

RELATIVE FEATURES OF THE PPARA (rs4253778), PPARGC1A(rs8192678) AND PPARG2(rs1801282) POLYMORPHISMS GENES IN ATHLETES ENGAGED IN CYCLIC TYPES OF SPORTS

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Abstract: *In this work, polymorphism of the PPAR gene have been tested in athletes involved in cyclical sports.*

Keywords: *PPARA, PPARGC1A, genetic polymorphism, cyclical sports.*

Introduction: Genes activated by peroxide proliferators (PPAR), which belong to the nuclear receptor family, are known to participate in the formation of proteins that have the property to bind specifically to the PPAR-sensitive elements of fat and carbohydrate metabolism gene promoters and to regulate their transcription [1]. To date, 3 types of these transcription proteins of PPAR family are known: PPAR α , PPAR γ and PPAR δ . These proteins, being transcription factors, control the expression of several dozens of genes, participating in fat and carbohydrate metabolism. At the same time, saturated and unsaturated long-chain fatty acids (LC), their derivatives, synthetic drugs (fibrates, thiazolidines), leukotriene, etc. can act as ligands. These genes are expressed in tissues where increased catabolism of fats occurs, particularly in slow muscle fibers, liver, heart and brown adipose tissue. According to O.Braissant and co-author. [11], the PPARA gene is expressed 7 times more in muscles than in adipose tissue.

According to P.Lefebvre and co-author. [21], the main purpose of PPAR α protein is to regulate lipid, glucose and energy homeostasis metabolism, body weight and inflammatory process by controlling the expression of genes involved in paroxysmal and mitochondrial oxidation, fatty acid transport, lipoprotein synthesis, triglyceride catabolism and metabolism of inflammatory factors. Fatty acids (FA) are one of the main energy substrates and are therefore important during exercise. Under aerobic exercise, there is an increase in the expression of the PPARA gene, as well as the cascade of subordinate genes, and there is an increase in LC utilization, which eventually increases the oxidizing potential of skeletal muscles [17]. D.K. Krämer D.K. study and co-author. [20], indicates an increased expression of the PPARA gene in the skeletal muscles of elite cyclists over long distances in comparison with the control group. Similar results were obtained in children engaged in synchronized swimming, cycling, diving, and boxing compared with the control group [8]. In conditions of low expression of PPARA gene there is a decrease in intensity of β -oxidation of LC and metabolism of tissues switches to glycolytic method of energy production, and, on the contrary, in conditions of over-expression of this gene there is a significant decrease in carbohydrate utilization and intensification of LC oxidation [14]. At the same time in myocardium under experimental conditions both reduction and increase of expression of PPARA gene causes its hypertrophy and cardiomyopathy [25].

The researchers have proved that the G allele of the PPARA gene is associated with the predominance of slow muscle fibers in physically active men [10], high rates of muscle endurance in children [2], and oxygen pulse (ratio of MPC to PM) in rowing academics [4], physical performance (according to PWC 170) in women engaged in fitness [7], the best muscle relief (due to low subcutaneous fat content) in the competitive period in bodybuilders and women engaged in fitness [3]. At the same time, the allele of PPARA gene is associated with the risk of myocardial hypertrophy of the left ventricle [4], which is associated with a decrease in LC oxidation and increased glucose utilization in myocardium due to reduced expression of PPARA gene.

Thus, the PPARAG allele can be considered as a genetic endurance marker. At the same time, the importance of increasing the expression of their alleles in different sports is ambiguous, which dictates the need to conduct research in this direction.

In the present work we have studied the distribution frequency of allele-genotype variants G2528C (rs4253778), C34G (rs1801282) and G> A (GLY482SER) (rs8192678) of PPAR gene polymorphisms in representatives of cyclic sport.

Research materials and methods.

