IIIa membrane glycoprotein complex. As a result of conformational changes, the complex acquires the ability to bind fibrinogen, thereby creating bridges between activated platelets. This results in the aggregation of blood platelets, which ends in the formation in the area of the vascular wall of the platelet thrombus.

The GP IIb/IIIa receptor is the major platelet receptor whose molecular defects can lead to platelet hyperaggregation. The complex is expressed by platelets, and the main ligand is fibrinogen. The complex consists of two subunits that are covalently interconnected. Subunits IIb and IIIa are encoded by different genes located close to each other on the 17th chromosome. The ITGB3 gene (GPIIIa) encodes a protein component of the platelet fibrinogen receptor. This receptor provides the interaction of platelets with blood plasma fibrinogen, resulting in platelet aggregation and thrombus formation [6].

In 1989, a point mutation C1565T in the second exon of the ITGB3 gene was described, which leads to the replacement of leucine (Leu) with proline (Pro) in the 33rd position of the GPIIIa protein (rs5918), which

entails conformational changes in the N-terminal disulfide loop GPIIIa belonging to the fibrinogen binding site.

Pro-33 carriers have increased ADP-induced platelet aggregation in vitro experiments, with increased signaling of complex IIb/IIIa and platelet cytoskeletal remodeling. Platelets carrying ITGB3 Pro33 have a lower activation threshold, i.e. more prone to aggregation.

It is noted that at variant 1565C of the ITGB3 gene, the risk of thrombosis is increased by 2.7 times [8]. According to some sources, the frequency of distribution in the European population is 85% and 15% for Leu-33 and Pro-33 variants, respectively [12, 13]. Allele C was found in 14% of European countries, and the distribution of the three genotype variants in the general population was as follows: C/C - 2%, C/T - 24%, T/T - 74% [1].

**Goal.** Analyze the results of a genetic study of platelet glycoprotein receptors for fibrinogen and platelet aggregation activity in patients with various forms of CAD in combination with type 2 diabetes (T2D).

**Materials and methods.** In the course of the study we examined 120 patients who were treated at the emergency cardiology department of Kyiv City Clinical Hospital #1: 30 patients with acute coronary syndromes (ACS), 30 patients with ACS in combination with T2D, 30 patients with chronic coronary syndromes (CCS), 30 patients with CCS in combination with T2D and 15 practically healthy (control group). Among the surveyed sick men there were 63 (52.5%), women - 57 (47.5%). The mean age of patients was 64.2 ± 10.01 years (40 to 84 years). The initial examination was performed on the first day after hospitalization of the patient.

All patients were treated according to the protocols of management of patients with stable angina, STEMI/non-STEMI, unstable angina. Patients received antiplatelet treatment with acetylsalicylic acid and clopidogrel. Treatment of T2D was performed according to the appointments of the endocrinologist [3].

The study of hemostatic parameters in venous blood was performed immediately upon admission of the patient to the emergency cardiology department.

Studies were performed in platelet-rich plasma (PRP) and platelet-poor plasma (PPP). The study of platelet functional activity was performed on a "Biola Aggregation Analyser" - laser aggregator with computerized analysis of the light transmission curves and the characteristics of platelet aggregates. The presence of spontaneous platelet aggregation and stimulated aggregation was studied. As aggregation inducers, ADP ("Reanal") at a final concentration of $1{,}5\times10^{-6}$ M and arachidonic acid (AA) ("Reanal") at a final concentration of $1{,}2\times10^{-6}$ M were used. All inductors were used at low concentrations, which consistent with current concepts and requirements for studies of platelet aggregation properties in thrombophilic conditions.

For molecular genetic analysis, DNA samples from patients isolated from venous blood by the sorbent method were used. The C1565T polymorphism of the ITGB3 gene was determined by the polymerase chain reaction (PCR) method using a two-primer system.

The results of the study were processed using statistical methods. When evaluating each metric group, the type of metric distribution was evaluated. Medians of the interquartile scale groups (25th and 75th percentile scores) were used to center the variables. For pairwise comparison of groups, the criterion U - Mann-Whitney was used. To assess the correlation of indicators between groups, we performed Spearman correlation analysis.

**Results of the research.** Analysis of the spread of the ITGB3 genotype in the study population of patients revealed that the presence of T2D was not associated with the polymorphisms of the gene, which is shown in table 1, so in the further study comparisons were made in generalized groups of patients with ACS (n = 60, group I) and CCS (n = 60, group II) without isolation of subgroups of patients with T2D.

