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Analysis of the Possible Reasons for the Decrease in the Effectiveness of Genetic Markers in Sports Search

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Abstract

The study of the processes occurring in the body under the influence of intense physical exertion, in order to increase the efficiency of the training process and the performance of athletes, is an important issue in the physiology of sports. It is known that the strength, speed, endurance and other morpho-functional features of a person are genetically determined. Therefore, the actual direction of research is the establishment of a spectrum of polymorphic genetic variants of genes associated with a predisposition to perform physical activities of varying intensity, as well as their phenotypic manifestation in professional activity.

However, despite the active search for genetic markers in sports with the use of modern high-tech technologies, it has not yet been possible to identify universal genes associated strictly with certain physical qualities. Perhaps, there is a number of factors that affect gene activity. Therefore, the purpose of the literature review is to search and analyze possible causes that can influence the activity of genes, for example, the most studied angiotensin-converting enzyme (ACE) gene associated with the development of specialized physical qualities in athletes.

Keywords: Sports • Polymorphisms • Genetics • Determinism • Success • ACE

Introduction

The steady growth of sporting achievements requires a significant improvement in the selection and training of athletes. The leading condition is an understanding of the body's adaptation mechanisms to dynamic physical exertion and enhancement of its functional capabilities.

It is known that the strength, speed, endurance and other morpho-functional features of a person are genetically determined. Establishing a spectrum of poly-morphic genetic variants of genes associated with a predisposition to perform physical activities of varying intensity as well as their phenotypic manifestation in professional activities will contribute to the development of a selection criteria system and training world-class athletes [1-8].

The official formation of "sports genetics" occurred at the Olympic scientific congress "Sport in Modern Society" in Tbilisi in 1980. The term "genetics of physical activity", proposed in 1983 by Claude Bouchard (Canada), marked the urgency of searching for genetic determinants of successful sports activity and the international project “HERITAGE” (Health, Risk Factors, Exercise Training and Genetics) had been already launched in 1995, in which several research centers participated, studying the relationship between genotypic and phenotypic traits [9].

Today, there is a great number of international projects in the world, aimed at finding genetic determinants that contribute to success in sports activities, for example, such as: “Genathlete” led by Claude Bouchard and Bernd Wolfarth [10], “Ironman” by Malcolm Collins [11], The Japanese Human Athlome Project (J-HAP) by Noriyuki Fuku and Powergene by Yannis Pitsiladis [12].

According to T. Raikinen et al. [13], in the framework of the “GENATHLETE” project, having analyzed 45 promising genetic markers, associated with endurance of 1,520 athletes from 7 countries (Australia, Ethiopia, Japan, Kenya, Poland, Russia and Spain), common or specific genes, related to desired physical qualities, had not been revealed. Similar studies, conducted by other research groups, had not established strict correlation patterns between phenotypic traits and genes [14-17]. It should be noted that C Santiago [15] in their work, having considered the genetic panel of the success of athletes, proposed by Jonathan P Folland [18], modifying it, concluded that the effectiveness among the examined athletes is not low and is only 70.2 ± 15.6 (%) *vs.* 60.8 ± 12.1 (%) of the control group. It is noted that this indicator did not make up 100% for any athlete. The same ambiguous results were obtained in smaller studies by independent laboratories in other countries.

However, despite some successes in the establishment of prognostically significant markers, it should be noted that the conducted studies do not provide a holistic view of the mechanisms of development of functional capabilities and physical performance of the body. Using the example of the most studied angiotensin-converting enzyme (ACE) gene, associated with the development of specialized physical qualities, we consider various factors that can influence the informativeness of the results.

