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Review

Genetic Biomarkers of Cardiovascular and Cerebrovascular Reserves in Athletes

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Abstract: As the practice of modern elite sports shows, the functional capabilities of the athlete's body have almost reached their limit. Further increase in the volume and intensity of physical activity is associated with the risk of desadaptative changes in the athlete's body. It is known that in endurance sports, the cardiovascular system is the main limiting factor in achieving a high athletic result. In this regard, a promising approach is to search for molecular genetic markers associated with high functional reserve of the cardiovascular system of athletes. A personalized approach in sports practice is an effective tool for sports selection, development of personalized training programs to optimize the health status and achieve high performance of an athlete, as well as for the prevention of sports traumatism. (1) Background: to conduct a systematic review of the studies of candidate genes and their single-nucleotide variants (SNVs) associated with the functioning of the cardiovascular system in cyclical sports athletes.(2) Methods: A search for publications between 2000 - 2021 in the databases SCOPUS, Web of Science, Google Scholar, PubMed, e-LIBRARY, using the key words and their combinations; (3) Conclusions: the Identification of genetic markers (SNVs and polymorphisms of the *ACE, BDKRB2, CMA1B, NOS3* and *VEGFA* genes) associated with the functional reserve of the cardiovascular system, can help cardiologists, sports physicians and trainers in developing personalized strategies for the selection of children / teenagers and the choice of sports specializations. Such a personalized approach will increase sports performance and reduce the risk of overtraining and failure to adapt during a difficult competitive period.

Keywords: *sports genetics; candidate genes; single nucleotide variant; polymorphism; cardiovascular system; athletes.*

Introduction

Modern sports are characterized by a constant increase in the share of competitive period in the training cycle. This places high demands on the functional, physical, and psychological capabilities of an athlete [1]. The issues of managing the training process (sports selection and choice of sports specialization) are becoming relevant, allowing athletes to achieve high results without compromising their health. It is generally recognized that the basis of modern sports training should be the principle of adequacy of the training load to the functional state of the athlete. In this regard, in recent years, the world scientific community has been actively working to identify biomarkers and their role in the physiological processes of the human cardiovascular system, which can be considered as personalized predictors of high athletic performance [2]. Sports are primarily associated with

hemodynamic and structural changes in the myocardium and coronary vessels. Positive adaptation of the myocardium and coronary vessels is externally expressed in clinical, electrocardiographic and echocardiographic changes that form "athlete's heart" [3]. Myocardial hypertrophy is an adaptive response to physical activity of a certain orientation. Sports with a speed-power bias cause pressure overload, endurance exercise causes volume overload. Figure 1 shows a diagram of the formation of myocardial hypertrophy in athletes training for endurance. In response to overload, cardiomyocytes mechanically stretch and activate intracellular hypertrophic signaling pathways to increase the synthesis of various proteins, such as structural and contractile proteins. These hypertrophic reactions increase the myocardial oxygen demand and promote angiogenesis in the myocardium to eliminate the negative effects of hypoxia and maintain the contractile function of the heart [4].

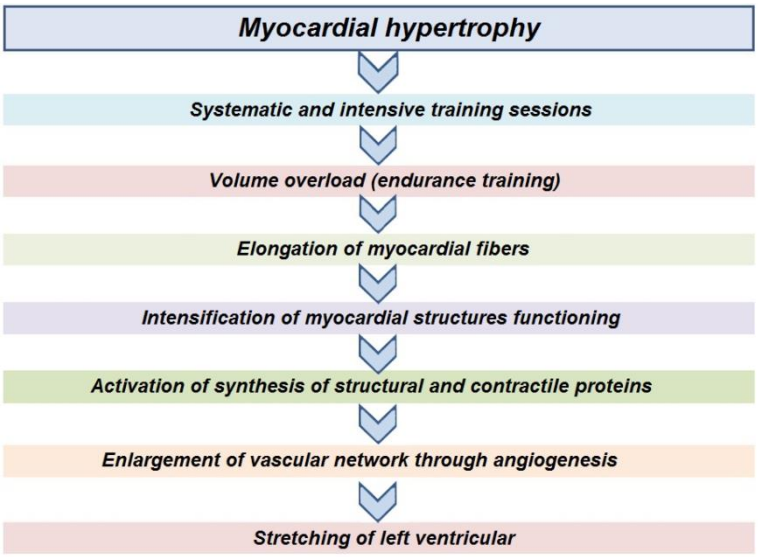

Figure 1. Mechanisms of physiological myocardial hypertrophy in athletes training for endurance.

Training and competitive activity in elite sport places extremely high demands on the athlete's body functional reserves mobilization. In endurance sports, increasing the size of the heart is fundamental to the ability to generate a large shock volume. Therefore, the cardiovascular system is the main limiting factor in achieving high athletic performance in athletes (endurance training). The discrepancy between the training effects and the functional reserves of the cardiovascular system can lead to desadaptative changes (**Figure 2**).

A decrease in plastic, energy processes and contractile function in the myocardium leads to the development of pathological myocardial hypertrophy and, as a consequence, hypertrophic cardiomyopathy (HCM). The prevalence of pathological myocardial hypertrophy among Olympic-level athletes is extremely rare. Structural and functional changes associated with HCM naturally weed out most people at earlier stages of training [5]. However, HCM is the main cause of sudden cardiac death in young athletes (aged 17 and younger) worldwide [6].

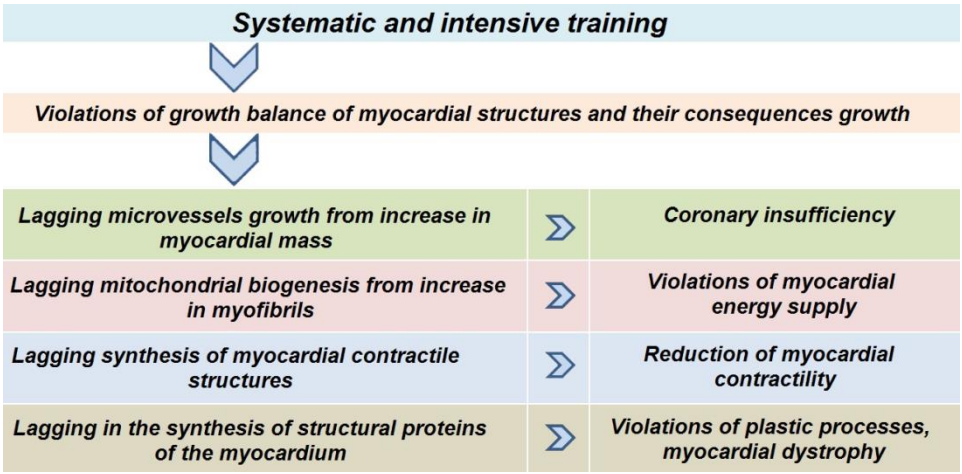

Figure 2. Mechanisms of pathological myocardial hypertrophy in athletes.

In recent years, the understanding of molecular processes and intercellular interactions coordinating the process of myocardial hypertrophy has significantly expanded. Despite this, it is still unclear how cardiomyocytes, endothelial cells, fibroblasts and smooth muscle cells coordinate myocardial hypertrophy and angiogenesis in response to physical exertion of different orientation (endurance or speed / strength) at the cellular level. Adaptive adjustments are largely due to genetic factors that affect not only the absolute physical performance of an athlete, but also cardiovascular reactions in response to physical exertion during a busy competitive period [2].

In this regard, one of the priority directions of sports genetics development is the search for candidate genes associated with high functional reserves of the cardiovascular system, which will ensure positive adaptation to stress and high athletic performance. Also an important area of sports genetics is the study of genetic predictors that make it possible to identify athletes at risk, with a high probability of adaptation processes disruption during doing professional sports. A personalized approach to the selection of critical values for the duration and intensity of training loads and the translation of the fundamental research results into the training process will preserve athletes' health and increase their athletic performance.

The aim is to conduct a systematic review of studies SNVs / on the polymorphisms of the candidate genes associated with the regulation of the functional state of the cardiovascular system in cyclical sports athletes.

Objective

To conduct a systematic review of the studies of candidate genes and their single-nucleotide variants (SNVs) associated with the functioning of the cardiovascular system in cyclical sports athletes.

Materials and Methods

The search strategies:

- We used keywords and their combinations: "sports genetics"; "candidate genes"; "single nucleotide variant"; "polymorphism"; "cardiovascular system"; "athletes" for the search full-text articles in SCOPUS, Web of Science, Google Scholar, PubMed, e-LIBRARY databases.

The inclusion criteria were:

- of open observational associative genetic case-control studies, genome-wide studies, Cochrane reviews;
- research works conducted between 2000 and 2021;
- the studied contingent included athletes of cyclic sports (track-and field (running disciplines), speed skating, swimming, rowing, cycling);
- athletes aged from 18 and older.

The exclusion criteria were duplicates; grey literature; abstracts or posters, preprints, conference materials, articles published earlier than 2000, research works in which the contingent is not athletes or athletes of other sports (not cyclical).

Only articles published in English and Russian and in peer-reviewed journals were extracted.

The systematic review was carried out according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA 2020). A flow chart is provided in (**Figure 3**).

Literature Search Process. After excluding duplicate results, the search retrieved 999 articles. From these research works, 849 were excluded because they did not correspond to the research topic or they did not have data of interest. A total of 105 full-text articles were evaluated for compliance with the requirements. After a full evaluation of the article, 49 articles were excluded because the contingent of the subjects did not meet the requirements (not athletes, did not match by sports, by age) or the studied single nucleotide variant (SNV)/polymorphisms were not associated with the functional reserve of the cardiovascular system (**Figure 3**). Thus, the final analysis included research work involving 4124 athletes and 23598 participants of the control group.