The research was conducted on the basis of a sample of sportsmen in 2018. The number of sportsmen was 60 people at the age of 18-30 years. Among them there were 20 athletes rowing and canoeing, 20 athletics athletes and 20 cyclists. When selecting specific persons, their national affiliation was not taken into account. Biological material for DNA isolation was taken in accordance with established human rights procedures, which were carried out with the written consent of the subjects [6].

Blood samples of athletes of different specializations and qualifications were collected on the basis of sports federations of Uzbekistan: athletics, cycling, rowing and canoeing. Venous blood in the amount of 1.5 ml was taken in 3 ml of EDTA solution (ethylenediamine tetra acetic acid) and stored at temperature -20°C.

DNA was isolated from whole blood on Ribo-prep kit (production of the kit was Interlabservice Company, Russia).

Detections of ACE gene polymorphism were determined by Real-Time PCR method (the kit was manufactured by NPF "LITECH" Ltd., Moscow, Russia).

For real-time PCR amplification, GeneAmp® PCR - ABI 7500 Fast Real-Time PCR with 96 cell block was used. The real-time amplification program included 100 sec pre-denaturation at 95 °C once, at 95 °C - 15 sec and at 64 °C - 40 sec included 45 repetitions. FAM and JOE detectors were introduced into the program. The obtained results were documented in the form of curve growth on two FAM and JOE detectors in graphic mode on the corresponding program (Fig.1).

Received results and discussion.

The results of the analysis of the distribution frequencies of allelegenotype variants of G2528C (rs4253778) of PPARA gene polymorphism in athletes, regardless of the sports studied, are presented in Fig. 2A. As it is seen from the presented data, among the examined sportsmen, the carriers of G/G genotype made 75,0%, and of G/C genotype - 21,7%. At the same time, among them the specific weight of carriers of C/C genotype of PPARA gene was only 3.3%. Therefore, the results of the study show that the polymorphism of G2528C(rs4253778) PPARA gene in athletes is distributed as follows: allele G and genotype G/G, responsible for endurance, prevail in the examined athletes compared to allele C and genotype C / C, possibly responsible for strength and speed. And heterozygous G/C genotype takes place in every fifth athlete (Fig.2A).

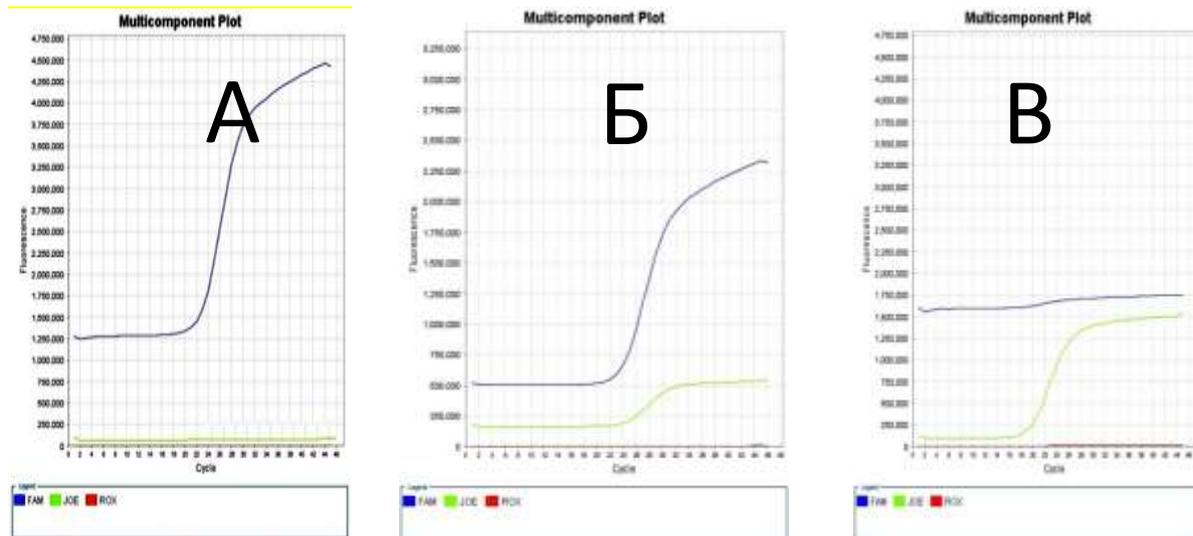


Figure 1: Real-time PCR results of the PPARA gene: A- homozygous genotype G/G; B- heterozygous genotype G/C and B- homozygous genotype C/C.