Objectives

The aim of this review is to conduct a literary analysis of practical achievements and theoretical assumptions in the field of sports genetics, on possible factors leveling the prognostic significance of genetic success markers using the *Ins/Del ACE* gene polymorphism as an example. The article is based on publications that are based on the study of the functionality of *ACE* protein, taking into account modern molecular genetic results on the subject over the past twenty-five years, presented in international databases on the Internet: “*HuGENE*” (www.hugenavigator.com), “NCBI” (www.ncbi.nlm.nih.gov), *“Ensembl*” (www.ensembl.org), “*Gencards*” (www.genecards.org).

Discussion

ACE gene and its functions

The angiotensin-converting enzyme (*ACE*) gene, discovered 20 years ago, was the first "structural element" that made a significant contribution to the development of sports genetics and ideas about the effect of genes on a person’s physical performance [19]. *ACE* is mapped on chromosome 17 (*17q23*), the size of which is 22 kb. (26 exons and 25 introns) [20]. The ACE gene is alternatively spliced, producing two isozymes: an endothelial or somatic form, as well as a testicular form [21].

In the international databases "*HuGE* Literature Finder" and the "National Center for Biotechnology Information" there are a large number of independent studies and Meta-analyses devoted to the problem of studying the association

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of the I/D polymorphism of the *ACE gene* with the development of specific physical qualities in athletes. However, it should be noted that there is no consensus, so there is no reason.

It has been established that the frequency of occurrence of the I allele and the II genotype of the *ACE gene* is significantly higher among athletes specializing in sports where endurance is necessary (cycling, long-distance running, rowing, etc.) [22-26], and D allele and homozygous DD genotype is significantly higher in athletes with speed qualities (running and swimming over short distances, martial arts, football, basketball) [27-32]. There is a number of studies that adhere to the opposite point of view [32-39], and that have not established associations at all [40-44]. The question arises, why is it not possible to identify "*strict*" genetic markers of success?

Intergenic interaction

First, it is necessary to have a clear idea of how much a gene is affected by the phenotype of an athlete. De Moor, et al. [45] using the twin method, analyzing 4,488 British adult monozygous and dizygotic twins, women concluded that the success of athletes is only 66% explained by a genetic trait, the remaining 34% by other factors. Understanding how genes work and their interactions (gene-gene relationship) can play a key role in assessing the promise of using markers since even the presence of the desired mutation in humans can simply be suppressed by the work of the "*antagonist gene*" and not contribute actively to sport.

In 2016, the work of Dhamrait, et al. [48], on the effect of mutations *(UCP3-55C> T (rs1800849); UCP2-866G> A (rs659366); UCP2 D/I (rs1800795))* in mitochondrial uncoupling proteins (*UCP*) on the activity of the *RAAS* system and ACE, in particular, was published. As test subjects selected: 250 healthy men - British and 262 patients with diabetes living in the territory of Denmark. It was established that the interaction between the level of *ACE synthesis* and UCP activity occurs on the basis of feedback: the effect of *Ang* II on changes in mitochondrial activity, through modification of UCP expression, and, as a consequence, changes in *Ang* II synthesis, by regulating the activity of *ACE*. It is shown that UCP can also affect *ACE* in and outside the vascular bed, in tissues and organs, which can create "crosstalk" between cellular and endocrine metabolism. The authors note that the identification of these patterns can be of great practical importance in sports, allowing you to control the body's metabolism, as well as to study the effect of mutations in the *ACE gene* on this process [46,47].

Of particular interest is the model experiment of Natasha A Hamilton et al. [48] on purebred horses, bred selectively, with certain physical qualities. Genetic analysis revealed an SNP located in the 16th intron, homologous to that which contains *Alu* repetition in humans. The detected conservative sequence of 18 b.p. (within this intron, identified as a potential binding site for the transcription factors *Oct-1, HFH-1*, and *HNF-3*β which can affect metabolism, smooth muscle, and cell differentiation. According to the authors, an understanding of the mechanisms of interaction of the *ACE gene* and transcription factors will allow to expand current understanding of the regulation of gene work, their interaction and to have practical significance, both in medicine and in sports.

