Published by :
http://www.ijert.org

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 6 Issue 06, June - 2017

Genotype Association with Sport Activity: The Impact of ACE and ACTN3 Gene Polymorphism on Athletic Performance

Alem Šećerović[1], Lejla Gurbeta[1,2], Enisa Omanović-Mikličanin[1,3], Almir Badnjević[1,2,4]
[1]Department of Genetics and Bioengineering, Faculty of Engineering and Information Technology, International Burch University, Sarajevo, Bosnia and Herzegovina
[2]Verlab Ltd. Sarajevo, Bosnia and Herzegovina
[3]Faculty of Agriculture and Food Sciences, University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[4]Technical Faculty Bihac, University of Bihac, Bosnia and Herzegovina

***Abstract*—The purpose of this paper is to provide an overview of genes that have an impact on athletic performance. In recent years, there is a visible progress in molecular biology techniques, which facilitate researches in the field of genetics related to the sport performance. The paper focuses on 2 genes which are most intensively studied in relation to the athletic ability – angiotensine I-converting enzyme (ACE) and alpha-actinin 3 (ACTN3). There are shown results from many researches, and they indicate that genetic factors have effect on sports performance, but also impact of training and environment is important. With new approaches, new polymorphisms are discovered, so research of this area of genetics is still in progress.**

Keywords- Athletic Performance; Genetics; Polymorphism; Genotype; Endurance; Strength; ACE; ACTN3.

I. INTRODUCTION

The healthcare system have changed over the past decades. Nowadays, employing machine learning techniques and modern machinery is not uncommon [1,2,3]. New methods and techniques are being developed on a monthly basis. Beside improving quality of care provided to the patients [4,5] healthcare system is leaning toward personalized medicine where medical decisions, practices, treatments are customized to the individual patient based on predicted response or risk of disease that highly depend on patient characteristics. The personalized healthcare can be especially important when patients are professional athletes.

It is found that athlete's performance is related to the biological properties of a person. Those properties can be metabolic or anatomical (e.g. length and elasticity of tendons, muscle tension and types of fiber). All these properties and phenotypes, combined together, make individual genetic profile.

There is increase in identification of different phenotypes related to the athletic performance over the past 20 years. Human gene map for exercise has been made based on the research results. The map is constantly updated with number of polymorphisms [6,7]. The first discovered polymorphism related to sport performance was– ACE (angiotensin-conversion enzyme) [8,9].

It is the ACE insertion/deletion polymorphism that has the effect on fitness and performance traits. Beside ACE, it was found that ACTN3 gene is related to athletic fitness [10]. As shown in the table below, there are some genes that could be a potential source of influence on people's athletic performance (Table I).

Investigation of challenging factors that affect human athletic performance is present in the field of study in sport science. We can divide those parameters on intrinsic (e.g., genetics, motor behavior, physiological and psychological profile) and extrinsic factors (e.g., training, nutrition, overall health conditions).

TABLE I. SUMMARY OF CANDIDATE GENES FOR ATHLETIC PERFORMANCE

Gene	Type of polymorphism	Physiological effect	Population	Major findings
ACE	Insertion/ deletion of an Alu element	Influences circulatory homeostasis	Power and endurance athletes	Association with fatigue resistance in skeletal muscle
BDKRB2	Insertion/ deletion of a 9bp repeat	vasodilator	Endurance athletes	Association with skeletal muscle metabolic efficiency
ACTN3	RFLP	Binds and anchors actin filaments	Power and endurance athletes	Influence on muscle function
CKM	RFLP	Catalyses the phosphorylation of creatine to phosphocreatine	Total and endurance athletes	Influence on VO2max
ADRA2A	RFLP	Regulation of adipose tissue lipolysis	Endurance athletes	Influence on the number of receptors of adipocytes
Na+ - K+- ARPase α2	RFLP	Influences the excitability of skeletal muscles	Endurance athletes	Regulation of VO2max response to training
PPARα	RFLP	Regulates lipid, glucose, and energy homeostasis	Power and endurance athletes	