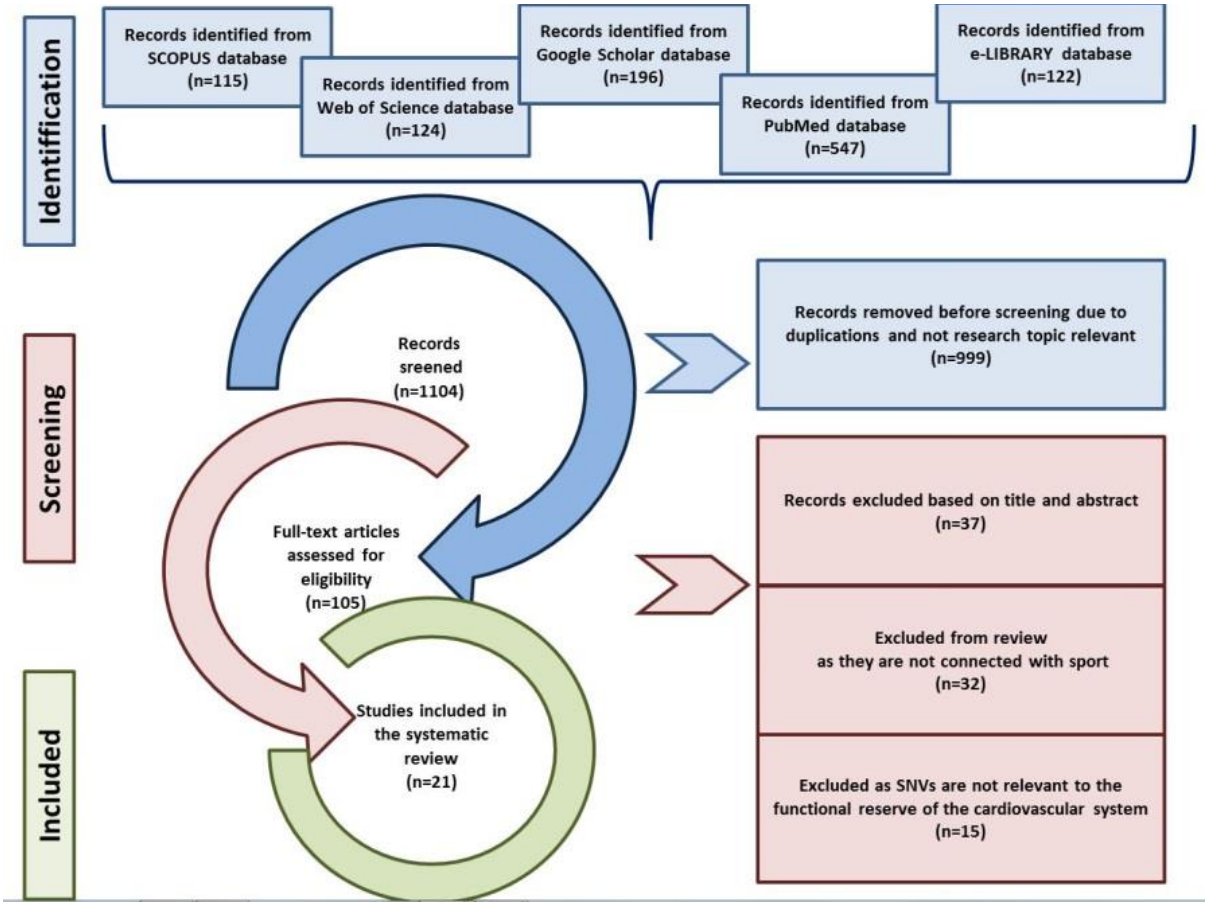

Figure 3. Flow diagram of the selection of articles referring to genes related to athletes' cardiovascular system reserves.

Study Characteristics. For all studies, we extracted the following data from original publications: first author and year of publication; distribution of genotypes for each ONV / polymorphism among athletes and controls, characteristics of the study design and the study population (numbers of athletes and controls, sport disciplines and host ethnicity). **Table 1** describes the major characteristics of included studies.

Table 1. Characteristics of the included studies.

Authors	Country/ Ethnicity	Groups (n)	Age (years) (M ± SD)	Sport type	Specialization
Tsianos G., et al., 2005	Caucasians	CG =100 EG =35	25.4±4.7	Swimming	Short, medium and long distances
Costa A.M., et al., 2013	Portugal	CG =100 EG =71	NR	Swimming	Short and middle distance
Silva H.H., et al., 2020	Portugal	CG =244 EG =250	NR	Different sports	Short, medium and long distances
Puthucheary Z., et al., 2011	America	CG =80 EG =42	NR	Swimming, triathlon	Short and long distances
Gunel T. et al., 2014	Turkey	CG =37 EG =37	21.1±3.1	Different sports	NR
Papadimitriou I.D. et al., 2016	Caucasians	CG = NR EG =255	NR	Cross - country athletics disciplines	Short, medium and long distances
	African lineage	CG = NR EG =91	NR		
Nazarov I.B. et al., 2001	Russia	CG = 449 EG =217	NR	Swimming, cross-country skiing, athletics	Short, medium and long distances
Rankinen T., et al., 2000	Canada, Germany, Finland, and the United States	CG = 189 EG =192	NR	Different sports	Short, medium and long distances
Tobina T., et al., 2010	Japan	CG = 335 EG =38	NR	Cross - country athletics disciplines	Long distances
Shenoy S., 2010	India	CG = 101 EG =29	20 - 25 years old	Triathlon	Long distances
Williams A.G., et al., 2004	Great Britain	CG = 115 EG =191	NR	Cross - country athletics disciplines	Short, medium and long distances
Silva H.H. et al., 2021	Portugal	CG =244 EG =250	NR	Different sports	Short, medium and long distances
Dautova A.Z., et al. 2015	Russia	CG = 43 EG =25	20.6±2.4	Cyclical sports	NR
Eynon N., et al., 2011	Israel	CG = 240 EG =155	35.9 + 12.2	Cross - country athletics disciplines	Short, medium and long distances
Grenda A., et al., 2014	Poland	CG = 230 EG =157	20.31 ± 2.67	Swimming	Short, medium and long distances
Williams A.G., et al., 2004	Great Britain	CG = 115 EG =191	NR	Cross - country athletics disciplines	Short, medium and long distances
Saunders C.J., et al., 2006	African lineage	CG = 203 EG =701	31.1±9.0	Triathlon	Fast Triath, Mid Triath, Slow Triath

Dawson E.A., et al., 2021	Great Britain	EG =40	21.0 ± 2.0	Healthy young male	Endurance / strength
Saunders C.J., et al., 2006	African lineage	CG = 203 EG =701	31.1±9.0	Triathlon	Fast Triath, Mid Triath, Slow Triath
Ahmetov I.I., et al., 2009	Russia	CG = 21132 EG =1423	24.4 ± 0.3	Different sports	Short, medium and long distances
Vinnichuck J.D. et al., 2000	Ukraine	EG =175	NR	Different sports	aerobic training / anaerobic training / mixed training

Abbreviations: N, number; M, mean; SD, standard deviation; CG, control group; EG, experimental group; F, female; M, male; NR, not reported.

After a detailed assessment, 21 full-text studies were identified on the relationship of SNVs / polymorphisms and functional reserves of the cardiovascular system of athletes.

Results

Our systematic review of associative genetic studies of the candidate genes encoding structural proteins and enzymes involved in the regulation of the functional state of the cardiovascular system has shown that the interest of researchers in sports genetics has been increasing in recent years. The most studied are five candidate genes (**Table 2**). The level of expression of these genes differs in skeletal muscles and myocardium (**Table 3**), which is probably important to take into account when translating the results of the genetic research into real sports practice.

Table 2. Candidate genes and their encoded proteins or enzymes involved in the regulation of the functional state of cardiovascular system in humans (adapted from [7]).

Gene	Location, chromosome	Protein / enzyme	Effect on functional state of the cardiovascular system
ACE	17q23.3 (26 exons)	Angiotensin I Converting Enzyme (ACE)	ACE plays a key role in the homeostasis of blood circulation, participates in the regulation of blood pressure and electrolyte balance.
CMA1	14q12 (5 exons)	Chymase 1 (CMA1)	CMA1 participates in the generation of vasoactive peptides. In the heart and blood vessels, CMA1, rather than ACE, is largely responsible for the conversion of angiotensin I to the vasoactive peptide angiotensin II.
BDKRB2	14q32.2 (3 exons)	B2 Bradykinin Receptor (BDKRB2)	BDKRB2 causes a variety of reactions, including vasodilation, edema, smooth muscle spasm and stimulation of pain fibers.
NOS3	7q36.1 (28 exons)	Nitric Oxide Synthase 3 (NOS3)	NOS3 acts as a biological mediator in several processes, including neurotransmission, antimicrobial and antitumor activity.
VEGFA	6p21.1 (9 exons)	Vascular Endothelial Growth Factor A (VEGFA)	VEGF plays a key role in the regulation of vasculogenesis and angiogenesis. This growth factor causes proliferation and migration of vascular endothelial cells and is necessary for both physiological and pathological angiogenesis.

Table 3. Genes responsible for energy metabolism and their expression in skeletal muscle and myocardium in humans (adapted from [8]).

Gene	Expression level in skeletal muscles (RPKM)	Expression level in myocardium (left ventricle) (RPKM)
ACE	1.425	2.163
CMA1	0.2515	0.3181
BDKRB2	0.3063	0.2344
NOS3	1.813	6.277
VEGFA	1.289	66.89

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4.1. ACE gene

The *ACE* gene (Angiotensin I Converting Enzyme) is localized on chromosome 17q23.3 (**Figure 4**). The gene encodes an enzyme involved in the regulation of blood pressure (BP) and electrolyte balance. It is part of the renin-angiotensin system (RAS), which regulates BP, fluid balance and salts in the body. As part of the RAS, the ACE enzyme plays a key role in the homeostasis of the circulatory system. In addition, RAS exists not only as an endocrine regulator, but also performs many local functions in various tissues and cells of the human body. ACE catalyzes the conversion of angiotensin I into the physiologically active peptide angiotensin II. Angiotensin II is a powerful vasopressor and a peptide that stimulates aldosterone, which controls BP and water-electrolyte balance. ACE also inactivates the vasodilator protein bradykinin. Accordingly, ACE is involved in increasing blood pressure [7].

