

# Angiotensin-converting enzyme gene: application possibilities in medicine and sports cardiology (literature review)

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**Aim.** Formation of modern ideas about the effect of angiotensin-converting enzyme polymorphism on the functioning of various body systems including in athletes.

**Methods of research.** Analysis and synthesis of the modern scientific literature data.

**Results.** According to modern ideas of sport molecular genetics, individual differences in the expression degree of certain physical and mental qualities of a person are largely determined by DNA-polymorphisms. Specific features of angiotensin converting enzyme I/D gene polymorphism influence on life-supporting systems functioning of human, who do not engage in sports, have been revealed. This polymorphism is widely covered by professional athletes from the point of view of physical qualities development possibility, but at the same time, the risk of pathological conditions development, taking into account regular intensive physical exertion, has not sufficiently studied. Knowledge of the innate personal physical abilities will help to predict the strengths and weaknesses of a person's physical and adaptive capabilities and, accordingly, to make a timely correct prognosis for personal sports prospects and carry out competent selection of athletes. This approach will allow them to progress quickly and achieve high results in sport.

**Conclusions.** A feature of genetic markers that do not change throughout life is the possibility of their determination immediately after child's birth, thus, the prognosis for indicators development that are significant in the conditions of sport activities can be made much earlier. In the available to us literature, ACE I/D gene polymorphism is primarily evaluated from the perspective of speed-strength development of physical qualities, but at the same time, genetic testing of beginner athletes should allow us to identify a risk group relatively to a number of pathological conditions progression that are genetically determined. Thus, despite numerous studies that allow an assessment of ACE gene polymorphism contribution to the life-supporting organs and systems state, the role of the ACE gene remains being insufficiently studied in sports medicine.

**Ключові слова:**  
ген ангіотензинперетворювального ферменту, поліморфізм, спортивна кардіологія.

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## Ген ангіотензинперетворювального ферменту: можливості застосування в медицині та спортивній кардіології

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**Мета роботи** – формування сучасних уявлень про вплив поліморфізму гена ангіотензинперетворювального ферменту на функціонування різних систем організму, в тому числі у спортсменів.

**Матеріали та методи.** Аналіз та узагальнення даних сучасної наукової літератури.

**Результати.** Відповідно до сучасних уявлень молекулярної генетики спорту, індивідуальні відмінності у ступені вираженості тих чи інших фізичних і психічних якостей людини багато в чому зумовлені ДНК-поліморфізмами. Виявлено особливості впливу I/D поліморфізму гена ангіотензинперетворювального ферменту на функціонування життєзабезпечувальних систем в осіб, які не займаються спортом. Цей поліморфізм доволі широко розкритий у професійних спортсменів із погляду можливості розвитку фізичних якостей, водночас недостатньо вивчені питання ризику розвитку патологічних станів з урахуванням регулярних інтенсивних фізичних навантажень. Знання вроджених фізичних здібностей допоможе прогнозувати сильні та слабкі сторони фізичних та адаптаційних можливостей людини та, відповідно, робити своєчасний і правильний прогноз спортивної перспективності й здійснювати грамотну селекцію спортсменів. Такий підхід дасть можливість їм швидко прогресувати та досягати високих результатів у спорті.

**Висновки.** Особливістю генетичних маркерів, не змінних протягом усього життя, є можливість їх визначення відразу після народження дитини, отже, прогноз розвитку показників, які є значущими в умовах спортивної діяльності, можна складати набагато раніше. У доступній нам науковій літературі переважно оцінюється I/D поліморфізм гена ACE з погляду перспективи розвитку швидко-силових фізичних якостей, але водночас генетичне тестування спортсменів повинно дати можливість виявити групу ризику щодо прогресування низки патологічних станів, генетично детермінованих. Отже, попри численні дослідження, що дають змогу оцінити вплив поліморфізму гена ACE на стан життєзабезпечувальних органів і систем, роль гена ACE залишається недостатньо вивченою у спортивній медицині.

**Ключевые слова:**  
ген ангиотензинпревращающего фермента, полиморфизм, спортивная кардиология.

## Ген ангиотензинпревращающего фермента: возможности применения в медицине и спортивной кардиологии

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**Цель работы** – формирование современных представлений о влиянии полиморфизма гена ангиотензинпревращающего фермента на функционирование различных систем организма, в том числе у спортсменов.