Analysis of the distribution frequencies of allele-genotype variant of another G>A(GLY482SER) (rs8192678) polymorphism of PPARGC1A gene, as shown in Fig. 2B, shows that G allele and G/G genotype of GLY482 PPARA occurred in almost half of the examined athletes. A similar pattern also occurred in relation to the heterozygous G/A genotype. At the same time, the allele and G/A genotype of this gene only occurred in every twentieth athlete. Therefore, both polymorphisms of the studied gene among the examined athletes are mainly represented by the G allele variant responsible for endurance.

Analysis of the distribution frequencies of C34G2(rs1801282) genotypes of PPAR gene polymorphism also shows that the SS genotype responsible for lipid oxidation and muscle endurance takes place in the overwhelming majority of athletes, regardless of their sport (Fig.2B). And CG heterozygous genotype of the studied gene is found in every fifth sportsman. At the same time, GG genotype was found in single sportsmen.

As described above, the G allele of the PPARA gene is associated with the prevalence of slow muscle fibers, high muscle endurance and the ratio of IGC (maximum oxygen consumption) to HP, as well as low risk of obesity [2, 5, 7, 10]. Consequently, most of the athletes surveyed have a genetically determined endurance. It can be assumed that these athletes can perform better at short distances. In fact, the study conducted by group N. Eynon and co-author. [12], Israeli athletes showed that the GG frequency of the genotype PPARA gene was higher among packers than among sprinters. However, it cannot be considered a definitive prediction that most of the athletes surveyed could perform better at short distances. As mentioned above, transcription factors regulate the expression of several dozens of PPARA genes, increasing the activity of some and suppressing others. Therefore, it is necessary to evaluate their activity (their methylation) - epigenetic status of an athlete [9]. This would allow, if an athlete is carrying a certain allele of a sports gene, to predict his sports results to some extent.