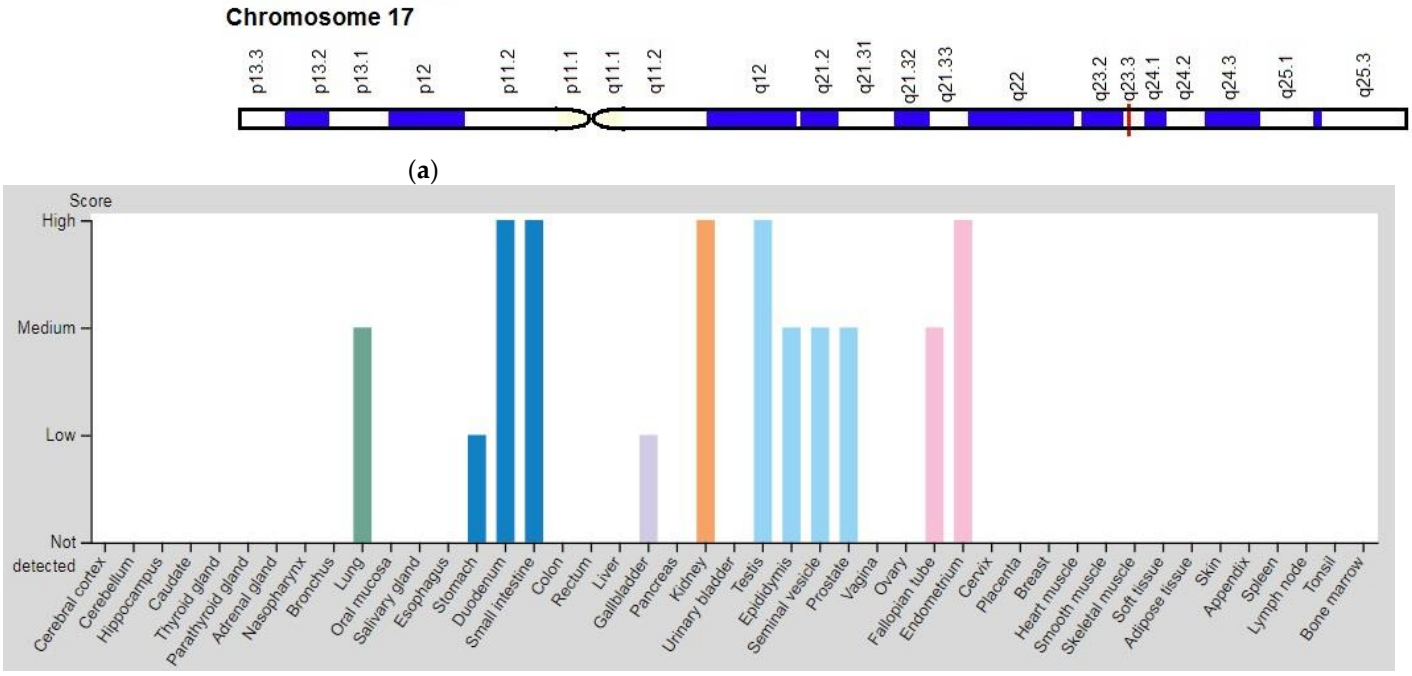


Figure 4. Location of the *ACE* gene on chromosome 17q23.3 (**a**) and tissue expression of angiotensin I converting enzyme (**b**) (adapted from [7, 8]).

Full-functional and low-functional / non-functional SNVs or polymorphisms of the *ACE* gene were identified earlier, of which the most well-known and studied is the insertion-deletion polymorphism rs4340. This polymorphism consists in the carrier of allele I (the presence of a deoxyribonucleic acid (DNA) fragment with a length of 287 nucleotide pairs in the 16 intron of the *ACE* gene) or allele D (the absence of this fragment). Based on the distribution of I / D alleles, three genetic variants are distinguished: the carriage of homozygous genotypes II and DD and heterozygous genotype ID [9, 10]. In carriers of the homozygous genotype DD, the activity of the ACE enzyme in the blood serum is almost twice as high as in carriers of the homozygous genotype II. At the same time, *ACE* activity

in carriers of the heterozygous ID genotype occupies an intermediate position [11]. A change in the enzymatic activity of ACE causes corresponding changes in the concentration of angiotensin II, which affects the intracellular metabolism of many tissues. It should be emphasized that angiotensin II not only regulates the functional state of hemodynamics, but also, as a growth factor, enhances the synthesis of structural proteins in cardiomyocytes, which can contribute to the development of myocardial hypertrophy [12].

The I allele is associated with high aerobic capabilities and is found with high frequency in elite long-distance runners, while the D allele is associated with high strength abilities of athletes [9, 10. 11].

The I / D alleles of the *ACE* gene is associated with changes in the mass of the left ventricle in response to an irritant (for example, physical or athletic activity) both in a state of health and in a state of pre-illness or illness. The D allele is associated with an increased myocardial response to an intensive training process and can be considered as a risk factor for the development of myocardial hypertrophy ("athlete's heart"). In addition, similar processes are observed in the skeletal muscles of athletes: the D allele is associated with a large increase in muscle strength in response to intense training in athletes. At the same time, allele I is associated with the lowest functional response of the cardiovascular system to intense sports loads [12]. Finally, this polymorphism has an effect on metabolism in the myocardium and skeletal muscles. In elite athletes in endurance sports, frequency of the allele I and frequency of the homozygous genotype II are significantly higher compared to control group (non-athletes) [12].

However, the results of associative genetic studies are contradictory in a number of cases. Gunel T. et al. [13] identified the homozygous genotype II in 32.43% of the control group and 8.11% of high-class Turkish athletes, and the genotype DD - in 37.84% in control group and 51.35% of high-class athletes. Heterozygous genotype ID was identified in 29.73% of control group and 40.54% of high-level athletes. Probably, these results were due to design features of the study and inclusion of athletes from different sports in the sample.

Ma F. et al. [9] conducted a meta-analysis of 366 articles devoted to the association between physical performance and the genotypes according of the I / D polymorphism of the *ACE* gene. The authors confirmed a significant association between the homozygous genotype II of the *ACE* gene compared with the D allele (DD + ID) with high physical performance of athletes training for endurance (OR, 1.23; 95% CI, 1.05-1.45).

Silva H.H. et al. [10] published a topic review of studies on a wide range of genomic profiles in elite athletes, including the *ACE* gene. The authors also demonstrated a significant association between the allele I with high aerobic capabilities of athletes.

Papadimitriou I.D. et al. [14] studied the association between the I / D polymorphism of the *ACE* gene and the best personal running time for 100, 200 and 400 meters (m) in a large group of elite athletes from Australia, Brazil, Greece, Jamaica, Italy, Poland, Russia, Lithuania, Spain and USA. A significant association between the homozygous genotype DD and the 200 m sprint time was found in athletes of the European. Using the Tukey multiple comparison test, athletes with the homozygous genotype DD (-0.60, 95% CI from -1.09 to -0.11) and the heterozygous genotype ID (-0.68, 95% CI from -1.18 to -0.18) had significantly less sprint time and running faster than athletes with the homozygous genotype II ($p < 0.05$). Similar data were obtained in the study of the best personal time in the 400 m running. Using genetic models, the authors found that the dominant D allele model (DD / ID compared to II) is best suited to explain 11.39% of the 400 m sprint time ($p = 0.001$) compared to the additive (9.78%, $p = 0.002$) and dominant I allele model (3.97%, $p > 0.05$). The percentage of observed variance (coefficient of determination, r 2) explained by the *ACE* genotype using the recessive model was 1.48%. Carriers of the DD and ID genotype did not have significant differences in the time of sprinting. This indicates that carrying one or two alleles D does not affect the speed of running at a distance of 400 m in elite athletes. At the same time, no cases of the homozygous genotype II were identified among male sprinters with a personal sprint time of 400 m less than the Olympic

qualification time (45.90 s). However, personal time in the 100 m run did not depend on the carrier of the studied alleles. The results of this study demonstrated that athletes with homozygous genotype II cannot claim high athletic performance (for example, at the Olympic Games) in running at distances of 200 and 400 m.

The authors point out that there are limitations in previous studies. Firstly, the authors examined ten cohorts of elite sprinters, including the fastest sprinters on Earth. Consequently, the number of "pure" elite sprinters in this study was much higher compared to previous associative genetic studies [15, 16]. Secondly, other studies most often included sprinters and power athletes from mixed sports, but in this study the authors included only elite sprinters in the 100, 200 or 400 m. In addition, the authors set clear criteria (the best personal running time for 100, 200 and 400 m within 15% of the world record) to guarantee a high level of performance for the elite sprinters they studied. So, the translation of the results of this study into real sports practice at the stage of selection and specialization will be very effective.

The obtained differences in the association of the studied genotypes may be due to the physiological characteristics of the cardiovascular system of infants at different distances (100, 200 and 400 m). In 100 m running, an athlete is required to accelerate for most of the race before he reaches his absolute maximum speed [17]. In longer sprint events (200 and 400 m), the acceleration phase is relatively shorter, and, rather, it is the ability to maintain maximum speed for a longer period of time that is a critical factor for winning Olympic competitions [18]. Acceleration depends on the reaction time, the center of gravity of the body relative to the blocks, the frequency of steps and the length of the step. At the same time, maintaining the absolute maximum running speed requires powerful cyclic muscle contractions and the effective use of energy systems (mainly glycolytic and creatine phosphate anaerobic systems), which are launched at different stages of the race. Considering the relationship of the genotypes by the I / D polymorphism of the *ACE* gene and athletic performance in running longer distances (200 and 400 m), it can be assumed that the carrier of the DD genotype consists in a greater effect on the metabolic potential of skeletal muscles and myocardium (switching from creatine phosphate to glycolytic anaerobic system) with repeated powerful contractions [18].