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 6 Issue 06, June - 2017

PPARGC 1A	SNP	Controls oxidative phosphorylation	Total athletes	Influence on VO2max
EPAS1	SNP	Involves in the hypoxia inducible factor pathway	Endurance athletes	Aerobic and anaerobic contributions to endurance
MTDN5	mtDNA RFLP	Increases VO2max	Sedentary subjects	Influence endurance

Some athletes show very high-performance levels even before taking part in training programs, but some athletes demonstrate better responses to training than others [11]. Even though the genetics is a remarkable influential performer, it is still in its developing phase of recent interest when it comes to human's athletic performance [12]. Until today, more than 200 polymorphisms have been associated with athletic performance. The number will increase in the following years [13]. Out of 200 genetic variants, only 10% are observed in athletes. Only a small number, more accurate less than 10, genetic variants have been associated with sports performance [14].

II. PERFORMANCE STRUCTURE

First which is important in attempting to describe impact of genetics factors on athletic performance is its multifactorial nature. Each sport discipline has its unique physical requirements. Those requirements are different between sports. Because of that, each study and experiment based on genetic influence on athletic performance, needs to be appropriate for the sport of interest.

In our body, a lot of systems must have interaction (musculoskeletal, cardiovascular, respiratory, nervous, etc.) and that is the reason why athletic performance is one of the most complex human traits. First difference between which is visible between athletes of different disciplines is in body morphology (i.e., height, body composition). Also, endurance, strength and power are primary factors that affect athletic performance.

Aerobic endurance denotes the ability to sustain an aerobic effort over the time. It is important parameter in distance running or cycling. Our cardiovascular system has ability to deliver oxygen to the working muscles, and muscles utilize that oxygen. Quantification measure for aerobic endurance is the maximal rate of oxygen uptake (VO2max).

Muscular strength is the ability of the muscle to generate force, and it is quantified by the one repetition maximum. Muscle power is the interaction between the force and velocity of a muscle contraction (ability to generate as much force as possible, as quickly as possible). Those 2 parameters are important in disciplines such as sprinting, jumping and weightlifting.

Some additional components of athletic performance are cognitive factors and injury sensitivity. However, environment also has impact on that traits. Person „trainability" is also influenced by genetic factors and it is reviewed by Bouchard [13]. Impact of environment versus genetic factors is not the same in each sport. For example, it differs in gymnastics vs. 100m sprint. Athletic status is therefore interaction of genetic traits and ideal environment [15].

There are many genes which are associated with performance, but most of discoveries are not replicated. Two exceptions are ACE and ACTN3 genes which are studied in several populations, and many experimental approaches and analysis are done on those two genes. Because of that, in this review article are considered those two most studied genes that have influence on physical performance. Literature which is related to ACE gene is reviewed. For this gene, there is a lot of articles that examine the effect of insertion/deletion polymorphism on fitness and performance. Beside ACE gene, a great attention is in scientific papers which is related to athletic performance – ACTN3 gene.

III. ACE GENE

Angiotensine converting enzyme is the gene which is most extensively studied in sports and physical performance [16,17,18]. First evidence for association of ACE gene and athletic performance is published in 1998 by Montgomery et al. [17]. ACE is located on the long arm of chromosome 17 (17q23). The gene is 21 kilo bases (kb) long and comprises 26 exons and 25 introns. In 1990, Rigat [19] and coworkers published an important report that provided the impetus to further study polymorphisms in this gene. They found a polymorphism involving the presence (insertion, I) or absence (deletion, D) of a 287-bp sequence of DNA in intron 16 of the gene. Angiotensin I-converting enzyme involved in catalyzing the conversion of angiotensin I into a physiologically active peptide angiotensin II [20,21]. Angiotensin II is a potent vasopressor and aldosterone-stimulating peptide that controls blood pressure and fluid-electrolyte balance. Despite the fact that ACE gene regulates blood pressure, it is also expressed in skeletal muscle and may influence its function [22].