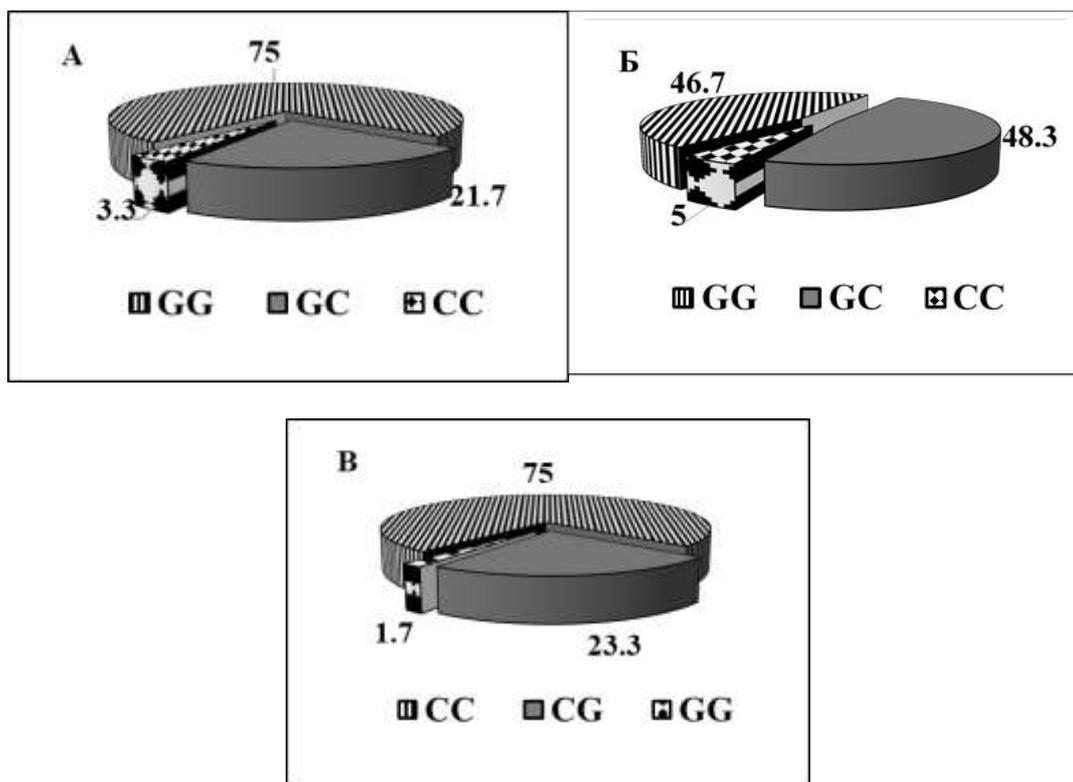


Fig.2. Distribution of genotypes G2528C (rs4253778) (A), G> A(GLY482SER) (rs8192678) (B) and C34G(rs1801282) (B) of the PPAR gene among athletes regardless of the sport (in %).

The results of these studies show that the frequency of heterozygous genotypes of the studied polymorphisms of the PPARA gene is also noticeable. The study was conducted by D.M.Flavell and co-author. [15, 16], suggests that replacement of the nucleotide G with C in position 2528 of the PPARA gene is accompanied by a decrease in gene expression and leads to a disturbance of lipid and carbohydrate metabolism regulation. Moreover, the study of carriers of this genotype among patients and healthy people shows that carriers of PPARA allele C have a relatively high risk of atherosclerosis, type 2 diabetes mellitus and coronary heart disease [15, 16]. At the same time, the study conducted by Y. Jamshidi and co-author. [19] testifies that the weight gain of the left ventricle is 2 times higher in G/C genotype carriers and 3 times higher in C/C genotype carriers than in G/G genotype carriers. Therefore, if we take into account that myocardial hypertrophy is caused by a decrease in the expression of the PPARA gene and a decrease in the LC oxidation, it is quite likely that the hypertrophic C allele effect is associated with a decrease in the LC myocardium and increased use of glucose for its energy needs.

According to E.Rosen and B.Spiegelman [27], PPARG gene localized in 3 chromosomes (3p25), as a result of alternative splicing may have 4 transcripts, which differ in 5'-ends with different number of nontransmitted exons: PPAR γ 1, PPAR γ 2, PPAR γ 3 and PPAR γ 4. In this case, if the isoform PPAR γ 1 is found in most tissues, PPAR γ 2 is specific for fat tissue [28]. In the opinion of R.K.Semple and co-author. [29], this transcription factor is involved in the regulation of genes associated with the synthesis of triglycerides, differentiation of fat cells and myoblasts, tissue sensitivity to insulin, and growth regulation.

To date, it is considered that the most studied polymorphism of the PPARG gene is Pro12Ala polymorphism (rs1801282 C/G), which is a replacement of nucleotide C by G in the 34 exon position B, which leads to the replacement of proline with alanine in the amino acid position 12 of the isoform protein PPAR γ 2.