In addition, a possible explanation of the metabolic effect of the studied *ACE* gene polymorphism on the sprint speed characteristics may be due to differences in the types of muscle fibers. Zhang et al. [19] showed that homozygous genotype II is associated with a higher percentage of type I muscle fibers focused on aerobic exercise, while the homozygous genotype DD is associated with a higher percentage of type II fast muscle fibers, which are more involved in anaerobic exercise.

The ability of this polymorphism of the *ACE* gene to influence not only the processes of systemic hemodynamics, but also the function of skeletal muscles, has been confirmed in several studies [20, 21]. The ACE catalyzes the conversion of the vasoconstrictor agent angiotensin I into angiotensin II, which not only has a more pronounced vasoconstrictor effect, but is also a muscle growth factor involved in skeletal muscle hypertrophy and myocardial hypertrophy caused by sports overload [21]. The carrier of the D allele is usually associated with a higher activity of the ACE enzyme. This leads to a higher concentration of angiotensin II and a higher proportion of fast muscle fibers. Theoretically, this can contribute to higher sprinting or strength performance of athletes.

Thus, it can be concluded that the carrier of the *ACE* gene allele I is associated with high aerobic athletic loads, and the carrier of the D allele is associated with high speed-strength and sprinting abilities.

4.2. CMA1 gene

The *CMA1* (Chymase 1) gene is localized in chromosome 14q12 (**Figure 5**). This gene encodes a chymotryptic serine proteinase belonging to the S1 family of peptidases. It is expressed in mast cells and is believed to be involved in the degradation of the

extracellular matrix, regulation of secretion of submucosal glands and generation of vasoactive peptides. In the heart and blood vessels, this enzyme, and not the ACE enzyme, is largely responsible for the conversion of angiotensin I into the vasoactive peptide angiotensin II [7]. Up to 80% of angiotensin II is produced in the ventricles of the heart due to CMA1. The CMA1 activity plays an important role in the remodeling of vascular and myocardial walls [22].

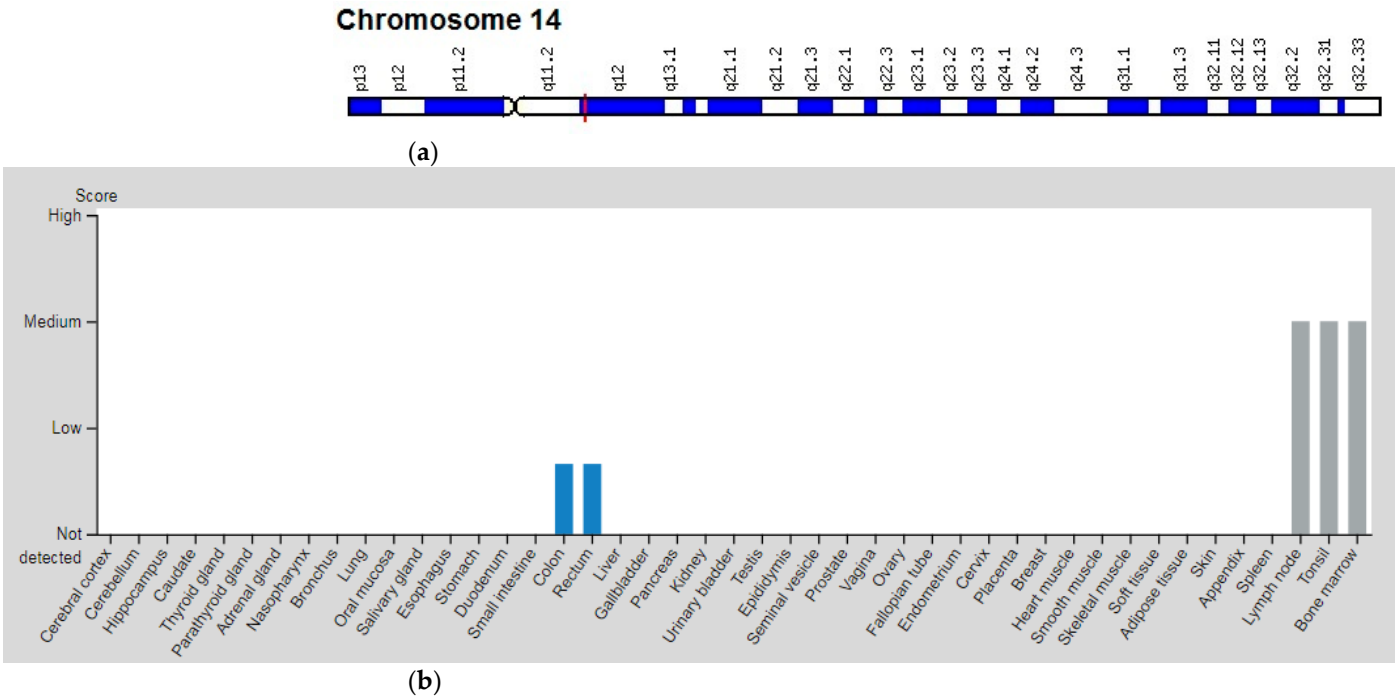


Figure 5. Location of the *CMA1* gene on chromosome 14q12 **(a)** and tissue expression of chymase 1 **(b)** (adapted from [7, 8]).

The results of the study by Chen L.Y. et al. [23] confirm the hypothesis of a dual pathway of formation of angiotensin II from CMA1 and angiotensin converting enzyme (ACE) in cardiac tissue. The results obtained in transgenic mice demonstrated that CMA1 can play a key role in myocardial remodeling by increasing the formation of angiotensin II and activation of matrix metalloprotease-9 protein (MMP-9), as well as regulating the expression of the collagen I gene (*COL1A1*).

The predominant role of CMA1 in the production of angiotensin II from angiotensin I in the human myocardium has been confirmed by numerous studies [24, 25, 26, 27, 28]. Using specific antibodies, Ferrario C.M. et al. [28] showed high expression of CMA1 in atrial cardiomyocytes of patients with various cardiac pathologies, and its activity was significantly higher in the left than in the right atrium. However, studies examining the role of CMA1 in myocardial remodeling in athletes are extremely few.

In the 5'-untranslated region of the *CMA1* gene, a point replacement of the nucleotide G by A was detected at position 1903 (G1903A, rs1800875). A change in the functional activity of the CMA1 enzyme as a result of this substitution may be associated with the functioning of the cardiovascular system in athletes, including when performing sports loads of varying intensity [10, 15].

Dautova A.Z. et al. investigated the association between alleles and genotypes of G1903A (rs1800875) of the CMA1 gene with indicators of the oxygen transport system of the body. The authors investigated the function of external respiration, indicators of red blood, hemodynamic parameters depending on the level of motor activity (athletes and non-athletes). The authors used DNA samples of 25 athletes specializing in various sports, and 43 young men (non-athletes) made up a control group. The frequency of the homozygous genotypes AA and GG, as well as the heterozygous genotype AG in athletes and

in control group had statistically significant differences ($p < 0.05$). The frequency of the homozygous genotype AA was 52% in athletes group, and the homozygous genotype GG - 40%. The frequency of the heterozygous AG genotype was minimal and amounted to 8%. In non-athletes, on the contrary, the frequency of the heterozygous AG genotype was more than half of the cases (58.1%), and the frequency of the homozygous AA genotype was 27.9%. The frequency of the homozygous genotype for the major GG allele was statistically significantly lower in non-athletes compared to athletes (13.9% vs. 40%, respectively). In athletes with the homozygous genotype for the minor AA allele, a statistically significant association was revealed with the parameters of cardiac output, volume and velocity of blood flow, microcirculation state, as well as with parameters characterizing the functional reserves of the respiratory system (vital capacity of the lungs). The carriage of GG and AG genotypes had no reliable associations with the studied parameters in the group of athletes. The results of the study allowed the authors to assume that the distribution of genotype frequency according the SNV in athletes was as follows: AA → GG →AG. Thus, the genotype to a certain extent influenced the formation of the phenotype of better tolerance of sports (physical) loads due to better functioning of the cardiovascular and respiratory systems [22].

4.3. BDKRB2 gene

The BDKRB2 (B2 Bradykinin Receptor) gene is localized on chromosome 14q32.2 (**Figure 6, a**). The gene encodes the bradykinin receptor. This small protein, consisting of 9 amino acid residues, causes many physiological reactions, including vasodilation, edema, smooth muscle spasm and stimulation of pain receptors. Bradykinin is released upon activation by pathophysiological conditions, such as trauma and inflammation, and binds to its bradykinin receptors of types B_1 and B_2. The B_2 type receptor binds to G proteins that stimulate the phosphatidylinositol-calcium secondary messenger system [7]. Most of the effects of bradykinin are realized through type B_2 receptors, which are expressed in various tissues (**Figure 6, b**).