**Материалы и методы.** Анализ и обобщение данных современной научной литературы.

**Результаты.** Согласно современным представлениям молекулярной генетики спорта, индивидуальные различия в степени выраженности тех или иных физических и психических качеств человека во многом обусловлены ДНК-полиморфизмами. Выявлены особенности влияния I/D полиморфизма гена ангиотензинпревращающего фермента на функционирование жизнеобеспечивающих систем у лиц, не занимающихся спортом. Данный полиморфизм достаточно широко освещен у профессиональных спортсменов с точки зрения возможности развития физических качеств, в то же время недостаточно изучены вопросы риска развития патологических состояний с учетом регулярных интенсивных физических нагрузок. Знание врожденных физических способностей человека поможет прогнозировать сильные и слабые стороны физических и адаптационных возможностей человека и, соответственно, делать своевременный и верный прогноз спортивной перспективности и осуществлять грамотную селекцию спортсменов. Такой подход позволит им быстро прогрессировать и достигать высоких результатов в спорте.

**Выводы.** Особенностью генетических маркеров, не меняющихся на протяжении всей жизни, является возможность их определения сразу после рождения ребенка, таким образом, прогноз развития показателей, значимых в условиях спортивной деятельности, можно составлять намного раньше. В доступной нам научной литературе преимущественно оценивается I/D полиморфизм гена ACE с точки зрения перспективы развития скоростно-силовых физических качеств, но в то же время генетическое тестирование начинающих спортсменов должно позволить выявить группу риска относительно прогрессирования ряда патологических состояний, генетически детерминированных. Таким образом, несмотря на многочисленные исследования, позволяющие оценить влияние полиморфизма гена ACE на состояние жизнеобеспечивающих органов и систем, роль гена ACE остается недостаточно изученной в спортивной медицине.

The actual problem of the modern training system of highly qualified athletes is the improvement of sport selection and sport orientation [13]. Modern professional sport makes the highest demands on the locomotor and functional characteristics of athletes. Nowadays, high-level sport is characterized by extremely intense and prolonged physical and neuropsychological loads, the range of which is limited by the genetic and physiological capabilities of the human body [15]. In connection of this, the issue of training process efficiency rising is thrown into sharp relief, as well as its aspects optimization, reserve capabilities determination and an athlete's body adaptive potential extension. It is obvious that the solution of this problem requires the principle of individualization at the early stages of sport trainings approach [3].

Individual features in the degree of adaptive changes in response to training incentives are largely determined by genetic factors that specify hereditary predisposition to the physical exertion tolerance. Knowledge of the innate personal physical abilities will help to predict the strengths and weaknesses of a person's physical and adaptive capabilities and, accordingly, to make a timely correct prognosis for personal sports prospects and carry out competent selection of athletes. This approach will allow them to progress quickly and achieve high results in sport [28].

It is known that personal physical qualities development and manifestation depend on both hereditary and surrounding factors. The human body undergoes definite morpho-functional and physiological changes under the influence of regular intense physical activity in the course of sport activity aimed to extend the range of functional capabilities and increase stress resistance [1]. The severity of these changes is determined by age and gender characteristics of individuals and to a greater extent by the peculiarities of their constitution.

Nowadays, there is a rapid development of sport molecular genetics in the arsenal of which highly effective technologies and methods have appeared that provide the ability to determine the molecular mechanisms of human physical qualities inheritance [4]. According to modern ideas of sport molecular genetics, individual differences in the degree of person's certain physical and mental qualities expression are largely determined by DNA-polymorphisms

[27]. Among the polymorphisms of the human genome, which are currently at least 13 million, the most common are single nucleotide polymorphisms of SNP, that is, single nucleotide positions in genomic DNA for which the population has different variants of sequences (alleles) [7].

Prediction of aerobic and anaerobic physical capacities of beginner athletes is possible only as a result of certain characteristics range complex assessment. In order to increase the effectiveness of such prognosis, it becomes necessary to create a diagnostic complex that includes the entire range of biochemical, physiological, and anthropometric methods, as well as a full-genome screening of loci associated with various physical qualities development and manifestation.