Effect of cations

According to modern literature data, a water-electrolyte balance can have a significant effect on the activity of enzymes. Using mathematical modeling and physicochemical methods, Mohd Akif found that chlorine ions could influence *ACE* [49]. Activity was characterized using an isothermal titration calorimetry (ITC)-based assay providing in depth information on the enzyme thermodynamic and kinetic parameters under varying chloride concentrations. *ACE* functionality is regulated through the interaction of the terminal domains of the protein with chlorine ions according to the principle of direct connection, the higher the concentration of chlorine, the more free/unbound *ACE*. However, it should be noted that, despite the sensitivity to chlorine, the activation of the C-domain requires a higher concentration of ions than the N-domain, which can also play an important role in the regulation of physiological processes of the body. The difference in affinity for *ACE* inhibitors trandolaprilat, enalaprilat and lisinopril between N- and C-domains is greater at high chloride concentration (300 mM), whereas for captopril the difference is greater at low chloride concentration (20 mM).

The authors noted that the results would serve as the basis for the development of specific drugs to combat hypertension due to selective control of ion exchange. Given that *ACE* is found in almost all tissues (brain, kidneys, bone marrow, pancreas, adipose tissue), where chloride levels can vary significantly, it is possible to control not only hemodynamics, but also all mediated *ACE* functions [52-54]. It must be emphasized that intense physical activity can provoke an imbalance of chlorine ions, affecting the activity of the angiotensin-converting enzyme. Therefore, the study of the mechanism of regulation of enzyme activity, taking into account the presence of Ins/Del polymorphism of the *ACE* gene, can increase the effectiveness of genetic studies.

Methylation

Epigenetic mechanisms, such as histone acetylation and methylation of *CpG* islets, are known to be processes that affect gene expression without altering the DNA coding sequence and are not limited to pre- and post-natal periods, arising throughout lifespan [53-56]. As a rule, hypermethylation of *CpG* gene promoter regions leads to the suppression of gene expression, while hypomethylated stimulate the opposite effect. It is important to note that the promoter of the human *ACE* gene also contains *CpG* islands that can influence gene expression [59-61].

Christoph Born et al. [60] found that hypometelation in the *-465 / -255* region (*24 CpG* site) of the ACE gene leads to a decrease in the production of *ACE*, and an increase in hypermeteralization leads to an increase in cardiovascular disease markers (CDM) such as *ICam -1, VCAM-1, E - selectins, P - selectins* and *MCP-1*, thereby increasing the risk of developing pathology. This discovery may be of practical importance, both in sports and in the pre nosological diagnosis of *CDM* in athletes, especially in light of recent events associated with an increase in cases of "sudden death syndrome" during training and competition [61]. However, it remains an open question about the effect of epigenetic mechanisms on the functional activity of the *ACE* gene of athletes when performing intensive physical activities, taking into account the presence or absence of insertion/deletion polymorphism [57,58-62].

Pharmacological action

Another aspect is the wide distribution of pharmacological drugs in sports, which allow increasing the efficiency of the training process and the effectiveness of athletes. However, in addition to positive effects, there are side effects that can lead to undesirable states, interacting with other substances in the body that affect protein synthesis or the efficiency of enzymes during exercise. In a mouse model experiment in Takako Fujiki et al. [63] proved the enhancing effect of H_2O_2 secreted by the vascular endothelium on the activity of the drug Temocapril, which inhibits the work of *ACE,* as well as stimulation of *eNOS* protein expression. There is a large number of works in clinical pharmacology devoted to the study of the effects of drugs of biologically active substances in the human body. In sports, similar studies in the scientific literature are practically not published, since in most cases the use of drugs is doping and is prohibited. Therefore, the study of the mechanisms of action on the body of various chemical substances contained in medicines, and in particular the enzyme and the *ACE* gene, during exercise, has yet to be studied, in order to increase the effectiveness of genetic selections in sports.