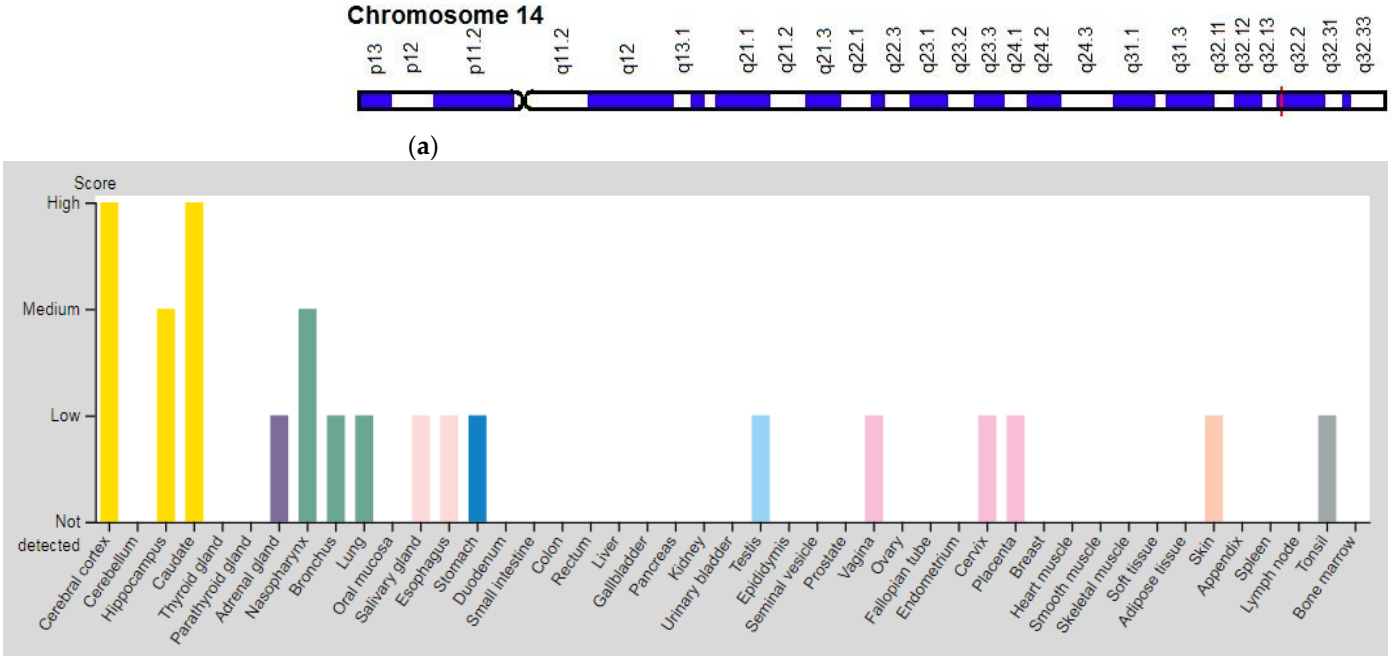


Figure 6. Location of the *BDKRB2* gene on chromosome 14q32.2 (**a**) and tissue expression of bradykinin receptor B2 (**b**) (adapted from [7, 8]).

The polymorphism rs5810761 (insertion / deletion of 9 pairs of nucleotides; +9 / -9 or I / D) was found in the first exon of this gene, which is functional and is actively studied by sports geneticists. Based on the distribution of +9 / -9 alleles, three genetic variants are distinguished: of the homozygous genotypes +9 / +9 and -9 / -9 and the heterozygous genotype +9 / -9 [29]. Carriers of the -9 allele (deletion) have a higher expression of the *BDKRB2* gene compared to carriers of the +9 allele, which means a more pronounced vasodilating effect.

Bradykinin receptors are also expressed in the plasma membrane of skeletal muscle cells and endothelium of blood vessels [30]. Activation of the *BDKRB2* gene leads to an increase in glucose uptake by skeletal muscles during physical activity, increased blood flow in skeletal muscles and, as a result, to higher physical endurance [31], which is of interest in sports medicine.

Eynon N. et al. [32] compared the frequency distribution of the -9/+9 polymorphism (rs5810761) of the *BDKRB2* gene between Israeli athletes engaged in various sports (endurance runners and sprinters), as well as between athletes of different sports status (elite level and national level). The frequency of the studied alleles/genotypes was compared by the authors between athletes and non-athletes. The association between the -9 / +9 genotypes of the *BDKRB2* gene and endurance indicators was also investigated. It was found that the distribution of alleles and genotypes was similar in the groups of endurance athletes, sprinters and in the control group of non-athletes ($p = 0.9$ for the alleles frequency and $p = 0.83$ for the genotypes distribution). No statistically significant differences were found between endurance athletes of the Olympic and national levels and between sprinters of the Olympic and national levels ($p > 0.09$ for all comparisons). There was no significant association between the carrier of the studied genotypes and endurance indicators ($p = 0.16$ for the interaction effect). The reasons for the lack of a significant association could be the following: a small sample size of sports cohorts, lack of confirmation with other cohorts of different ethnic origin.

These results are comparable to the study by Grenda A. et al. [29], in which the authors investigated the association between athletic achievements in Polish swimmers (time to overcome the distance) and polymorphism -9 / + 9 (rs5810761) of the *BDKRB2* gene. The analysis included the best individual results in swimming, expressed in points of the International Swimming Federation (FINA), achieved in short, medium and long distance competitions. Differences in the distribution of genotypes + 9 / -9 in all observed Polish swimmers were statistically insignificant compared to the control group ($p = 0.19$ and $p = 0.26$). No statistically significant gender differences in the frequencies of alleles and the genotypes were found, both among swimmers and in the control group. Differences in the frequency of the -9 allele between all Polish swimmers and the control group did not reach statistical significance (45% vs. 40%; $p = 0.20$). Similarly, differences in the frequency of the -9 allele were not statistically significant in long-distance swimmers compared with the control group (47% vs. 40%; $p = 0.26$). However, male swimmers with the homozygous genotype +9 / +9 of the *BDKRB2* gene showed a tendency to higher results in short-distance competitions than in long-distance competitions, but the differences were statistically insignificant ($p > 0.05$) [29]. Thus, the study did not reveal a significant association between the alleles and genotypes of this polymorphism under study and the results in swimming, regardless of the distance specialization and gender of Polish swimmers. However, the authors point to a limitation in their study associated with a small number of Olympic-level swimmers in Poland. In this regard, the relatively small sample size in this study may cause an ambiguous assessment of the results obtained.

It should be remembered that high achievements in sports are a multifactorial aspect and both the influence of external environmental factors (nutrition, sleep-wake cycle, training-rest mode, training process, etc.) and the study of a combination of genotypes associated with the quality of "endurance" or with the quality of "speed-strength" in athletes are important. It is from these positions that Williams et al. [31] investigated the role of a combination of the *ACE* and *BDKRB2* genes genotypes in the predisposition to high

athletic performance in British Olympic-level runners. All athletes were divided into three groups depending on the running distance: predominantly anaerobic load (sprint ≤ 200 m), mixed aerobic and anaerobic load (400-3000 m) and predominantly aerobic load (endurance ≥ 5000 m). Among the observed British runners, there was a tendency to a linear increase in the frequency of the -9 allele with an increase in the running distance. The share of the "-9" allele increased from 0.382 (sprint) to 0.412 (400-3000 m runners) to 0.569 in athletes in long-distance running ≥ 5000 m, respectively (p = 0.06 for a linear trend; p = 0.04 for comparison ≤ 5000 vs ≥ 5000 m). Haplotype analysis of the *ACE* and *BDKRB2* genes demonstrated their statistically significant association with running distance (≤ 5000 vs ≥ 5000 m), both in general (p = 0.001 Fisher's exact criterion) and only for British runners of European origin (p = 0.003). The study demonstrated that the -9 (rather than +9) allele of the *BDKRB2* gene is associated with higher metabolic efficiency of skeletal muscles, as well as endurance in runners. Moreover, these associations were strongest among athletes with greater functional activity of bradykinin receptors, which corresponded to the carrier of the *ACE* gene allele I (high generation of bradykinin ligand) and the *BDKRB2* gene allele -9 (high expression of bradykinin receptors).

4.4. NOS3 gene

The *NOS3* gene (Nitric Oxide Synthase 3) is localized on chromosome 7q36.1 (**Figure 7**). The *NOS3* gene encodes endothelial nitric oxide (NO) synthase (eNOS), which has a vasodilating effect, thereby realizing vasomotor control in both conductive and resistant vessels. eNOS regulates BP [33]. Some SNVs of the *NOS3* gene are associated with a tendency to spasm of coronary vessels [34] and peripheral vessels [35].

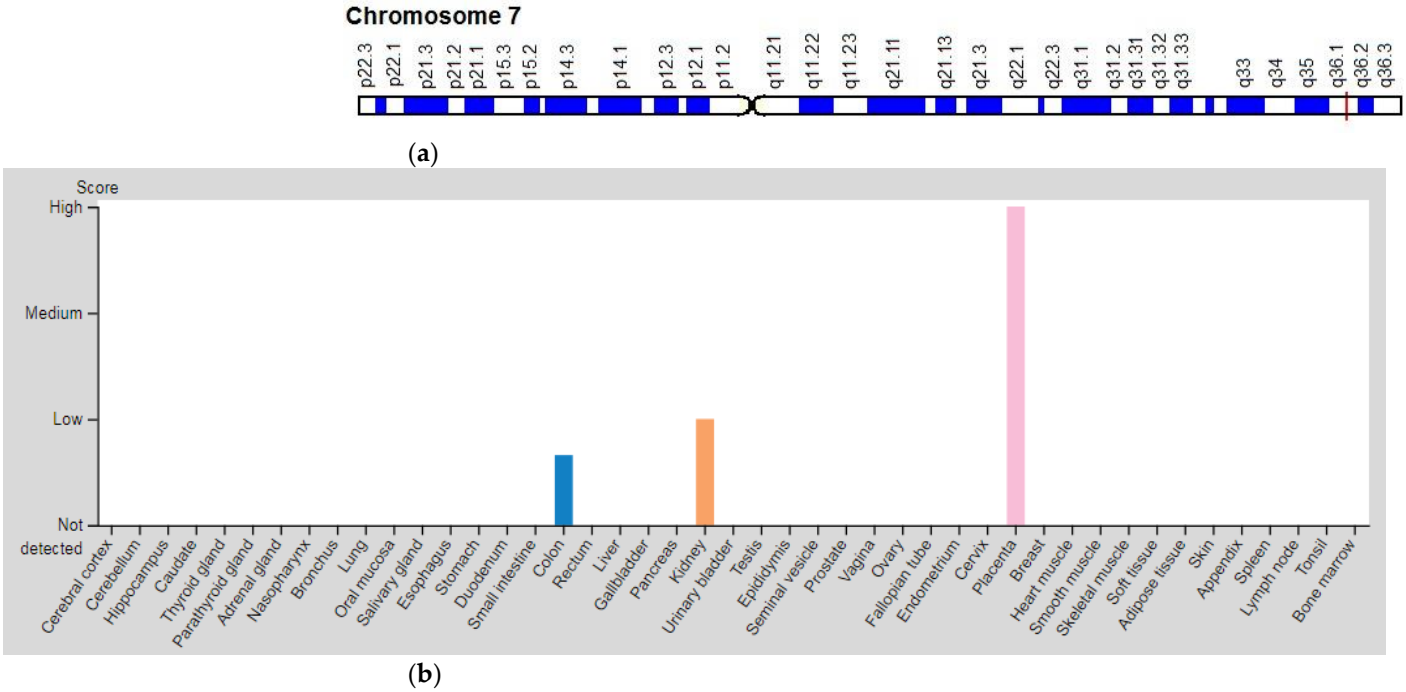


Figure 7. Location of the *NOS3* gene on chromosome 7q36.1 **(a)** and tissue expression of endothelial nitric oxide synthase **(b)** (adapted from [7, 8]).