The study of the relationship between Pro12Ala polymorphism of the PPARG gene and the cross-sectional area of muscle fibers shows that in active men the presence of this allele was associated with a larger cross-sectional area of slow muscle fibers [30], with high values of the athletes' body mass index and maximum arbitrary force and its increase in response to physical activity of force [31]. Therefore, our results show that among the studied athletes the specific weight of those whose muscle endurance due to intensification of fat oxidation is of high priority. However, there are a certain number of athletes who may have strength qualities. However, their specific weight is noticeably less than athletes with potential endurance. Учитывая, что изучаемые нами виды спорта отличаются по потребностям силовым, скоростным качествам и выносливости. В связи с этим нами было изучено частот распределения аллельно-генотипных вариантов изучаемых полиморфизмов гена PPARA. Результаты этого анализа представлены в рисунке 3 А, Б и В.

As can be seen from the presented data, the specific weight of G/G carriers of the genotype PPARA (G2528C (rs4253778)) is 65.0%. At the same time, the specific weight of such athletes and cyclists reaches 80.0%. Consequently, the prevalence of slow muscle fibers and high levels of muscle endurance with fat catabolism are more common among cyclists and athletes than among rowers. Indeed, a study by D.K.Krämer and co-author. [20] conducted in elite long-distance cyclists shows a high expression of the PPARA gene in skeletal muscles compared to the control group. A study conducted in children engaged in synchronized swimming, cycling, diving, and boxing also showed similar results [8].

The specific gravity of heterozygous G/C genotype PPARA, although almost comparable in the studied sports, was slightly higher among rowers and athletes compared to athletes and cyclists (Fig.3A). The lowest specific gravity occurred in relation to the C/C genotype of the studied PPARA polymorphism. While this genotype was practically not found among the studied athletes and cyclists, 10% of the oarsmen had this genotype. This difference in frequency of occurrence of this genotype PPARA is probably due to the fact that athletes differ in the chosen distance, requiring mainly the manifestation of endurance or the manifestation of mixed qualities (endurance and speed-force). Indeed, according to I.I. Akhmetov and co-authors. [1, 10], in the group of sportsmen engaged in sports with preferential manifestation of endurance the frequency C allele of PPARA gene is significantly lower and significantly higher in the group of sportsmen engaged in sports with manifestation of mixed qualities of variable power. The differences in the frequency of this allele we have identified may be due to the sports qualification of the athletes we have examined. This assumption is supported by the data obtained when estimating the distribution of allele frequencies depending on the sports qualification: the C allele frequency of the PPARA gene decreases with the growth of sportsmen's qualification with the preferential manifestation of endurance from 13,4% for a candidate master of sports to 3,3% for a master of sports of international class and a honored master of sports.

The analysis of frequency distribution of allelegenotype variants of other G>A(GLY482SER) (rs8192678) polymorphism of PPARGC1A gene shows almost identical tendency, as in the analysis of G>A(GLY482SER) (rs8192678) polymorphism of PPARGC1A gene (Fig.3B), with some quantitative differences. At the same time, the frequency of G/G genotype occurrence from 40% in rowers to 55% in cyclists increases. On the contrary, the frequency of heterozygous G/A genotype decreases from 60% in rowers to 40% in cyclists. In addition, if athletes and cyclists C / C genotype of the gene PPARA (G2528C (rs4253778)) almost never met, the A/A genotype of the gene PPARGC1A (rs8192678) among these athletes is found with a frequency of 10 and 5%. In general, in terms of average specific weight, this practical genotype does not differ from that of the PPARA gene (G2528C (rs4253778)). (Fig.3A,B).

As can be seen from the data presented in Fig.3B, in contrast to the above mentioned polymorphisms, the analysis of the results of studies of C34G2(rs1801282) polymorphism of the PPARG2 gene shows that the highest frequency of occurrence of CC of genotype, which is also responsible for increased metabolism of fats and its associated muscle endurance, is observed among athletes (85%). And athletes of cyclists and oarsmen share is slightly inferior to athletes (Fig.3B).

