ORIGINAL ARTICLE

ASSOCIATION BETWEEN SINGLE POLYMORPHISM IN THE LOCUS RS17216473 OF THE GENE THAT ENCODES 5-LIPOXYGENASE-ACTIVATING PROTEIN AND RISK OF MYOCARDIAL INFARCTION

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ABSTRACT

The aim: To study the association between A/A, G/A, A/A genotypes, alleles A, G of the SNP rs17216473 of the gene that encodes ALOX5AP and the risk of myocardial infarction within the Ukrainian population.

Materials and methods: PCR in real time and the analysis to discriminate alleles were used. The statistical processing was carried out by χ2 criteria and by χ2 criteria with Yates correction.

Results: For the first time the SNP rs17216473 of gene that encodes ALOX5AP has been established to be statistically significantly associated with the risk of myocardial infarction in Ukrainian population. The connection with genotype A/A was opposite to that with genotype G/G. That is, A/A contribution to myocardium infarction has been statistically significant whereas, G/G has been statistically significantly associated with the absence of myocardial infarction. G/A genotype has not been statistically significantly associated with myocardial infarction. It has also been established a statistically significant connection exists between the risk of myocardial infarction and the presence of allele A (minor allele) of the polymorphism. Allele G, however, has a statistically significant association with the absence of myocardial infarction. All humans-homozygotes with the minor allele A had suffered from myocardial infarction. In the control group, humans-homozygotes with the minor allele A were not found.

Conclusions: Summarizing our obtained results, we assume the carriers of G/G genotype to have a minimal risk of myocardial infarction onset, the carriers of G/A genotype to have a moderate risk and the carriers of A/A to have a great risk.

KEY WORDS: single nucleotide polymorphism, getetics, myocardial infarction

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INTRODUCTION

The incidence of cardiovascular diseases is increasing, and the causes are varied [1, 2].

Single nucleotide polymorphisms (SNP) are directly related to the development of cardiovascular diseases. The SNP of the ALOX5 and ALOX5 AP genes that encode 5-lipoxygenase and its activating protein are assumed also to contribute to these diseases onset [3, 4, 5].

The areas of polymorphic loci (SNP) of the ALOX5AP and ALOX5 genes are clearly specified, and the quantity of such loci is extremely high.

One of the research methods is to establish an association between different polymorphic locuses of the corresponding genes and the diseases of the cardiovascular system. Herewith, one analyzes the statistical relationship between the corresponding SNP and myocardial infarction, stroke, atherosclerosis, etc.

Helgadottir A and co-authores were the first to show SNP ALOX5AP gene to be connected with the risk of myocardial infarction [3]. This association has been confirmed [4, 6], but some authors [5, 7, 8] deny the connection between SNP ALOX5AP and myocardial infarction. It has been stated that the correlation between SNP ALOX5AP and C-reactive protein exists [9]. Data exists regarding SNP ALOX5AP gene`s contribution to coronary artery disease [10, 11, 12], including the threat of its onset [13], there is also data stating an absence of such a contribution, but the presence of the connection between SNP ALOX5 gene and coronary artery disease [14]. Despite this, according to the literature data, some polymorphisms of the ALOX-5AP and ALOX5 genes are reported to be associated with cardiovascular diseases, including myocardial infarction.

The exact contribution of rs17216473 of ALOX5AP gene to the cardiovascular diseases development was mentioned in the following works. Tsai and coauthors [11] who had examined European-Americans pointed that SG13S377 specifically has been significantly linked to the risk of ischemic heart disease. This correlation was specified to be independent from other polymorphisms. Conversely, Huang with co-authors [6], who had examined the Chinese, showed the absence of the connection between rs17216473 and ischemic heart disease. The absence of any statistically significant association between SNP rs17216473 ALOX-5AP gene and myocardium infarction in a polyethnic

group was reported by David R. Crosslin and co-authores [12]. Concurrently, myocardial infarction, specifically in Europeans was verified to depend highly on haplotype B (rs17216473 (A), rs10507391 (A), rs9315050 (A) and rs17222842 (G)). However, the other polymorphism of haplotype B was specified to be the most significant [12].