Physical exercises have been shown to enhance endothelial NO-dependent dilation of both large and small vessels [36, 37]. Regular physical activity enhances the synthesis and release of NO, and also increases the bioavailability of NO. During exercise, the content of oxygen free radicals increases, which, in turn, affect the activity of NOS. Repeated exercises and stimulation of NO bioactivity eliminate this radical imbalance, which leads

to a greater potential for NO bioavailability. At the same time, it has been shown that the increase in bioactivity of NO disappears within a few weeks after stopping training [38].

Studies of coronary circulation indicate a significant role of NO in the expansion of epicardial coronary vessels during exercise (sports training). At the same time, NO-dependent vasodilation decreases in the presence of external risk factors and is absent or significantly reduced in occlusive vascular atherosclerosis [39].

SNV rs2070744 of the *NOS3* gene (replacement of thymine (T) with cytosine (C) at the position of nucleotide -786 (T-786C) is associated with the functional capabilities of the cardiovascular system, which can affect sports results in cyclical sports athletes [38, 40]. The major T allele and the homozygous TT genotype are associated with increased activity of the *NOS3* gene promoter, resulting in increased eNOS expression and NO synthesis in tissues. The minor C allele and the TC or CC genotypes are associated with a decrease in eNOS expression and a decrease in NO synthesis [41]. Consequently, the SNV can contribute to the interindividual differences in the response of the cardiovascular system to physical activity of different orientation (endurance or strength training), which is largely mediated by the NO- vasodilator response [37]. It is hypothesized that the homozygous TT genotype should be taken into account during sports selection and dosing of sports loads. This will help to choose an individual a type of physical exercise to maximize the health benefits of an athlete, thereby optimizing the adaptation of the cardiovascular system to training process, reducing the risk of developing cardiovascular diseases in athletes.

In the study by Dawson E.A. et al. [34], the association between the alleles (genotypes) SNV rs2070744 of the *NOS3* gene with interindividual differences in changes in the function of the cardiovascular system after performing physical activities of different orientation (4-week resistance training and endurance training) was studied. Firstly, the authors found that both training regimens were effective in building muscle strength. Secondly, both types of training led to improved blood flow in the peripheral arteries (in particular, improved blood flow in the brachial arteries). The improvement of the functioning of the cardiovascular system in athletes was noted both during endurance training and during training with weights. However, the mechanisms leading to such effects are different. Endurance exercises are associated with a prolonged increase in blood flow to active tissues, primarily to the myocardium and skeletal muscles. Vascular function is improved at the same time by increasing the production of eNOS, increasing the level of antioxidants and reducing markers of oxidative stress. This, in turn, leads to increased bioavailability of NO and to improved vasodilation in response to the stimulus. On the contrary, physical exercises with weights are associated with short-term vascular spasm, increased blood pressure and local ischemia. Therefore, transmural pressure can be a relevant physiological stimulus for the adaptation of coronary and peripheral vessels in response to physical load with a burden. Thirdly, the authors found that there are individual differences in the adaptation of the cardiovascular system to endurance and weight training. Probably, individual differences in adaptive mechanisms are partly explained by the carrier of the studied alleles and the genotypes of T-786C of the *NOS3* gene. In particular, the homozygous genotype for the major TT allele was associated with an improvement in vascular function only after endurance training, while the heterozygous TC genotype and the homozygous CC genotype for the minor allele were associated with a tendency to improve vascular function only after training with weights. Taken together, this study highlights the potential role of the *NOS3* gene studied by the SNV in a personalized approach to choosing a training regime and optimizing peripheral vascular health indicators in athletes.

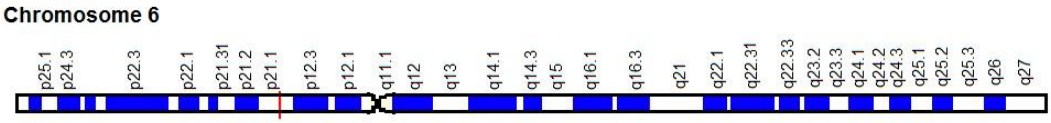
Another common mutation of the *NOS3* gene associated with the functional capabilities of the cardiovascular system is the SNV (rs1799983) of the *NOS3* gene, representing the replacement of G by T at the position of nucleotide 894 (G894T), which leads to the replacement of glutamic acid (Glu) in exon 7 by aspartic acid (Asp) [42]. This SNV

associated with decrease of NO synthesis and subsequently affects the peculiarities of adaptation of the cardiovascular system to performing physical activities of different directions.

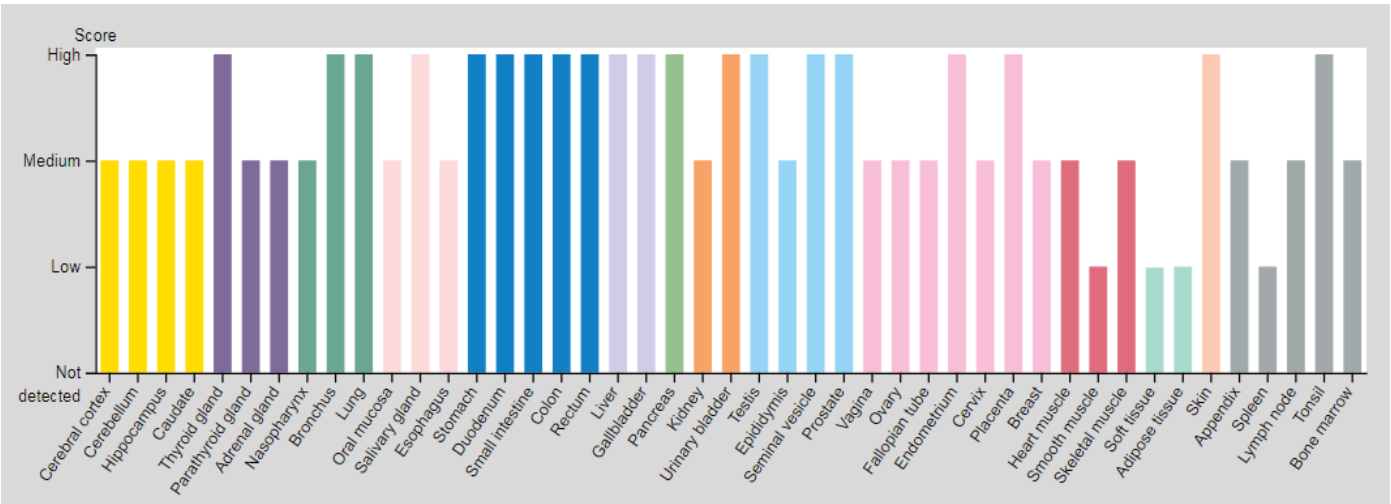
Saunders et al. [43] identified association between SNV / polymorphism of the *BDKRB2* (rs5810761) and the *NOS3* (rs1799983) genes, which encode components of the kallikrein-kinin system (KKS), with indicators of ultrahigh endurance in triathletes. The study involved 443 European male triathletes and 203 healthy men of control group. When divided into tertiles, there was a significant linear trend in the distribution of the *NOS3* GG homozygous genotype among the fastest (35.0%), medium (40.4%) and slowest (46.9%) participants (p = 0.039). The total finish time of triathletes with the homozygous genotype GG of the *NOS3* gene and the homozygous carrier of the +9 allele of the *BDKRB2* gene was statistically significantly longer (athletes ran slower) than athletes with other combinations of genotypes (p = 0.001). Saunders et al. It was demonstrated that the effect of the homozygous genotype GG of the *NOS3* gene, associated with high endurance in runners, is phenotypically manifested only in carriers of the homozygous genotype -9 / -9 of the *BDKRB2* gene. With other combinations of genotypes, combinations of genotypes of the studied SNVs, the homozygous genotype GG did not demonstrate a statistically significant positive association with an increase in athletic endurance and a reduction in finish time in triathletes of European origin [29].

4.5. VEGFA gene

The *VEGFA* (Vascular Endothelial Growth Factor A) gene is localized on chromosome 6p21.1 (**Figure 8**). The *VEGFA* gene encodes a protein of the same name, which plays a key role in the regulation of vasculogenesis and angiogenesis. This growth factor causes proliferation and migration of vascular endothelial cells and is necessary for both physiological and pathological angiogenesis [44].



(**a**)



(**b**)

Figure 8. Location of the VEGFA gene on chromosome 6p21.1 (a) and tissue expression of vascular endothelial growth factor A (b) (adapted from [7, 8]).