Таблиця 1

**Distribution of ITGB3 gene polymorphism**

| ACS (n=60) | | | |
|---|---|---|---|
| ITGB3 polymorphism | With T2D (n=30) | W/o T2D (n=30) | p 1-2 |
| | 1 | 2 | |
| T/T | 22 (73,34%) | 21 (70%) | p>0,05 |
| T/C | 5 (16,67%) | 5 (16,67%) | p>0,05 |
| C/C | 3 (10%) | 4 (13,34%) | p>0,05 |
| CCS (n=60) | | | |
| | With T2D (n=30) | W/o T2D (n=30) | p 1-2 |
| | 1 | 2 | |
| T/T | 27 (90%) | 26 (86,67%) | p>0,05 |
| T/C | 3 (10%) | 2 (6,67%) | p>0,05 |
| C/C | 0 | 2 (6,67%) | p>0,05 |

Genotyping of patients showed that the polymorphism of the ITGB3 gene in group I had the following distribution: T/T – 71,7% (n = 43), T/C – 16,6% (n = 10), C/C – 11,7% (n = 7), and in group II: T/T - 88,3% (n = 53), T/C - 8,3% (n = 5), C/C - 3,3% (n = 2) (Fig. 1).

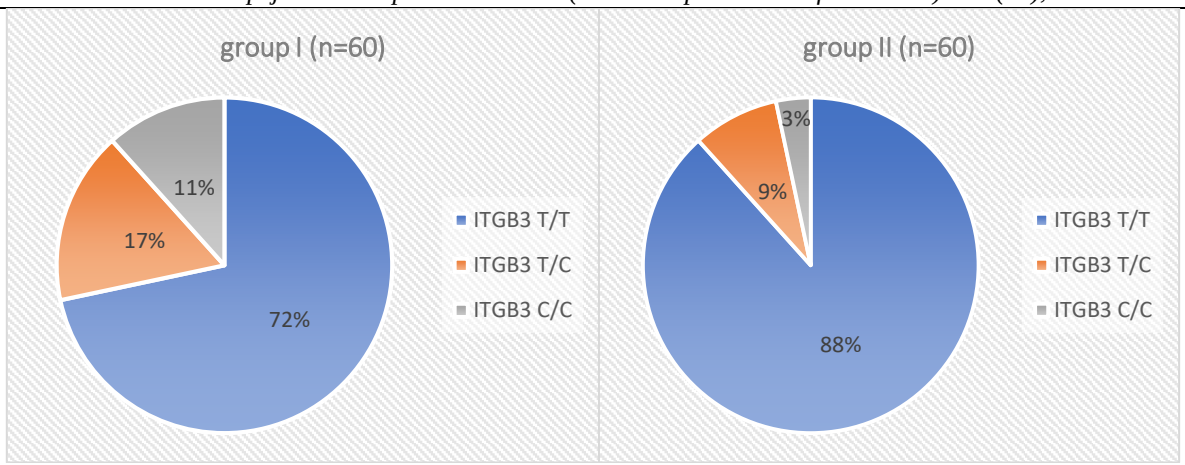


*Fig. 1. Distribution of genotypes among patients*

Thus, a mutation of the C allele of the ITGB3 gene was observed in 28% of patients with ACS, instead, it was present in only 12% of patients with CCS. Therefore, patients with a C-allele were more likely to develop ACS, the basis of which is known to be activation of coronary thrombus formation. Given the exceptional role of platelets in the pathogenesis of coronary thrombosis and the importance of glycoprotein receptors in its realization, it is possible to state the importance of genetic predisposition to the disease in this scenario.

To confirm the role of ITGB3 gene polymorphisms in the activation of hemocoagulation processes, platelet aggregation capacity in group I was studied (Table 2). All patients in this group were divided into subgroups depending on the ITGB3 gene polymorphism.