The majority of the data referres to haplotypes and there are few studies done that would allow one to clearly link genotypes AA, AG or GG of rs17216473 polymorphism to cardiovascular diseases, or, vice versa, would show the absence of such an association. In our opinion, the study of particular SNP genotypes and alleles is just as important as the study of haplotypes.

The polymorphic nucleotide is in intron, therefore rs 17216473 is an intron polymorphism.

There are three genotypes in accordance with polymorphic nucleotide: AA, AG, GG and two alleles – A and G. The rest of this sequence is identical in all members of the Homo sapiens species.

The relationship between these genotypes and the risk of developing cardiovascular diseases is of great significance, since it is precisely such an association that will accurately answer the question; is this polymorphism related to the development of these diseases, or are they caused by other polymorphisms of ALOX5AP gene?

Polymorphism of this particular locus of chromosome 13, where the rs17216473 of the ALOX5AP gene is located, has been insufficiently studied. There are only few works where this polymorphism is mentioned.

There is a total absence of any data regarding the contribution of SNP rs 17216473 (SG13S377) of the ALOX5AP gene to the development of cardiovascular diseases in the Ukrainian population.

The study of the connection between rs17216473 polymorphism (SG13S377) of the ALOX5AP gene and the risk of cardiovascular diseases development in the Ukrainian population has been carried out for the first time only very recently.

In the present work, we aimed to study the association between the single-nucleotide polymorphism rs17216473 of the 5-lipoxygenase activating protein (ALOX5AP) gene and the risk of myocardial infarction among representatives of the Ukrainian population. To this end, we checked the presence or absence of a statistically significant association between the single nucleotide polymorphism (A/G) rs17216473 (SG13S377) of the ALOX5AP gene and the risk of myocardial infarction within the Ukrainian population.

MATERIALS AND METHODS

CONTINGENT UNDER THE STUDY: MYOCARDIAL INFARCTION GROUP, CONTROL GROUP

Leukocytes of human whole blood were researched in 95 people with myocardial infarction (myocardial infarction group) and in 110 individuals of the control group. Blood collection was carried out by medical staff at medical institutions.

Blood sampling was carried out in patients with myocardium infarction who were being treated in the hospital of National Scientific Center «M.D. Strazhesko Institute of Cardiology», department of cardioreanimation, the department of therapy № 4 of Bogomolets National Medical University. Blood sampling for the control group was carried out in healthy donors of corresponding age in the Kyiv City Center of Blood.

REAGENTS

The following reagents were used in the work: the kit DIAtom DNA Prep («Isogene», Russia) having contained lysing reagent (Guanidine isothiocyanate), sorbent (*NucleoS*), saline solution to wash off DNA, ExtraGene to detach DNA from the sorbent, the mixture of probes for PCR TaqMan® for PCR. To prepare water solutions one used deionisation water.

GENOTYPING

DNA was extracted from blood samples using the kits DIAtom DNA Prep («Isogene», Russia). The kit contained lysing reagent guanidine isothiocyanate, sorbent *NucleoS*, saline solution and ExtraGene to detach DNA from the sorbent. The method is based on the usage of guanidine isothiocyanate as a lysing reagent for cell lysis, solubilization of cell debris, and denaturation of cell nucleases. DNA is actively being absorbed on *NucleoS*™ under the presence of lysing reagent and then easily washed off from proteins with saline solution with ethanol. Subsequently, the DNA was extracted from the sorbent and transferred to sterile DNA-free and RNA-free microtest tubules («Eppendorf», USA). The obtained DNA was used for PCR in real time.

One determined the allele polymorphism of ALOX5AP gene (G→A) having used probes TaqMan® SNP Assay C_11599359_10. Amplification was performed with 7500 Fast Real-time PCR System («Aplied Biosystems» USA).