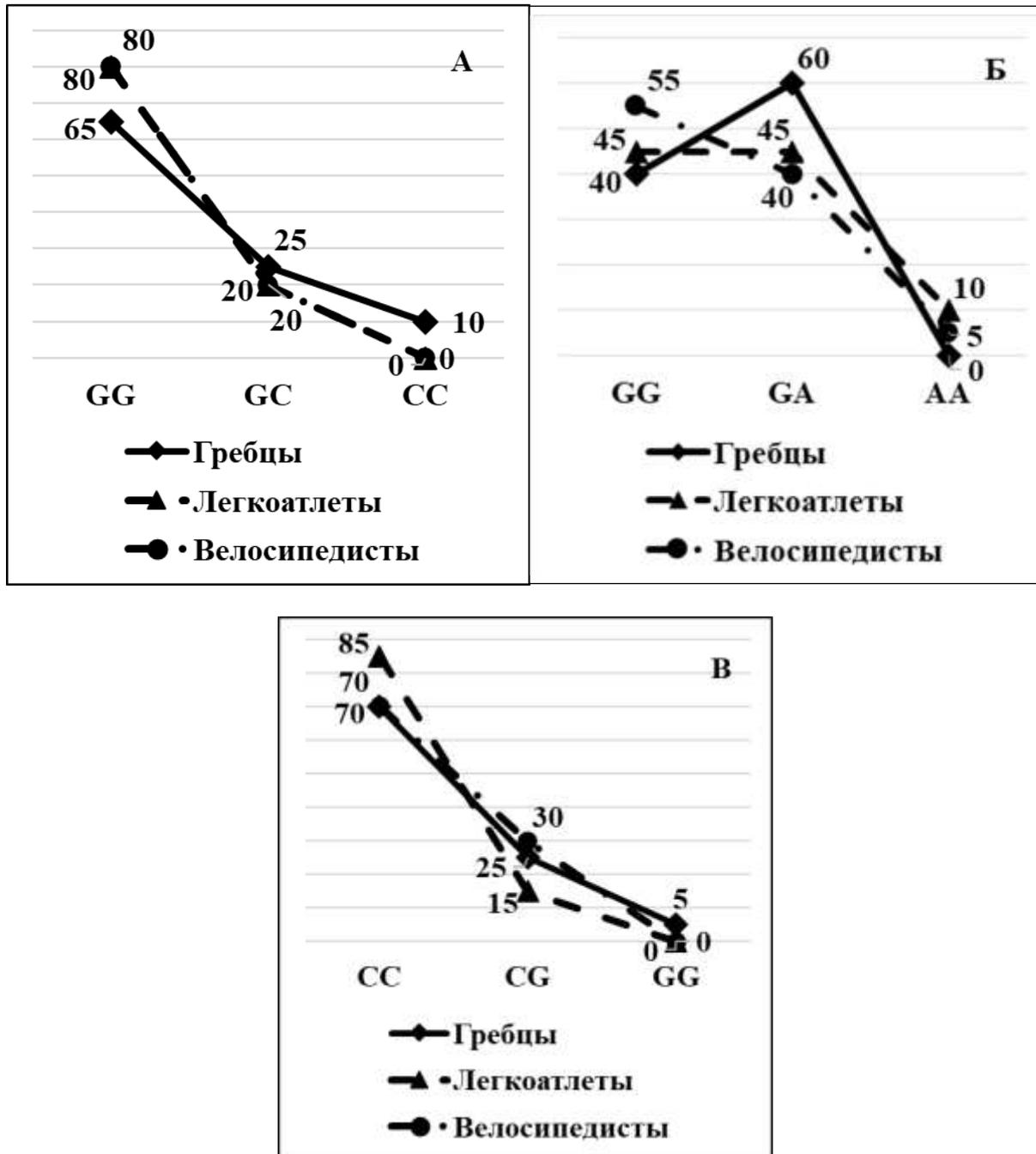


Fig.3. Distribution of genotypes G2528C (rs4253778) (A), G> A(GLY482SER) (rs8192678) (B) and C34G2(rs1801282) (B) of the PPAR gene among rowers, athletes and cyclists (in %).