ACE D allele is associated with higher circulating, so this allele affect performance in more power or strength oriented sports. I allele of ACE gene is associated with decreasing circulating levels of angiotensine II, so it can facilitate cardiac output during some hard exercise. I allele is also favor muscle efficiency, which is important for long-distance runners. D allele is present mostly among power oriented sports, while I allele is present in elite endurance athletes [23].

To be successful in endurance sports, it requires high level of aerobics which is measured by maximal oxygen uptake (VO2max), while power events depends on muscular speed. Because of that it is not common to see athlete which is good in 100 m sprint as well as in 10 000 m running.

There is a study which is carried between 39 Portuguese Olympic swimming candidates. They were divided in 2 homogeneous groups: short distance swimmers (SDS) and middle-distance swimmers (MDS). First group (between 50 and 200m swimmers) is mainly anaerobic event, while second group (400-1500m swimmers) is mixed anaerobic and aerobic event. Also, group of 32 non-elite swimmers is studied. Control group of 100 persons was taken from the Portuguese population. Results showed higher DD genotype (P=0.029) and allelic frequency (P=0.021) of short distance swimmers compared to controls. It just confirmed previous

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 6 Issue 06, June - 2017

observations that D allele is associated with SDS and that D allele is related to more power oriented sports [24,25].
One another study performed Papadimitriou et al. [25] showed a weak association between DD genotype and power oriented sports. 101 Greek athletes were subjected to investigation. 73 of them are power oriented athletes, while 28 are sprinters) and 181 controls. Results showed that sprinters had higher frequency of DD genotype compared to control group (55.8% vs 31.5%). A lot of evidences about association of ACE polymorphism and athletic phenotype are not definitive. It is reported by Amir et al. [26] that D allele is more present in Israel marathon runners than in sprinters.
Association of ACE I/D polymorphism with different sport disciplines is very challenging and it is not so simple. Polymorphism is common with I allele 50%, and sport performance can depend on several biological and environmental factors. To make a solid conclusion this study need a very large number of samples (several hundreds). Genome wide analysis studies can be performed, to analyze linkage between hundreds of polymorphisms [27].

IV. ACTN3 GENE

Researchers, after years of examination, have identified that more than 200 genes have impact on physical performance. One of the most-studied genes is R577X polymorphism of the α-actinin-3 gene (ACTN 3). ACTN3 gene is located on the long arm of the chromosome 11q 13.2. It is also named „speed gene“ [28,29,30]. This gene encode the α-actinin-3 protein, which is, together the α-actinin-2 protein, an important structural component of the Z disc, where they anchor actin thin filaments, helping to maintain the myofibrillar array [31,32]. Some studies showed that absence of α-actinin-3 GHSDHFGHprotein is important to sprint and power performance in athletes [33,34]. α-actinin-2 can be found expressed in all skeletal muscle fibers, while α-actinin-3 is expressed only in type 2 fibers. ACTN3 gene has a nonsense polymorphism R577X, that may influence muscular performance. This is a transition of a cytosine to thymine at codon 577 of ACTN3 gene, which for result has replacement of arginine residue (R allele) by a premature stop codon (X allele). It is proven in many studies that physiological consequences of an α-actinin-3 deficiency leads to different fiber type composition of human muscle. The R577X polymorphism is found in every human population [30].
First associations between ACTN3 genotype and athletic performance are shown by Yang et al. [35] 50% of elite white sprinters had RR genotype, while 30% healthy white control and 31% of elite endurance athletes had the same genotype. White elite endurance athletes had a little bit higher frequency of the XX genotype (24%) compared to controls (18%). It gives a conclusion that presence of ACTN3 protein (577R) is associated with better success in sprint or power performance. Lack of ACTN3 (577X) may be advantage for endurance athletes. This is confirmed by some studies in which are visible associations between 577X allele and elite endurance athlete performance [36].