To clarify which of nucleotides, A or G, was present in the locus rs17216473 of ALOX5AP gene we determined the genotypes in the researched groups (the myocardial infarction group and the control group). For this purpose one made analysis to discriminate alleles with 7500 Fast Real-time PCR System Software (Applied Biosystems Foster City, USA) and counted the amount of the alleles and the quantity of people having had the corresponding genotype (A/A; A/G; G/G) within the healthy group (the control) and the patients with myocardium infarction. The contribution of three said genotypes and A and G alleles is being analyzed in the current study.

STATISTICAL ANALYSIS

In order to establish the association between the genotypes G/G, A/G, A/A, alleles A and G in the polymorphic locus of rs17216473 of ALOX5AP gene and the risk of myocardial infarction we compared the control groups with myocardial infarction groups separately for each genotype by $\chi 2$ criteria

Table I. The distribution of genotypes G/G, G/A and A/A in the control group and in the miocardial infarction group

The genotype	G/G		G/A		A/A	
The researched groups (N= the researched individuals)	The number of genotype carries, individuals	The percentage (%) of genotype carries in the group	The number of genotype carries, individuals	The percentage (%) of genotype carries in the group	The number of genotype carries, individuals	The percentage (%) of genotype carries in the group
The control groups N=110 (total amount)	89	80,9	21	19,1	0	0
Myocardial infarction groups N=95 (total amount)	63	66,3	24	25,3	8	8,4
Total amount of control and myocardial infarction groups N=205	152	74	45	22	8	4

Table II. The distribution of G and A alleles in the control group and in the myocardial infarction group

Alleles	Allele G		Allele A	
The researched groups (N= the amount of alleles)	The amount of G alleles in the group	The allele G percentage in the group (%)	The amount of A alleles in the group	The allele A percentage in the group (%)
The control group N=220 (the total amount)	199	90,5	21	9,5
The myocardial infarction group N=190 (the total amount)	150*	79	40*	21

*- statistically significant difference between A and G alleles , $p<0,005$.

and by $\chi 2$ criteria with Yates correction. For this purpose, we built the four-fold contingency tables were in a such separate group we compared the genotype from the control group (health), genotype of myocardial infarction group, the carriers of other genotypes (not having this genotype) from the control group and myocardial infarction group respectively. In order to state the association between the alleles and myocardial infarction we compared the amount of A and G alleles in the control group and myocardial infarction group respectively. The statistical significance was estimated by $\chi 2$ criteria (Pearson criteria). The association was considered statistically significant under $p<0.05$.

RESULTS

The number of genotype G/G carriers in the control group made 89 individuals or 80.9% of all carriers of G/G, G/A, A/A genotypes that was 110 individuals. There were also 21 G/A carriers in the control group or 19.1 % of all genotypes carriers. The carriers of A/A genotype were not found among healthy individuals. In myocardial infarction group the genotype A/A was determined in eight individuals, which made 8.4% of all carriers of researched genotypes (the total amount is 95 individuals), the number of G/G genotype carriers made 63 individuals or 66.3%, there were also 24 carriers of G/A genotype that is 25.3% respectively (Table I).

In the control group, the amount of the alleles G was 199 which made 90.5 % of the total amount (220 alleles) in this group (G and A). The amount of the alleles A in the control group made 21 and 9.5 % respectively of the all the alleles in the group.

In the myocardial infarction group, the amount of the G alleles was statistically significantly less than in the control and made 150. The percentage of G alleles was also lower in comparison with the control and made 79 % of all the alleles in this group (the total amount is 190). On the contrary, the number of alleles A in myocardial infarction group was statistically significantly higher than in the control group and made 40 or 21% of all the alleles in this group respectively (Table II).

At the current stage of the study we wanted to know whether the myocardial infarction is due to or whether there is any connection between the risk of myocardial infarction and the genotype or/and the alleles of the examined patient. That is, whether nucleotide G substitution for A in the rs17216473 locus of the ALOX5AP gene can contribute to the myocardial infarction.

For this purpose, we studied the absence or presents of the statistically significant association between the genotypes G/G, A/G, A/A and the alleles A and G in polymorphic locus rs17216473 of ALOX5AP gene and myocardial infarction.