The *VEGFA* gene expression is stimulated by a large number of pro-angiogenic factors, including: hypoxia-induced factor (HIF); epidermal growth factor (EGF); fibroblastic growth factor (FGF); others. In addition, the level of VEGFA expression is influenced by blood pH, partial pressure and concentration of O2 in the inhaled air [45], which will change in response to physical exertion. As a consequence, the severity of VEGFA expression will depend on the intensity of physical activity [46]. The capillary supply of skeletal muscles is an important factor determining the ability to perform prolonged and intense physical exertion (endurance training). Skeletal muscle capillarization and exercise-induced angiogenesis are partially regulated by VEGFA. Among the studied SNVs of the *VEGFA* gene, SNV in the promoter (regulatory) region of the gene are of particular interest. For example, the replacement of cytosine with guanine at position -634 (-634 G/C; rs2010963) increases the activity of the gene and, accordingly, determines individual differences in the level of its expression in tissues, including skeletal muscles and myocardium [47].

When studying the association between the alleles and genotypes of the specified SNV (rs2010963) with the aerobic capabilities of the body of Russian cyclical sports athletes, Akhmetov I.I. et al. [48] found that the frequency of the minor C allele was statistically significantly higher in athlete group than in control (non-athletes) group (29.2 vs. 24.5%, respectively; $p = 0.0026$). The prevalence of the homozygous genotype GG was 50.6% among athletes (57.6% in the control group), the heterozygous genotype GC was noted 40.4% in athlete group and 35.8% in the control group, and the homozygous genotype CC - 9% and 6.6% in athletes group and in control group, respectively. It was also found that a higher frequency of the minor C allele is observed in long-distance runners compared to athletes of other sports. The minor C allele was statistically significantly associated with high aerobic capabilities of the athletes' body (in terms of the maximum power of the performed load and maximum oxygen consumption). In addition, the allele C was associated with a significant contribution to the energy supply of aerobic metabolism of skeletal muscles (according to the values of the maximum lactate content). The obtained results allowed the authors to conclude that the minor C allele can be a genetic predictor of the development and manifestation of the quality of endurance in athletes and play a key role in sports selection.

In a study by Vinnichuck J.D. et al. [46] the content of VEGFA in serum during oxidative stress caused by physical exertion was studied. The study involved Ukrainian athletes with different training specifics. The first group included athletes who train for endurance, with a predominantly aerobic type of energy supply of muscular activity. The second group consisted of athletes with a mixed aerobic-anaerobic type of energy supply of muscular activity. The third group included athletes of speed and power sports, whose physical activity is realized mainly due to the anaerobic mechanism of energy supply. The highest serum level of VEGFA was observed in athletes training for endurance - from 122.8 ± 3.4 to 126.2 ± 4.1 pg /ml (-1). Intermediate values of VEGFA serum level were noted with a mixed energy supply mechanism - 102.4 ± 4.91 pg/ml (-1). The lowest values of VEGFA serum level were detected in athletes of the third group (with a predominantly anaerobic mechanism of energy supply of muscular activity) and amounted to 78.5 ± 5.2 pg /ml (-1). In addition, the initial serum level of VEGFA (before exercise) in athletes of all groups was statistically significantly higher ($p < 0.05$) than in control group (non-athletes). Subsequently, a correlation analysis was carried out, which established a statistically significant positive correlation between the degree of antioxidant protection and the concentration of VEGFA ($p < 0.05$). The authors concluded that angiogenesis is one of the mechanisms of adaptation of muscle tissue and myocardium to hypoxia during physical exertion, especially during endurance loads.

There are studies devoted to the study of the role of VEGFA in physiological and / or pathological processes in the myocardium [49], [50], [52], [54]. It is known that physical activities of different directions (speed-strength or endurance) cause adaptive changes in the structure and function of the myocardium in response to overload by pressure or

volume. The consequence of this is the development of left ventricular myocardial hypertrophy. One of the manifestations of pathological remodeling of the heart is ineffective myocardial hypertrophy, accompanied by a decrease in physical performance of athletes. Currently, the question of the physiological limits of left ventricular hypertrophy in highly qualified athletes is relevant for sports medicine [46].

The relationship between VEGFA expression and myocardial function is two-way. On the one hand, VEGFA activates cardiomyocytes, causing morphogenesis, contractility and wound healing. On the other hand, VEGFA is produced by cardiomyocytes during inflammation, mechanical stress and cytokine stimulation. Moreover, high serum level of VEGFA have been found in patients with various cardiovascular diseases, and often correlate with an unfavorable prognosis and severity of the disease [49].

In the study by Braile M. et al. [49] summarized the knowledge about the expression of VEGFA and its effect on cardiomyocytes, as well as the role of VEGFA in cardiovascular diseases, which are the cause of premature death worldwide, including among athletes.

In a mice model with a specific deletion of the *VEGFA* gene, vasculogenesis / angiogenesis changes negatively in cardiomyocytes and a thinner wall of the left ventricle is formed [50]. These experimental data confirm the mutual transmission of signals from cardiomyocytes to endothelial cells during myocardial formation. Interestingly, in knockout mice with the *VEGFA* gene turned off, the microvascular network of the myocardium is underdeveloped, but the structure of the coronary arteries is preserved, including various signaling pathways for vasculogenesis / angiogenesis in the myocardium and epicardial coronary arteries. Knockout mice demonstrated impaired myocardial angiogenesis with subsequent development of ischemic cardiomyopathy and heart failure. In addition, these mice had tortuous, irregularly shaped, dilated coronary capillaries, which indicates incomplete vascular remodeling. Consequently, VEGFA induces myocardial angiogenesis and increases the permeability of coronary vessels and proliferation of endothelial cells [48]. Factors involved in increasing VEGFA expression in mice with hypertrophied cardiomyocytes include HIF-1α [51, 52].

In a mice model, Rose B.A. et al. [53] found that the activity of mitogen-activated protein kinase p38 (p38 MAPK) is necessary for hypoxia-induced proangiogenic activity of cardiomyocytes and that activation of p38 MAPK in cardiomyocytes is sufficient to stimulate mediated paracrine signaling of proangiogenic activity. The authors also demonstrated that cardiomyocyte-specific inactivation of p38α in the mice heart disrupted compensatory angiogenesis after pressure overload and contributed to the early onset of heart failure. As a result, it was concluded that p38 MAPK plays an important role in the interaction between cardiomyocytes and the vascular network, regulating stress-induced *VEGFA* expression in cardiomyocytes. The activity of p38 MAPK (as part of the stress-induced signaling pathway) significantly affects both pathological and compensatory remodeling of the myocardium.

However, there is currently insufficient data on the level of expression and release of *VEGFA* in human cardiomyocytes. Further studies are needed to determine the role of *VEGFA* in the development of physiological and/or pathological remodeling of the myocardium in athletes.

In general, associative genetic studies of SNVs of the *VEGFA* gene are not numerous, although the biological, physiological and pathophysiological prerequisites demonstrated above indicate the importance of studying this direction in personalized sports medicine in the future. Currently, only the role of the minor allele C of SNV rs2010963 (-634 G/C) has been studied the *VEGFA* gene, which is associated with high aerobic capacity in athletes. The role of the *VEGFA* gene in the development of physiological and / or pathological remodeling of the myocardium in athletes needs further study and may be important for understanding the molecular mechanisms of adaptation of the musculoskeletal and cardiovascular systems to aerobic loads, choosing the optimal sports specialization and professional training of professional athletes [66].

Discussion

Our systematic review has demonstrated that the physiology and pathophysiology of processes occurring in the human body involving proteins and enzymes encoded by the studied genes (ACE, CMA1, BDKRB2, NOS3 and VEGFA) have been studied quite well, both in normal and pathological conditions. However, the development of sports genetics in this direction is still at the beginning of its outset. The main results of the included research works are presented in Table 4.

Table 4. The main results of the included studies.

Authors	Gene	Groups	Main results	p -*value*	Associations
Tsianos G., et al., 2005	*ACE* I / D	LD ULD	The frequency of the ACE I allele is greater amongst those who best compete internationally at distances of 25 km (ULD). This was reflected in altered genotype distributions: only one of 19 individuals competing over the lower range of distances was of II genotype, whilst only one of the 15 ULD group was of DD genotype.	P = 0.01	These data thus support an association of the ACE I allele with elite endurance athletic performance.
Costa A.M., et al., 2013	*ACE* I / D	CG SD LD	he frequency of the D allele in elite short-distance swimmers differed significantly from that in the control group. The frequency of the D allele significantly differs depending on the distance between competitions only among elite swimmers.	P = 0.021 (CG; SD) P = 0.05 (SD; LD)	Thus, these data confirm the association of the ACE D allele with elite athletic performance on speed/strength.
Gunel T. et al., 2014	*ACE* I / D	CG SD	The ACE II genotype was identified in 32.43% of the control group and 8.11% of elite athletes, the DD genotype in 37.84% of the control group and 51.35% of the elite athletes, and the ID genotype in 29.73% of the control group and 40.54% of the elite athletes.	NR	Thus, these data confirm the association of the ACE D allele with elite athletic performance on speed/strength.
Puthucheary Z., et al., 2011	*ACE* I / D	CG Swimming Triathlon	It has been demonstrated that allele I is associated with endurance-oriented competitions, especially in triathlon. Meanwhile, the D allele is associated with strength- and power-oriented performance and has been found in significant excess among elite swimmers.	NR	These data thus support an association of the ACE I allele with elite endurance athletic performance. ACE D allele with elite athletic performance on speed/strength.
Papadimitriou I.D. et al., 2016	*ACE* I / D	running 100 m running 200 m running 400 m	Caucasian sprinters with the ACE DD genotype had faster best 400-m sprint time than their ACE II counterparts.	P = 0.003	Thus, these data confirm the association of the ACE D allele with elite athletic performance on speed/strength.
Nazarov I.B. et al., 2001	*ACE* I / D	CG SD	There was an excess of allele D (frequency 0.72, among the outstanding SDA group	P=0.001	These data thus support an association of the ACE I allele with elite