Table 2

**Indicators of platelet hemostasis in the examined patients**

| | ITGB3 gene polymorphism | | | Control group (n-15) |
|---|---|---|---|---|
| | T/T (n=43) | T/C (n=10) | C/C (n=7) | |
| | 1 | 2 | 3 | |
| Spontaneous platelet aggregation: Degree, %; Speed, %/min. | 2,47 [1,7; 3,7]***<br>2,24 [1,6; 3,1] | 4,37 [2,5; 5,9]***<br>2,91 [1,9; 5,2] | 4,81 [4,2; 6,1]***<br>3,89 [2,9; 4,2]*** | 0,88 [0,5; 1,1]<br>1,64 [1,3; 2,8] |
| Average size of units | 1,19 [1,0; 2,4]* | 1,13 [0,9; 1,7] | 1,01 [0,9; 2,5] | 1 [0,9; 1,1] |
| AA-induced platelet aggregation: Degree, %; Speed, %/min. | 21,5 [15,3; 30,1]***<br>16,7 [10,0; 24,3]*** | 22,5 [18,9; 30,1]*<br>16,85 [11,6; 29,4]* | 26,25 [21,8; 33,5]*<br>24,95 [12,3; 49,2] | 36,4 [32,0; 42,6]<br>41,9 [24,1; 56,0] |
| ADP-induced platelet aggregation: Degree, %; Speed, %/min. | 37,2 [21,3; 44,6]*<br>25,12 [10,4; 64,2] | 43,13 [33,2; 60,2]<br>43,65 [26,2; 81,1] | 72,9 [56,4; 86,4]**<br>95,7 [88,1; 113,0]*** | 43,5 [36,5; 52,6]<br>48,9 [44,4; 73,5] |

It was found that indicators of the degree of spontaneous platelet aggregation were significantly different from the control group in all subgroups of the examined patients, with the highest indicator was recorded in the subgroup C/C - 4,81 [4,2; 6,1], which exceeded the control value by 5.46 times ($p<0.001$). Note that the presence of C-allele was associated with an increase in the degree of spontaneous aggregation relative to T/T polymorphism by 76.92% in the T/C subgroup ($p<0.01$), and by 94.74% in the C/C subgroup ($p<0.001$). The corresponding changes also affected the speed of spontaneous platelet aggregation.

Analyzing the indicators of AA-induced platelet aggregation, it was found that its degree in the subgroup of patients with C/C genotype was greater by 22% compared to the T/T subgroup and by 16.6% - compared to the T/C subgroup, the difference between the subgroups did not become statistically significant ($p>0.05$). Significantly lower values for the control group in all subgroups of patients can obviously be explained by treatment with acetylsalicylic acid, which has an effect on AA metabolism, which leads to a decrease in the response of platelets to this inducer. Thus, the severity of the decrease in the degree and rate

of AA-induced platelet aggregation can be considered as a criterion for the effectiveness of therapy. It should be noted that in the absence of a significant difference in these parameters between subgroups of patients with different polymorphisms of the ITGB3 gene, a clear tendency to lower values of AA aggregation was observed in patients with the native T/T genotype. Instead, platelets of patients with the C/C genotype showed a less adequate response to treatment, which was confirmed by the absence of a statistically significant difference in AA-aggregation of platelets from control.

Regarding to the degree of ADP-induced aggregation in the subgroups, it was noted that the highest indicator was recorded in the C/C subgroup, it was 1.68 times higher than the control group ($p<0.01$). It should be noted that all patients received treatment with clopidogrel, which has a direct effect on ADP-platelet aggregation. Therefore, the increase in platelet response to this inducer can be regarded as a paradoxical response and evidence of drug inefficiency. Carrier of the mutant C allele was found to cause an increase in ADP aggregation relative to the T/T genotype by 15.94% in the T/C group ($p>0.05$) and a significant increase in the C/C subgroup as compared to the T/C group. (69.02%, $p<0.05$) and relative to the T/T group (95.7%, $p<0.001$). The rate of ADP-induced aggregation had similar trends in degree. Thus, the speed index in the C/C subgroup was 2.19 times and 3.8 times higher than in the T/C subgroups ($p<0.01$) and T/T ($p<0.001$), respectively.

In the group of patients with CCS, the indices of the degree of spontaneous platelet aggregation were significantly different from the control group in all subgroups of the examined patients, that is, similar to the trend observed in patients of group I (Table 3). The highest rate of spontaneous aggregation was recorded in the C/C subgroup - 2.18 [2.04; 2.31], which exceeded the control value by 2.48 times ($p<0.05$). Although the cross-group comparison showed no significant difference, the tendency for an increase in spontaneous platelet response was clearly observed in patients with the existing C-allele. However, no similar changes in the rate of spontaneous aggregation were observed.