Table III. The association between G/G, G/A, A/A genotypes and myocardial infarction by Pearson criteria (χ2)

The genotype	With myocardial infarction (the number of individuals)	Without myocardial infarction (the number of individuals)	χ2 (The value of criteria/ p)	χ2 with Yates correction. (The value of criteria/ p)
G/G	63	89	5.663/0.018 (p<0,05)*	4.927/0.027 (p<0,05)*
Not G/G	32	21		
G/A	24	21	1.134/0.288 (p>0.05)	0.802/0.371 (p>0.05)
Not G/A	71	89		
A/A	8	0	9.639/ 0.002 (p<0.005)**	7.525/0.007 (p<0.05)
Not A/A	87	110		

*- statistically significant difference between G/G genotype and other ones (not G/G) , p<0,05.
**- statistically significant difference between A/A genotype and other ones (not A/A), p<0,05.

Table IV. The association between A and G alleles and myocardial infarction by Pearson criteria (χ2)

The allele	With myocardial infarction (the amount of alleles)	Without myocardial infarction (the amount of alleles)	χ2 (The value of criteria/ The level of significance)	χ2 with Yates correction. (The value of criteria/ The level of significance)
A	40	21	10.660/0.002 (p<0.005)*	9.770/ 0.002 (p<0.005)*
G	150	199		

*- statistically significant difference between A and G alleles , p<0,005.

The analyzing of the connection between G/G, G/A, A/A genotypes and myocardial infarction showed the presence of statistically significant association between A/A genotype and the myocardial infarction and, on the contrary, G/G genotype was established statistically significantly rarely in individuals with myocardial infarction than the other genotypes (A/G and A/A) (Table III).

As it is seen, two monozygous genotypes were shown to link to myocardial infarction wherein the connection with A/A was opposite to that with G/G. That is, A/A contribution to myocardium infarction was statistically significant and, on the contrary, G/G was statistically significantly associated with the absence of myocardial infarction (Table III).

Taking into consideration said above we checked the association between A and G alleles, and myocardium infarction. The statistically significant connection between A and G alleles and myocardium infarction was established, and as for the genotypes, the A allele contribution to myocardial infarction was opposite to that with G, namely, A was statistically significantly associated with myocardium infarction and G, vice-a-versa, was statistically significantly linked to the absence of it (Table IV).

DISCUSSION

Genotype G/G/ was the most widely distributed among our researched individuals. The total number of carriers of this genotype (from the control and myocardial infarction groups) was 152, 74 % of the total number of all researched persons (205). Genotype G/G also prevailed in the control (healthy), totaling 80.9 %. Its domination among the healthy people was larger than that in the total group (80.9% and 74 % respectively). Genotype G/G was also present in myocardial infarction group (63 individuals) at 66.3 % (Table I), but its percentage became lower in myocardium infarction group compared to the healthy group and total group. Therefore, it is necessary to clarify, whether G/G genotype contributes to the prevention of myocardial infarction or whether it is a good prognostic sign to avoid myocardial infarction. There is a statistically significant difference between G/G and other genotypes for myocardial infarction (Table III), namely, the absence of myocardial infarction. Thus, G/G genotype can be considered dependable prognostic marker that essentially decreases the risk of myocardial infarction onset (Table III).

When analyzing the myocardial infarction groups, one sees that G/G was also prevalent (66.3% against 25.3% for G/A, 8.4% for A/A respectively) (Table I). This fact can be explained by, first, this genotype`s great distribution in Ukrainian population, and second, that the SNP polymorphism of rs17216473 of ALOX5AP gene is not the only that contributes to myocardium infarction and other cardiovascular diseases onset. The other polymorphism (rs1722842) of haplotype B was shown to be sufficiently associated with ishemic heart disease [6]. David R. Crosslin and co-authores [12] showed a very high dependence between haplotype B and myocardial infarction in Europeans, but the most significant was the other polymorphism [3, 4] established the association between an increased risk of myocardial infarction in Icelandic population and haplotype A, which contains rs17222814, rs10507391, rs4769874 and rs9551963 polymorphisms. According to the data that was received by meta-analysis of Chinese population by Huang and co-authors [6] the rs17222814G, rs10507391T, rs4769874G, rs9551963A polymorphisms of haplotype A were linked to myocardial infarction. Thus, the carriers of the G/G genotype from the myocardial infarction group can also be carriers of other SNP of ALOX5P gene.