		MD	and an excess of allele I (frequency 0.63 among the outstanding MDA group.	P=0.032	endurance athletic performance. ACE D allele with elite athletic performance on speed/strength.
		LD			
Tobina T., et al., 2010	*ACE* I / D	CG	The frequency of the I/I genotype was not significantly higher, and the frequency of the D/D genotype was not significantly lower in elite runners than in non-athletes. In contrast, the frequency of the I/D genotype tended to be lower in elite runners than in the non-athletes.	P = 0.055	The I allele of the ACE gene I/D polymorphism is not a strong genetic factor affecting human endurance performance in Japanese elite runners.
		LD			
Shenoy S., 2010	*ACE* I / D	CG	Allele I was significantly increased in triathletes. The same trend was found in the genotypic distribution, as triathletes had an excess of genotype II.	P= 0.02	It can be concluded that there might be a positive association between I allele of ACE gene and endurance.
		Triathletes			
Dautova A.Z., et al. 2015	*CMA1* (rs1800875)	CG	The A/A (0.52) and G/G (0.4) genotypes prevailed in athletes, while the A/G (0.58) genotype was most common in the control group. The interrelations of polymorphic variants of the gene with the indicators of red blood, hemodynamics and external respiration, as well as with the physical endurance of the body and tolerance to muscle load were revealed. The closest connections between the studied traits were found in the polymorphic variant of *CMA* A/A.	P= 0.00002	*CMA* A/A is associated with high oxygen transport system capabilities
		EG			
Eynon N., et al., 2011	*BDKRB2* *+9/-9*	CG	There was no interaction between *BDKRB2* -9/+9 polymorphisms in relation to endurance	P=0.16	The *BDKRB2* -9/-9 genotype is not associated with endurance performance, at least among Israeli athletes.
		SD			
		LD			
Grenda A., et al., 2014	*BDKRB2* *+9/-9*	CG	The distribution of +9/-9 *BDKRB2* genotypes in all swimmers, as well as in long-distance swimmers, did not differ significantly from the control group.	P =0.26 (CG;EG)	Polymorphism (-9/+9, rs5810761) within the *BDKRB2* gene is not associated with swimming performance, regardless of distance specialization in Polish swimmer cohorts.
		SD			
		MD			
		LD			
Williams A.G., et al., 2004	*BDKRB2* *+9/-9* *ACE* *I / D*	CG (SD) (MD) (LD)	The *ACE* I / *BDKRB2* -9"high king receptor activity" haplotype was significantly associated with endurance (predominantly aerobic) event among elite athletes	P = 0.003	The *ACE* I / *BDKRB2* -9 haplotype was significantly associated with endurance event among elite athletes.
Dawson E.A., et al., 2021	*NOS3* (rs2070744)	Endurance training	The TT genotype was associated with an improvement in vascular function only after endurance training, while the TC genotype and CC genotype were associated with a tendency to improve vascular function only after training with weights.	P = 0.016 (TT) P = 0.056 (TC; CC)	The association of *NOS3* c genotypes suggests differences in the adaptation of the cardiovascular system to a certain regime of chronic exercise.
		Weight training			

Ahmetov I.I., et al., 2009	*VEGFA* (rs2010963)	CG EG	The frequency of the C allele was statistically significantly higher in the group of athletes than in the control group of non-athletes. The C allele was statistically significantly associated with high aerobic capabilities of the athletes' body (in terms of the maximum power of the performed load and maximum oxygen consumption).	P = 0.0026	The C allele can be a genetic predictor of the development and manifestation of the quality of endurance in athletes.

Abbreviations: CG, control group; EG, experimental group; NR, not reported; LD, long distances; ULD, ultra-long distances; MD, middle distances; SD, short distances.

The main difficulty is the differences in the comparison groups. In the research works we analyzed, as a rule, the association of SNV candidate genes was studied in groups of athletes and non-athletes or in groups of athletes of various sports or in groups of athletes with different training specifics (short, medium and long distances). Due to the different criteria of the comparison groups, a potential distorting effect of the results level is possible. In addition, different authors present different criteria for the cardiovascular system performance: maximum oxygen consumption, speed of overcoming the distance, hemoglobin concentration, heart rate, stroke volume of blood, etc. Also, other environmental factors (other than sports) were not taken into account by the researchers. In this regard, it is not possible to talk about the cumulative effect of genetic and non-genetic predictors on the cardiovascular system adaptation to strenuous sports loads in professional athletes. This explains the need for further research in the future.

The endothelium of blood vessels plays an important role in the optimal functioning of the cardiovascular system, as well as in the pathogenesis of various diseases [54]. The endothelium realizes its effects through the release of vasoactive substances: vasodilating (nitric oxide, bradykinin, etc.) and vasoconstricting (oxygen free radicals, angiotensin II, etc.). The proteolytic blood systems KKS and RAS, regulating the synthesis and degradation of bradykinin and angiotensin II, are involved in the regulation of cardiovascular homeostasis [55]. Skeletal muscles and myocardium contain complete KKS and RAS. Bradykinins can be locally released there and receptors for them can be expressed [56].

However, it is not yet clear exactly how the interaction of KKS and RAS can affect the phenotypes of professional athletes training for strength/speed or endurance. There is evidence that bradykinin acting through bradykinin receptors, which are encoded by the BDKRB2 gene, can affect local blood flow in skeletal muscles and glucose uptake by skeletal muscles during physical activity. In turn, these processes determine the higher endurance of athletes during training and competition periods [31, 57]. The ability of *ACE* gene I/D polymorphism to influence not only the processes of systemic hemodynamics, but also the function of skeletal muscles, has been confirmed in several studies [17, 18]. ACE catalyzes the conversion of the vasoconstrictor angiotensin I into angiotensin II, which not only has a more pronounced vasoconstrictor effect, but is also a muscle growth factor involved in skeletal muscle hypertrophy and myocardial hypertrophy caused by sports overload [18]. The D allele carrier is associated with higher activity of the ACE enzyme. It leads to a higher concentration of angiotensin II and a higher proportion of fast muscle fibers. Theoretically, it can contribute to higher sprinting or strength performance of athletes, which is confirmed by many research works [12, 13, 14, 61, 65]. The *ACE* gene allele I carriage is associated with high aerobic athletic loads [12, 61, 63, 64]. An exception is the research work by Tobina T. et al., 2010 [60], in which it was found that the allele I of the polymorphism I/D of the ACE gene is not a strong genetic factor affecting human endurance indicators in elite Japanese runners.

No research works have been found in the population of athletes confirming the association of the -9 (rather than +9) allele of the *BDKRB2* gene with higher metabolic efficiency of skeletal muscles, as well as with endurance in runners. Only one work confirmed

that the *AKAI*/*BDKRB2* -9 haplotype was significantly associated with high aerobic capabilities among elite athletes (long-distance running).

The predominant role of CMA1 in the production of angiotensin II from angiotensin I in the human myocardium has been confirmed by numerous research works [30, 31, 32, 33, 34]. Using specific antibodies Ferrario C.M. et al. (2016) [34] showed high expression of CBFA1 in atrial cardiomyocytes of patients with various cardiac pathologies, and its activity was significantly higher in the left than in the right atrium. However, studies examining the role of CMA1 in myocardial remodeling in athletes are extremely few.

It is believed that improved glucose uptake by skeletal muscles and myocardium is mediated by bradykinin-induced synthesis of NO [58]. In addition, bradykinin-induced NO synthesis can modulate mitochondrial respiration control. NO is a vasodilator that reversibly inhibits oxygen utilization in rat skeletal muscle mitochondria in physiological concentrations [51]. It has been suggested that under physiological conditions NO regulates mitochondrial metabolism, optimizes the ratio between oxygen consumption and energy production [59]. If NO synthesis is reduced, oxygen consumption by skeletal muscles and myocardium during exercise will increase, reducing the working muscles efficiency. Elevated bradykinin levels associated with the *ACE* gene allele I, increased expression of the *BDKRB2* gene in skeletal muscles, and/or increased eNOS activity will lead to an increase in NO synthesis. As a result, oxygen consumption decreases and the efficiency of skeletal muscle and myocardial contraction increases, which will contribute to more effective performance of endurance sports loads [30]. It has also been shown that physical exercises enhance endothelial NO-dependent dilation of both large and small vessels [41]. Regular physical activity enhances the synthesis and release of nitric oxide (NO), and also increases the bioavailability of NO. Studies of coronary circulation indicate a significant role of NO in the epicardial coronary vessels expansion during exercise. At the same time, most of the studies were conducted in patients with chronic heart failure. There are isolated studies conducted on athletes. Saunders et al. demonstrated that the effect of the homozygous genotype GG of the *NOS3* gene, associated with high endurance in runners, is phenotypically manifested only in homozygous genotype -9/-9 of the *BDKRB2* gene carriers. With other combinations of genotypes, combinations of the studied SNV genotypes, the homozygous genotype GG did not demonstrate a statistically significant positive association with an increase in athletic endurance and a reduction in finish time in triathletes of European origin [24].

Conclusions

Summing up the results of this review, I would like to note that an important gap that should be kept in mind when interpreting the literature in this area is the lack of large population samples to achieve sufficient statistical power to make firm conclusions. Differences in skill level, specifics of sports, ethnicity further complicate this issue. This explains the need for further research and data exchange between research centers around the world.

Limitations

The limitation of our review is the 20-year period of publication analysis. The authors acknowledge that increasing the analysis time by more than 10 years (for example, from the date of the opening of databases) may be useful in the future. Secondly, this research work did not take into account the potential distorting effect of the results level due to the different criteria of elite athletes. Thirdly, there may be a potential distorting effect of the level of results due to the different criteria of the comparison groups. For example, some research works compare athletes' data with data from a control group of people leading a sedentary lifestyle. For other authors, the control group consists of athletes, but not elite ones. There are comparison groups depending on the distance (short, medium and long distances) without a control group. Fourth, due to the diversity of definitions of

endurance/strength exercises and the data of some research works on mixed sports disciplines, phenotypic heterogeneity cannot be excluded. All of these factors could lead to a potential systematic selection error.

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