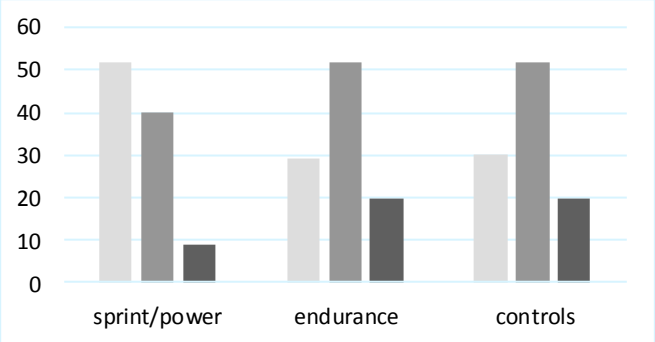

Figure 1. ACTN3 genotype frequencies in controls and sprint/power and endurance athletes (from Yang et al., 2003.)

Eynon et al. [37] presented the ACTN3 R577X polymorphism in Israeli population. 155 athletes were analyzed and 240 non-athletic individuals as controls. All the athletes were divided in two groups – endurance group consisted of 74 long distance runners and sprint group consisted of 81 sprinters. Results showed higher number of XX genotype in first group of endurance athletes, compared to 14% sprinters and 18% controls groups. Later on athletes were divided in two sub-groups – top level and national level. It is found that R allele is more often found in top-level sprinters. The hypothesis that ACTN3 R allele is associated with top-level sprint performance is supported with this data, but XX genotypes may not be critical to endurance performance. Some other studies did not show association between endurance performance and XX genotype, so it can be concluded that that association is not strong as association with reduced performance and power activities [38].
The ACTN3 R557X polymorphism has also been studied in three groups of elite European athletes. 633 athletes and 808 controls were used. Confirming the previous literature, power athletes were 50% less likely to have XX genotype, while endurance athletes were approximately 1.88 times more likely to have XX genotype vs. The RR genotype. Some further analysis is necessary to discover if some other polymorphisms are contributing in determining sports performance.

V. DISCUSSION

There are some differences in anatomy and physiology of males and females that play role in athletic performance. Some of parameters are gender – specific. XX genotype of ACTN3 gene is present in female endurance athletes, but the same genotype is not present in male endurance athletes [39]. Also, muscle anatomy is more affected by deficiency of ACTN3 in women than in men [40,41]. One more important parameter in this kind of researches is ethnicity [42]. In Russian athletes' R allele is associated with endurance sports, while most other studies associate X with that disciplines.

Also, another issue of researches of this kind is how to determine which sport disciplines are endurance, and which are strength based. Also, question is where to place sports which are mixture of endurance and strength based disciplines. In some articles 200m disciplines are marked as sprint disciplines [43], while in other articles are used 400m disciplines [44]. This differences surely affect statistical parameters.

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 6 Issue 06, June - 2017

One more limitation in studies of this type is small sample size. Mainly, in these tests are included elite athletes. That fact shortens the choice and the spectrum of performance. Maybe enlistment of retired athletes will broaden the choice. Nevertheless, with the promising rate of development of biomedical engineering [45,46] this research can be extended to athletes in population of Bosnia and Herzegovina and Balkan region.

Many clinicians and sport scientists may be expecting more from molecular studies that can be delivered. One step forward will be discard both the dualistic approach to nature versus nurture and philosophy that gene is a magic bullet. Sport performance is the result of interactions among a host of genes and environmental constraints.

In researches on ACE gene is found association between I and D allele in elite athletes. Those two alleles have different effect on athletic ability. I allele is associated with endurance performance (Montgomery et al. 1998 [47].;Gayagay et al. 1998. [48]; Myerson et al. [49]; Collins et al. 2004. [50]), while D allele is associated with sprint power disciplines (Woods et al. 2001. [51]; Nazarov et al 2001. [52]). Also, there are some reports which do not show association between athletic performance and ACE polymorphism (Rankinen et al. 2000. [53]; Taylor et al. 1999. [54]). those disagreements in results are difficulties in studies of this type, and maybe are present because of experimental design.