G/A genotype was not as widely distributed as G/G, having only consisted of 45 individuals and 22 % of all the researched. The genotype presence increased in myocardial infarction group (24 individuals and 25.3 % of all the researched) and decreased in the control one (21 individual and 19.1 % of all the researched) (Table I). However, its contribution to myocardial infarction onset is not essential; there was no statistically significant difference between G/A genotype and other genotypes (Table III).

A/A genotype`s distribution was significantly less than others, having made only eight individuals or 4 % of total researched individuals. All of the A/A carriers were in the myocardial infarction group (8.4 % of all events of myocardial infarction), and there were none of them in the control group (Table I). The association between A/A genotype and myocardial infarction showed a statistically significant difference between A/A genotype and other genotypes (Table III). Interestingly, all A/A caries were only found in the myocardial infarction group. This can be explained, on the one hand, by A/A genotype`s rare distribution and, on the other hand, by their absence among donors of blood. There were carriers of the other two genotypes among donors that is naturally occurring. Of course, we can`t make the conclusion that there are no healthy people of the corresponding age among the carriers of A/A genotype, but at the same time, A/A genotype can be a serious prognostic sign for the onset of myocardial infarction or/and other cardiovascular diseases. We believe that the association between A/A genotype and cardiovascular diseases is worthy of being studied further. We cannot exclude the possibility that this genotype by itself causes the onset of some cardiovascular diseases, in particular, myocardial infarction upon reaching a certain age.

Thus, two monozygous genotypes were found to play the opposite role in an onset of myocardium infarction, that is, G/G counteracts to this disease development and A/A controversially, contributes to it.

Therefore, a minor allele was assumed to play a key role in myocardial infarction onset and G allele was believed presumably to be as defensive factor. A allele was found almost twice as often in patients with myocardial infarction (40 cases) compared with healthy ones (21 cases), which makes 21% and 9,5% respectively. On the contrary, allele G was more common in healthy people (90.5%) of approximately the same age than in patients suffering from myocardial infarction (79%) (Table II). The statistically significant association between A and G alleles and myocardium infarction showed that G allele can be considered to be preventive factor for myocardium infarction and, conversely, minor A allele can be considered to be the risk factor (Table IV).

Thus, not only does the presence of A nucleotide instead of G in polymorphic locus increases the risk of myocardial infarction, but homozygosity for both alleles (that is for minor gomozygoous A/A). Such a risk for heterozygous G/A was not established because of the presence of the opponent allele (G). Therefore, when only analyzing the SNP without genotyping one gets both genotypes having polymorphic nucleotide A. Those are G/A and A/A wherein G/A genotype masks A nucleotide contribution.

David R. Crosslin and co-authors [12] established the same role of A allele in the risk of myocardial infarction for the other polymorphism of haplotype B in Europeans, wherein almost every test showed a significant association between myocardial infarction and A allele instead G allele in rs17222842.

The data on the role of rs17216473 polymorphism is few and contradictory; mostly they dispute the data we obtained. So, the absence of a statistically significant association between SNP rs17216473 ALOX5AP gene and myocardium infarction was shown by David R. Crosslin and co-authores [12]. Helgadottir, and co-authores (2005) [4] also did not establish the essential correlation between haplotype B and the risk of myocardial infarction in Scottish people but found such an association in a group of English people.

Haplotype B also did not correlate with myocardial infarction in some researches [7, 8] This study had been carried out on a large group within the Central European population) (Germany) [8].