As a result of numerous studies in the field of physical genetics activity, more than 50 DNA loci linked to aerobic and anaerobic energy systems have been identified [14]. It should be noted that not a single endophenotype, but a complex of characteristics which determine any final phenotype, has been chosen as an object of this kind research. The application of this approach proceeds from the notion of synanthropic traits (interrelated signs that determine the final phenotype) and synanthropic genes.

## The aim

**The aim of the study** – formation of modern ideas about the effect of angiotensin-converting enzyme polymorphism on the functioning of various body systems including in athletes.

## Methods of research

Analysis and synthesis of modern scientific literature data.

## Results and discussion

A classic example of a specific gene association variation with a complex of synanthropic features, which is based on the gene pleiotropy phenomenon, is the angiotensin converting enzyme (ACE) I/D gene polymorphism. The

angiotensin-converting enzyme hydrolyses angiotensin-I decapeptide into the angiotensin II vasopressor, plays a key role in renin-angiotensin system (RAAS) activity regulation, which is responsible for blood vessels tone control, water-salt homeostasis maintaining, nourishing and stimulation of vessels and myocardium smooth muscle cells proliferation, and also affects fibrinolysis, platelets activation and aggregation [2].

The ACE gene produces 2 isoforms: 1) endothelial or somatic form which is expressed in many tissues, including vascular endothelial cells, renal epithelial cells, Leydig cells, duodenum, lungs, pulmonary blood vessels, prostate and 2) testicular form that is expressed only in sperm [21].

The ACE gene is characterized by insertion-deletion (I/D) polymorphism in the 16<sup>th</sup> intron of chromosome 17q23. The fragment with length of 300 nucleotide pairs (n. p.) presence or absence is considered to be a marker for angiotensin converting enzyme gene polymorphism, the fragment 490 n. p. is typical for insertion (I), and 190 n. p. for the deletion (D). In accordance with the insertion/deletion of a given DNA fragment in the homo- or heterozygous state, the following genotypes are identified: II – homozygous for the presence of insertion; DD – homozygous for deletion; ID – heterozygous [24].

The association of the polymorphic insert of Alu-repeat (I/D polymorphism) in the 16<sup>th</sup> intron of the ACE gene with the level of angiotensin-converting enzyme in plasma was revealed. This polymorphism determines about 47 % of the variability of the ACE level in plasma and is associated with manifestations of essential hypertension, hypertrophic cardiomyopathy and ischemic heart disease [8]. Persons with a D/D genotype (the genotype was observed approximately in 36 % of people), have the maximum ACE blood level, with I/I genotype (about 17 % of people) – ACE blood level is less by half and heterozygote have intermediate blood enzyme level [9].

The ACE gene polymorphism has a significant effect on cardiovascular system diseases development and progression. Biochemical manifestations of the DD genotype are: increase in ACE level and activity and angiotensin II level, decrease in bradykinin level and sensitivity to sodium, insulin resistance. The phenotypic manifestations of this genotype include: hypertension, left ventricular (LV) myocardial hypertrophy, coronary artery spasm, myocardial infarction, more frequent development and severe kidney diseases, high risk of sudden death. In addition, in the presence of genotype D/D, smoking increases the risk of myocardial infarction by a factor of two. The presence of variant D in both homozygous and heterozygous forms corresponds approximately to a twofold increase of fatal myocardial infarction risk. High levels of arterial pressure in D/D genotype carriers cause the progression of hypertensive disease, initiating hypertrophic changes in the LV. Allele I and genotype II, in contrast, are factors that protect against hypertension development [10].

It is known that I/D polymorphism significantly affects the progression of glomerular and tubulointerstitial kidney diseases. DD homozygotes have a higher concentration of angiotensin II receptors, which contributes to the progression of not only systemic, but also intrarenal hypertension. There is a number of conflicting data on DD polymorphism role in renal failure progression, which is probably related to

ethnic characteristics [11]. The prevalence of DD genotype was revealed in patients with hereditary kidney pathology (glomerulonephritis, polycystosis), while the course of the disease is accompanied by a decrease in the glomerular filtration rate [6].

It was determined that if patients have type 2 diabetes, then the heterozygotes for ACE gene ID polymorphism reach compensation and subcompensation in diabetes treatment more often than in homozygotes carrying genotypes II and DD, the risk of patients' microvascular complications with the ID genotype is lower than of those patients with genotypes II and DD [12].