Table 3

**Indicators of platelet hemostasis in the examined patients**

| | ITGB3 gene polymorphism | | | Control group (n-15) |
|---|---|---|---|---|
| | T/T (n=43) | T/C (n=10) | C/C (n=7) | |
| | 1 | 2 | 3 | |
| Spontaneous platelet aggregation: Degree, %; Speed, %/min. | 1,11 [0,8; 1,4]*<br>2,09 [1,3; 2,9] | 1,59 [1,5; 1,9]**<br>2,91 [2,5; 2,9] | 2,18 [2,0; 2,3]*<br>2,13 [1,64; 2,6] | 0,88 [0,5; 1,1]<br>1,64 [1,3; 2,8] |
| Average size of units | 1,01 [0,84; 1,16] | 0,78 [0,74; 0,84] | 1,53 [1,01; 2,04] | 1 [0,9; 1,1] |
| AA-induced platelet aggregation: Degree, %; Speed, %/min. | 33,2 [24,2; 41,7]<br>44,13 [34,1; 52,1] | 36,2 [36,2; 36,5]<br>62,3 [52,1; 62,9] | 40,52 [38,9; 42,2]<br>99,52 [70,1; 129] | 36,4 [32,0; 42,6]<br>41,9 [24,1; 56,0] |
| ADP-induced platelet aggregation: Degree, %; Speed, %/min. | 33,6 [26,1; 43,2]*<br>31,3 [12,7; 44,3]* | 54,8 [49,3; 60,2]<br>86,8 [78,6; 101] | 81,4 [76,4; 86,4]*<br>107 [101; 113]* | 43,5 [36,5; 52,6]<br>48,9 [44,4; 73,5] |

It was found that the rate of AA-induced platelet aggregation in the subgroup of patients with C/C genotype was higher by 21% compared to subgroup T/T ($p>0.05$) and by 11.9% - compared to subgroup T/C ($p> 0.05$). When comparing the indicators of the degree of aggregation in the subgroups with the control group, no significant difference was found ($p>0.05$). The rate of AA-induced aggregation in the C/C mutation subgroup was 125.51% and 59.74% higher, respectively, than in the T/T and T/C subgroups, respectively ($p>0.05$ for both cases).

Analyzing the indicators of the degree of ADP-induced aggregation in subgroups, it was noted that the highest indicator was recorded in the C/C subgroup - 1.68 times higher than the control group ($p<0.01$). Carrier of the mutant C-allele was found to cause an increase in ADP aggregation relative to the T/T genotype by 63.1% in the T/C group ($p<0.01$) and a significant increase in the C/C subgroup as compared to the T/C group. (48.5%, $p>0.05$) and relative to the T/T group (142.26%, $p<0.05$). The speed of ADP-induced aggregation had similar trends in degree. Thus, the speed index in the C/C subgroup was 1.23 times higher and 3.42 times higher than in the T/C subgroups ($p>0.05$) and T/T ($p<0.05$), respectively.

The assessment of the interdependence between platelet hemostasis and ITGB3 gene polymorphisms, shown in Table 4, in the group of patients with ACS revealed a significant positive correlation between the

degree of spontaneous aggregation, the degree and speed of ADP-induced aggregation and gene mutation.

Таблиця 4

**Оцінка кореляційних зв'язків між показниками тромбоцитарного гемостазу та поліморфізмів гена ITGB3**

| | Group I (n=60) | | Group II (n=60) | |
|---|---|---|---|---|
| | ITGB3 | P | ITGB3 | P |
| Spontaneous platelet aggregation: Degree, %; Speed, %/min. | 0,534766<br>0,249234 | p<0,05<br>p>0,05 | 0,362285<br>0,134566 | p<0,05<br>p>0,05 |
| Average size of units | -0,042208 | p>0,05 | -0,049226 | p>0,05 |
| AA-induced platelet aggregation: Degree, %; Speed, %/min. | 0,147514<br>0,154478 | p>0,05<br>p>0,05 | 0,104433<br>0,385296 | p>0,05<br>p<0,05 |
| ADP-induced platelet aggregation: Degree, %; Speed, %/min. | 0,466312<br>0,449846 | p<0,05<br>p<0,05 | 0,442282<br>0,472420 | p<0,05<br>p<0,05 |

At the same time, when looking for a correlation between the analyzed parameters in the group of patients with CCS, a significant positive correlation was found between the degree of spontaneous platelet aggregation and the mutation of the allele, as well as between the rate of AA-induced aggregation, indicators of ADP-induced aggregation and polymorphism.