However, in the most studies it was reported the said polymorphism contributed to ischemic heart disease. David R. Crosslin [12] showed the statistically significant association between the rs17216473 polymorphism of ALOX5AP gene and the early onset of ischemic heart disease. Linsel-Nitschke et al [10] confirmed the correlation between haploptype B and the increased risk of coronary artery disease in German patients. B haplotype is supposed to contribute to pathogenesis of coronary artery disease in Europeans [10].

Tsai and co-authors [11] established that the SG13S377 (rs17216473) polymorphism of B haplotype was greatly and statistically significantly associated with the risk of ischemic heart diseases. This connection was without reference to the other polymorphisms, age, sex and the level of cholesterin. On the contrary, Huang and co-authors [6] pointed at an absence of correlation between rs17216473 and ischemic heart disease having based on the meta-analysis of Chinese population. However, it is necessary to emphasize that Tsai and co-authors [11] examined the white Americans but Huang and co-authors [6] examined Chinese. It is quite clear that Ukrainians are genetically closer to white Americans than to Chinese.

The role of the rs17216473 polymorphism of the ALOX-5AP gene in the myocardial infarction development in the Ukrainian population has been studied for the first time, the association between genotype A/A, allele A and the risk of myocardial infarction onset in Ukrainian population has been shown for the first time. Moreover, in the course of this study, humans-homozygotes with the minor allele A (A/A) were identified in the Ukrainian population for the first time. All of them had suffered from myocardial infarction. In the control group (healthy at about the same age), humans-homozygotes with the minor allele A were not found.

Consequently, all carriers of A/A genotype are proposed to belong to the group with an essential risk of myocardial infarction onset in Ukrainian population wherein the carri-

ers of G/G genotype are considered to belong to the minor risk of this disease onset, the carriers of G/A genotype have the medium risk of myocardial infarction onset.

The data we received may in the future be of interest to preventive medicine, for example, minimizing aggressive factors such as smoking, stress, unhealthy diet for people-carriers monozygotes A / A of the specified polymorphism. On the other hand, the data from our study may be further used for professional selection in activities that involve excessive stress, such as in the Armed Forces or in the police.

Surely, SNP in locus rs17216473 of ALOX5AP can`t be the only polymorphism that contributes to cardiovascular diseases and myocardial infarction in particular. In the recent study, which had performed in the Chinese population, the LTA4-H rs2540487 genotype was associated with the risk of myocardial infarction in overdominant model, wherein no associations of ALOX-5AP rs10507391, LTA4-H rs2072512 or rs2540477 and myocardial infarction were observed [15]. Some polymorphyns of ALOX5 gene were shown to associate with the reduced risk of stroke, exactly the rs3740107 in the recessive model in a Chinese Han population [16] and the GG genotype of rs2029253 [17]. The carriers of C allele in rs730012 of *LTA4H* gene and the rs6538697 CC genotype of *LTA4H* gene had an increased risk of ischemic stroke [17].

Beyond all doubt, the SNPs` particication in cardiovascular diseases needs the further study.

CONCLUSIONS

1. The polymorphism rs17216473 (SG13S377) of gene encoding ALOX5AP has been established to be statistically significantly associated with the risk of myocardial infarction in Ukrainian population.
2. A/A genotype has been shown to contribute to myocardium infarction and on the contrary, G/G has been associated with the absence of it. G/A genotype has not been statistically significantly associated with myocardial infarction.
3. It has been established the statistically significant connection between the risk of myocardial infarction and the presence of allele A (minor allele) of said polymorphism. Allele G, vice-a-versa, has been statistically significantly linked to the absence of myocardial infarction.
4. All humans-homozygotes with the minor allele A (A/A) had suffered from myocardial infarction.

Summarizing our obtained results, we assume the carriers of G/G genotype to have a minimal risk of myocardial infarction onset, the carriers of G/A genotype to have a moderate risk and the carriers of A/A to have a great risk.