At the same time, the frequency of occurrence of CV heterozygous genotype of the studied gene was the lowest among athletes, unlike cyclists and rowers. Therefore, the distribution of allelegenotype variants of the studied polymorphism of the studied genes

family testifies to the uneven distribution among the examined sportsmen of cyclists, athletes and rowers. The most endurance proved to be among athletes of track and field athletes and relatively less among cyclists and rowers.

According to B.N.Finck and D.P.Kelly, [14] gene PPARGC1A is expressed mainly in slow muscle fibers of skeletal muscles, myocardium, brown fat, kidneys and to a lesser extent in liver, pancreas and brain. The expression of this gene is regulated by proteins from different signaling pathways such as CAMKIV, CREB, AMPK, p38 MAPK, calcineurin A, EBox binding proteins, GATA, MEF2, NF- κ B, NRs, NRF-1, FOXO1, p53, SRE and can also be supported by its own expression product and nitrogen oxide [1]. It should be noted that gene PPARGC1A along with PPARA is involved in metabolism switching in myocardium from carbohydrate to fat immediately after birth. However, the increased expression of this gene, as shown by the results of a study by J.J. PPARGC1A. Lehman and co-author. [22], may lead to uncontrolled proliferation of mitochondria in cardiomyocytes and disturbance of sarcomer structure in them with cardiomyopathy development. The results of our studies show that the G/G genotype of the PPARGC1A gene is found in about half of the sportsmen examined and the possibility of its overexpression is practically eliminated.

Gly482Ser polymorphism is important among the detected variations in the PPARGC1A gene. It consists in replacing the G nucleotide with A at 1444 position of the 8th exon. In the opinion of C. Ling and co-authors. [23], the 482Ser allele of the PPARGC1A gene is associated with a decrease in oxidation processes and mitochondrial biogenesis in cells due to a decrease in the expression of this gene. Indeed, the Gly482 allele of the PPARGC1A gene was found to be associated with high MPC indices and high physical performance, while the frequency of the other 482Ser allele was significantly lower in these sportsmen in comparison with the control group [24]. The role of 482Ser allele of PPARGC1A gene in suppression of development and manifestation of endurance is testified by the results of N studies. Stefan and et al. [26], that the carriers of PPARGC1A 482Ser allele revealed a low increase in aerobic performance in comparison with homozygotes of Gly482 allele on the background of endurance training.

Thus, the results of the conducted researches show that among sportsmen engaged in the studied sports the specific weight of carriers of G/G genotype is rather high, both polymorphism of G2528C (rs4253778) of PPARA gene and polymorphism of GLY482 of PPARGC1A gene. Consequently, among athletes, cyclists and oarsmen, the frequency of athletes whose muscle endurance and utilization of LC is genetically determined is quite high. At the same time, sports success requires the presence of certain alleles and genotypes of this gene in the athlete based on the sport and its specific requirements for physical qualities. Indeed, the highest carrying among the studied sports of G/G genotype of the studied polymorphisms of PPARA gene was among the sportsmen of bicyclists and athletes.

The obtained data are a kind of help in assessing physical abilities and prospects of athletes' sports success in the studied sports. Moreover, it points to the necessity to take into account the received genetic determinants when planning and forming individual training programs at the pre-competition stages of their preparation.

Conclusions:

1. Among athletes involved in cycling, athletics and rowing the highest proportion of G/G genotype carriers and GLY482 polymorphisms of PPARGC1A gene.
2. The distribution frequency of G and G/G allele genotype G2528C (rs4253778) polymorphisms of the PPARA gene is the highest among cyclists and athletes compared to rowers.

3. G/G and G/A genotypes GLY482 of the polymorphisms of the PPARA gene and CC genotype C34G PPARG2 are almost equally distributed among cyclists, athletes and rowers.

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