Articles associated with ACTN3 gene show relation between RR genotype and power performance. Male and female sprint athletes have more 577R alleles. Some studies did not provide evidence for relation between endurance disciplines and XX genotype.

VI. CONCLUSION

Some evidence suggests that an auspicious genetic profile, combined with well-organized training, is important, but not crucial for making success in sport. A few genes are constantly associated with athletic performance, but it is not so strong to be predictive in talent selection. Person's genetic profile does not define his destiny. Good athlete needs to have strong mental and physical constitution and strong determination to fight for glory. Impact of genetics is surely remarkable, and the knowledge of persons genome helps in selecting the best discipline for them.

The future of studying genes that affect athletic performance is promising. There is so many polymorphisms that are associated with athletic phenotypes, but definitive conformation of that is difficult task. New experimental approaches are used to solve some mysteries, and there is remarkable progress in this area of genetics. Some people think that genetic profile could be used to detect the talents, but it must be considered that research of this area is still in its phase of development.

REFERENCES

[1] Veljovic E, Spirtovic – Halilovic S, Muratovic S, Osmanovic A, Badnjevic A, et.al., "Artificial Neural Network and Docking Study in Design and Synthesis of Xanthenes as Antimicrobial Agents", CMBEBIH 2017. IFMBE Proceedings, vol 62. pp 617-626, Springer, Singapore. DOI: 10.1007/978-981-10-4166-2_93

[2] Abdel-ilah L, Veljović E, Gurbeta L, Badnjević A. „Applications of QSAR Study in Drug Design", International Journal of Engineering Research & Technology (IJERT), 6(06), June 2017

[3] Badnjevic A, Beganovic E, Music O. „Facts about solution based and cartridge based devices for blood gas analyses", IEEE 18th International Conference on System, Signals and Image Processing, pp:1-5, 16-18 June 2011, Sarajevo, Bosnia and Herzegovina.

[4] Badnjevic A, Gurbeta L, Boskovic D, Dzemic Z. „Measurement in medicine – Past, present, future", Folia Medica Facultatis Medicinae Universitatis Saraeviensis Journal, 2015; 50(1): 43-46

[5] Badnjevic A, Gurbeta L, Boskovic D, Dzemic Z. „Medical devices in legal metrology", IEEE 4th Mediterranean Conference on Embedded Computing (MECO), pp: 365-367, 14 – 18 June 2015, Budva,

[6] Montgomery HE, Marshall R, Hemingway H, et al. Human gene for physical performance. Nature. 1998;393:221-2.

[7] Hagberg JM, Rankinen T, Loos RJ, et al. Advances in exercise, fitness, and performance genomics in 2010. Med Sci Sports Exerc. 2011;43:743-52.

[8] Roth SM, Rankinen T, Hagberg JM, et al. Advances in exercise, fitness, and performance genomics in 2011. Med Sci Sports Exerc. 2012;44:809-17.

[9] Bray MS, Hagberg JM, Perusse L, Rankinen T, Roth SM, et al. The human gene map for performance and health-related fitness phenotypes: the 2006-2007 update. Med Sci Sports Exerc 2009; 41:35 73.

[10] Gibson WT. Key concepts in human genetics: understanding the complex phenotype. Med Sport Sci. 2009;54:1-10.

[11] Tucker R, Collins M. What makes champions? A review of the relative contribution of genes and training to sporting success. Br J Sports Med. 2012;46:555-61. K. Elissa, "Title of paper if known," unpublished.

[12] Bouchard C. Overcoming barriers to progress in exercise genomics. Exerc Sport Sci Rev. 2011;39:212-7.

[13] Williams AG, Folland JP. Similarity of polygenic pro. les limits the potential for elite human physical performance. J Physiol. 2008;586:113-21.

[14] Tucker R, Collins M. What makes champions? A review of the relative contribution of genes and training to sporting success. British Journal of Sports Medicine. 2012 Jun 10; 46(8):555–61. This review discusses the interactions between genetic and environmental factors (specifically training or deliberate practice) and their respective influences on athletic performance. [PubMed: 22535537]R. Nicole, "Title of paper with only first word capitalized," J. Name Stand. Abbrev., in press.