REFERENCES

1. Kaminsky F., Sokurenko L., Chaikovsky Yu. Status of rats myocardium under subchronic mercury exposure and its pharmacological correction. Curr Issues Pharm Med Sci. 2016; 29(4): 167-70.
2. Chen C., Jin Y., Lo I.L. et al. Complexity Change in Cardiovascular Disease. Int J Biol Sci. 2017; 13(10): 1320-1328. doi: 10.7150/ijbs.19462.
3. Helgadottir A., Manolescu A., Thorleifsson G. et al. The gene encoding 5-lipoxygenase activating protein confers risk of myocardial infarction and stroke. Nat. Genet. 2004; 36(3): 233-239.
4. Helgadottir A., Gretarsdottir S., Clair D. et al. Association between the gene encoding 5-lipoxygenase-activating protein and stroke replicated in a Scottish population. Am. J. Hum. Genet. 2005; 76(3): 505-509.
5. Lemaitre R.N., Rice K., Marciante K. et al. Variation in Eicosanoid Genes, Non-fatal Myocardial Infarction and Ischemic Stroke. Atherosclerosis. 2009; 204(2): 58-63.
6. Huang H., Zeng Z., Li J. et al. Variants of arachidonate 5-lipoxygenase-activating protein (ALOX5AP) gene and risk of coronary heart disease: A meta-analysis. Arch. Med. Res. 2010; 41(8): 634-641.
7. Zee R.Y., Cheng S., Hegener H.H. et al. Genetic variants of arachidonate 5-lipoxygenase-activating protein, and risk of incident myocardial infarction and ischemic stroke: anested case-control approach. Stroke. 2006; 37(8): 2007-2011.
8. Koch W., Hoppmann P., Mueller J.C. et al. No association of polymorphisms in the gene encoding 5-lipoxygenase-activating protein and myocardial infarction in a large central European population. Genet. Med. 2007; 9(2): 123-129.
9. Burdon K.P., Rudock M.E., Lehtinen A.B. et al. Human Lipoxygenase Pathway Gene Variation and Association with Markers of Subclinical Atherosclerosis in the Diabetes Heart Study. Mediators Inflamm. 2010; 201(17): 153-162.
10. Linsel-Nitschke P., Gotz A., Medack A. et al. Genetic variation in the arachidonate 5-lipoxygenase-activating protein (ALOX5AP) is associated with myocardial infarction in the German population. Clin. Sci. (Lond). 2008; 115(10): 309-315.
11. Tsai A.K., Li N., Hanson N.Q. et al. Associations of genetic polymorphisms of arachidonate 5-lipoxygenase-activating protein with risk of coronary artery disease in a European-American population. Atherosclerosis. 2009; 207(2): 487-491.
12. Crosslin D.R., Shah S.H., Nelson S.C. et al. Genetic effects in the leukotriene biosynthesis pathway and association with atherosclerosis. Hum. Genet. 2009; 125(2): 217-229.
13. Kostulas K., Gretarsdottir S., Kostulas V. et al. PDE4D and ALOX5AP genetic variants and risk for Ischemic Cerebrovascular Disease in Sweden. J. Neurol. Sci. 2007; 263(1-2): 113-117.
14. Assimes T.L., Knowless J.W., Priest J.R. et al. Common polymorphisms of ALOX5 and ALOX5AP and risk of coronary artery disease. Hum. Genet. 2008; 123(4): 399-408.
15. Li Y., Xu X., Zhang D. et al. Genetic variation in the leukotriene pathway is associated with myocardial infarction in the Chinese population. Lipids in Health and Disease, 2019; 18(1): 25. doi: 10.1186/s12944-019-0968-9.
16. He J., Sun S., Zhang M. et al. Association analysis of ALOX5 gene polymorphisms with stroke risk: a case-control study in a Chinese Han population. International journal of clinical and experimental pathology. 2016; 9(4): 4432-4437. www.ijcep.com /ISSN:1936-2625/IJCEP0022558
17. Wang G.N., Jin-Song Z., Cao W.J. et al. Association of ALOX5, TA4H and LTC4S gene polymorphisms with ischemic stroke risk in a cohort of Chinese in east China. World J Emerg Med. 2013; 4(1): 32–37. doi: 10.5847/wjem.j.issn.1920-8642.2013.01.006

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