Ethnicity

The ethnicity of athletes may also be equally important [5,11,63-69]. The «National Center for Biotechnology Information» [19] published papers in which the Ins / Del association research results of the *ACE* gene polymorphism with the development of physical qualities (speed, endurance) in groups of athletes (running) have the opposite meaning (Table 1).

According to the data of Table 1, the I allele is associated among the athletes with endurance and it is more informative than the deletion of the *ACE* gene. It should be noted that a larger part of the work was carried out on athletes of European and African origin, but the fact does not reflect their true ethnicity, and only indicates that they belong to a common racial group, which may also affect the effectiveness of the experiments. The presented results also prove that the geographical features of the living conditions of populations, as well as the process of adaptation to them, can correct the work of the gene and the phenotype as a whole. Therefore, the search and selection of promising genetic markers should be carried out taking into account the ethnicity of the athlete in the formation of the analyzed groups. However, the factor is not taken into account in many studies, which can also reduce the information content of the data obtained.

Risk of illness

One of the most pressing problems of modern sports medicine is the study of "sudden death syndrome" (SDS) among qualified athletes. About 85% of all cases of SDS are caused by functional disorders of the cardiovascular system. It should be noted that the death rate from SDS among qualified athletes aged 12 to 35 years is 2.5 times higher than this figure for people not involved in sports [61]. However, the problem remains practically uncovered. Why does the Ins / Del polymorphism of the ACE gene, depending on the context, is considered a mutation that promotes the development of physical qualities and the progression of diseases?

For example, comparing the studies of Robert A Scott et al. [44] with Negar Firouzabadi et al. [70] and Atousa Moradzadegan et al. [71], conducted on a population, residing in Iran, it can be concluded that the D allele and D / D genotype of the ACE gene in the first case are associated with the development of endurance in Iranian athletes, and in two other cases they are associated with an increased risk development of coronary artery disease and coronary artery disease.

Is it true then that the athletes' risk of developing the disease under conditions of exposure to intense physical exertion can be correlated with a group of patients in a particular case? Where is the border, at the crossing of which changes are observed in a positive or negative direction, and what are the mechanisms of its regulation still to be studied?

Conclusion and Future Directions

The literature review is an attempt to explain the possible factors and mechanisms that mask the efficiency of gene work, which reduces the effectiveness of the search for specialized markers. Many aspects are relevant and require further conceptual work. However, nowadays, one of the options for increasing the effectiveness of research results is the use of a new approach to work. For example, the development of a single standard of genetic research in the field of sports genetics, which will be decisive for the selection and conduct of work by all researchers. This standard may need to include a single number of subjects, an analysis of ethnicity up to the third generation of parents, a single age group, and the development of a modern, strictly specialized model of classifying various sports. Another development option is the creation of experimental groups of athletes, depending on the type of nutrition and pharmacological support, and without them, in order to track and compare the success of a person, taking into account the polymorphisms of interest.

It is promising to increase the number of model experiments on animals because many animals, such as horses and dogs, are bred in purebred, "narrow-profile" breeds, with a set of strictly defined qualities, and also have homologous structures to human genes. Therefore, conducting genetic testing on animals can expand current knowledge of the mechanisms of regulation and interaction of genes, and can serve as a fundamental basis for understanding the work of the gene-gene, gene-environment systems for humans.

One of the possible drawbacks of the model of the conducted research is that most of them are cross-sectional, and do not reflect the dynamics of fluctuations in the functional parameters of athletes during the training macrocycle. Consequently, carrying out longitudinal work can allow tracking the success of an athlete over the entire length of time and analyzing the possible influence of various factors, including genetic polymorphisms.

Taking into account the above, it can be concluded that an understanding of the mechanisms of action of epigenetic, biological and other factors on genes can contribute to broadening the understanding of the fundamental principles of functioning of various body systems under conditions of intense physical activity, which can effectively develop the specific qualities of athletes speed or endurance) taking into account genetic features.

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