**Conclusions:**

1. Polymorphisms of the ITGB3 gene in patients with acute and chronic coronary syndromes are not associated with the comorbid presence of type 2 diabetes.

2. The degree of spontaneous platelet aggregation has a clear dependence on the ITGB3 genotype, with the presence of a mutated C-allele accompanied by an increase in aggregation capacity, the maximum values of which are observed in the case of a homozygous C/C mutation.

3. Evaluation of the effectiveness of dual antiplatelet therapy based on the analysis of platelet response to mechanism-dependent aggregation inducers indicates the insufficient effect of acetylsalicylic acid and, in particular, clopidogrel in patients with C/C genotype. This suggests the presence of a genetic component in the formation of resistance to antiplatelet drugs.

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***Pitakova Ivelina MD,***
*ophthalmology*
*Eye Clinic "St. Nicholas"*

## HOW DO WE CLASSIFY BLINDNESS - H54 ACCORDING TO ICD – 10

***Д-р Ивелина Йорданова Питакова***
*офталмолог ОМЦ*
*"Св. Николай Чудотворец" – Варна*

## КАК КЛАСИФИЦИРАМЕ СЛЕПОТАТА – Н54. ПО МКБ – 10

*Keywords: blindness, ICD-10, low vision, DR, ARMD*
*Ключови думи: слепота, МКБ-10, ICD-H54, ДР, АМД*

Visual acuity is a measure of the ability of the visual sensory system to distinguish the smallest details of visual objects. Visual acuity and field of vision are considered the two criteria by which groups of the visually impaired are classified. According to the best visual acuity with the correction of the better-sighted eye, there are two main types of visual deficits – blindness and low vision. Globally, approximately 1.3 billion people are estimated to live with some form of visual impairment. Most people with visual impairments are over 50 years of age.

The definitions of low vision and blindness are very varied. The World Health Organization provides the following definition (1): according to the WHO, reduced vision is defined as visual acuity <0.3 (logMAR ~ to 0.52) and / or field of vision <20°, and blindness as visual acuity <0.05 (logMAR ~ to 1.30) and / or field of vision <10°. Blindness, Latin *Anopia,* is a condition of functional loss of visual perception, which may be due to ophthalmic or neurological causes. Different definitions of reduced vision and blindness exist in countries around the world. For instance in the United States (2) the definition is as follows: "Low vision refers to visual impairment that cannot be corrected by surgery, pharmaceuticals, glasses or contact lenses; it is often characterized by partial vision, such as blurred vision, blind spots or tunnel vision." The Canadian National Institute for the Blind (3) says that "... vision between 20/60 and 20/190 is called partial blindness or low vision. If the change in vision is up to 20/200 or worse, the person will still have some vision but will be classified as blind if their field of vision or the perimeter they can see is less than 20° – despite the fact that their vision is better than 20/200". According to Greek law, a blind person is defined as a person whose visual acuity is less than 1/20 in the better eye with the best possible correction. (4) A person even with satisfactory visual acuity, but with peripheral vision limited to 10 degrees or less, is presumed to be blind.

Israel has maintained a register of the blind since 1987. Patients are monitored by ophthalmologists and recorded if they have a visual acuity of < or = 0.05 (20/400) or a field of view with a radius of <20 degrees. This report includes data on 18,891 persons registered between 1987 and 1999. The main causes of blindness in the complete registry are age-related macular degeneration (AMD) and glaucoma (14%), followed by diabetic retinopathy (11%). (5) The Tajimi-town study on the prevalence and causes of low vision and blindness in the Japanese adult population identified low vision and blindness as BCVA for the better eye from 20/60 to 20/400 and worse from 20/400, respectively. (6)

**Blindness classification**

**1. ICD-10**

The International Statistical Classification of Diseases and Related Health Problems (7) was first introduced in 1893. The ICD-10 was developed in 1992 by WHO and consists of 21 sections (Table 1), using the letter H in class 7, *Diseases of the eye and its appendages*. The IBC is revised periodically, and after many revisions, the 11th version is already underway.