Numerous studies results favour for interaction of ACE gene I/D polymorphism with high sport achievements [16].

The ACE I allele prevails in the group of long-distance runners compared to the sprinters and control group [25], which is in complete conforms the data on the association of this allele with high values of maximum oxygen consumption (MOC) [23], the prevalence of slow muscle fibers in m. vastus lateralis [22], as well as a reduced risk of myocardial hypertrophy development (a factor limiting cardiorespiratory endurance) in response to physical exertion [26].

Much attention is paid to the study of muscular activity influence on the physiological parameters of the organism in connection with ACE various allelic variants [17]. A high correlation between increased left ventricular mass after endurance training with the ACE elevated level in the blood and a D/D genotype was established. During the strength training of the quadriceps femur, the association of its strength with the ACE gene D allele was determined. Later these data were confirmed by measuring the isometric and isokinetic strength of this muscle in the D/D genotype carriers. The observed effect, apparently, depended on the different ratio of fast and slow muscle fibers. Individuals, who have the D/D genotype, the ratio of slow fibers to fast fibers was approximately the same, while slow fibers were predominant in I/I individuals [18].

There is data on the frequency of athletes' ACE gene genotypes distribution in different kinds of sport. The D/D genotype predominates (31 %) among sportsmen who specialize in speed-power kinds of sport. Its frequency is reduced to 24 % for sports requiring endurance and for athletes of the mixed group to 17 %. Thus, athletes with ACE gene D/D genotype are more predisposed to speed-strength physical qualities development and persons with genotype I/I – to perform long-term physical work [19].

Certain studies cover the role of ACE gene in sports cardiology. Thus, athletes who keep up regular training program mostly aerobic kinds of sport (long distance running, skiing, cycling) have mainly increased the left ventricular cavity with a proportional increase in its walls thickness. This is caused by the increased cardiac output during exercising, i.e. reloading the volume of the left ventricle, as well as increasing systemic blood pressure. Left ventricle eccentric hypertrophy develops without changing the ratio of left ventricle wall thickness to its diameter [20]. Athletes with static or isometric trainings (weightlifting, martial artists and thrower hurlers) develop concentric hypertrophy with an increase in left ventricle wall thickness without its cavity size change, which is caused by afterload on the heart increase due to an increase in systemic arterial pressure during physical exercises [29].

According to echocardiography, athletes have an increase in left ventricle posterior wall and interventricular septum thickness by approximately 15–20 % compared to untrained people. The diastolic size of the left ventricle in most athletes is approximately 10 % greater than that in untrained people, but it is within the reference values [5].

At the same time, according to Drozdovska S. (2014), the heart echocardiographic parameters of athletes who specialize in speed-power athletics do not statistically differ significantly from the average population. Most athletes have no signs of pathological cardiac remodeling. It is established that ACE gene D/D genotype contributes to more adequate adaptation to the speed-strength work in athletics.

## Conclusions

Thus, despite numerous studies that allow an assessment of ACE gene polymorphism contribution to the life-supporting organs and systems state, the role of the ACE gene remains being insufficiently studied in sports medicine.

In the available to us literature, ACE I/D gene polymorphism is primarily evaluated from the perspective of speed-strength development of physical qualities, but at the same time, genetic testing of beginner athletes should allow us to identify a risk group relatively to a number of pathological conditions progression that are genetically determined.

It is important to note that the most accurate definition of a predisposition to sports should be made on the basis of significant number of markers analysis including phenotypic (anthropometry, functional diagnostics), as only by this way the environmental influence on genetically fixed signs can be reflected. At the same time, it is possible to evaluate the degree to a particular sport predisposition, indicating possible chances of achieving high results and risks of adverse cardiovascular events development. A feature of genetic markers that do not change throughout life is the possibility of their determination immediately after child's birth, thus, the prognosis for indicators development that are significant in the conditions of sport activities can be made much earlier.

**The perspective of further research** is further study of various angiotensin-converting enzyme gene polymorphisms effects on life-supporting organs and systems functions in highly skilled athletes with the aim to develop an algorithm for athletic performance prediction in the early stages of certain physical qualities development.

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