[15] Myerson S, Hemingway H, Budget R, Martin J, Humphries S, Montgomery H. Human angiotensin I-converting enzyme gene and endurance performance. J Appl Physiol. 1999;87:1313–1316.

[16] Woods D, Hickman M, Jamshidi Y, Brull D, Vassiliou V, et al. Elite swimmers and the D allele of the ACE I/D polymorphism. Hum Genet. 2001;108:230–232.

[17] Montgomery HE, Marshall R, Hemingway H, Myerson S, Clarkson P, et al. Human gene for physical performance. Nature. 1998;393:221–222.

[18] Gordon SE, Davis BS, Carlson CJ, Booth FW. ANG II is required for optimal overload-induced skeletal muscle hypertrophy. Am J Physiol Endocrinol Metab. 2001;280:E150–159.

[19] Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest. 1990;86:1343–6.

[20] Jones A, Montgomery HE, Woods DR. Human performance: a role for the ACE genotype? Exerc Sport Sci Rev. 2002;30:184–190.

[21] Wagner H, Thaller S, Dahse R, Sust M. Biomechanical muscle properties and angiotensin-converting enzyme gene polymorphism: a model-based study. Eur J Appl Physiol. 2006;98:507–515.

[22] Yamin C, Amir O, Sagiv M, Attias E, Meckel Y, et al. ACE ID genotype affects blood creatine kinase response to eccentric exercise. J Appl Physiol. 2007;103:2057–2061.

[23] Tsianos G, Sanders J, Dhamrait S, Humphries S, Grant S, Montgomery H. The ACE gene insertion/deletion polymorphism and elite endurance swimming. Eur J Appl Physiol. 2004;92:360–362.

[24] Nazarov IB, Woods DR, Montgomery HE, Shneider OV, Kazakov VI, et al. The angiotensin converting enzyme I/D polymorphism in Russian athletes. Eur J Hum Genet. 2001;9:797–801.

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 6 Issue 06, June - 2017

[25] Papadimitriou ID, Papadopoulos C, Kouvatsi A, Triantaphyllidis C. The ACE I/D polymorphism in elite Greek track and field athletes. J Sports Med Phys Fitness. 2009;49:459–463.

[26] Amir O, Amir R, Yamin C, Attias E, Eynon N, et al. The ACE deletion allele is associated with Israeli elite endurance athletes. Exp Physiol. 2007;92:881–886.

[27] De Moor MH, Spector TD, Cherkas LF, Falchi M, Hottenga JJ, et al. Genome-wide linkage scan for athlete status in 700 British female DZ twin pairs. Twin Res Hum Genet. 2007;10:812–820.

[28] MacArthur DG, North KN. A gene for speed? The evolution and function of alpha-actinin-3. Bioessays. 2004;26:786–795.

[29] Berman Y, North KN. A gene for speed: the emerging role of alpha-actinin-3 in muscle metabolism. Physiology (Bethesda) 25:250–259.

[30] Beggs AH, Byers TJ, Knoll JH, Boyce FM, Bruns GA, Kunkel LM. Cloning and characterization of two human skeletal muscle alpha-actinin genes located on chromosomes 1 and 11. J Biol Chem. 1992;267:9281–9288.

[31] Blanchard A, Ohanian V, Critchley D. The structure and function of alpha-actinin. J Muscle Res Cell Motil. 1989;10:280–289.

[32] Yang N, MacArthur DG, Gulbin JP, Hahn AG, Beggs AH, et al. ACTN3 genotype is associated with human elite athletic performance. Am J Hum Genet. 2003;73:627–631.

[33] Druzhevskaya AM, Ahmetov, Astratenkova IV, Rogozkin VA. Association of the ACTN3 R577X polymorphism with power athlete status in Russians. Eur J Appl Physiol . 2008;103:631–634.

[34] Santiago C, Gonzalez-Freire M, Serratosa L, Morate FJ, Meyer T, et al. ACTN3 genotype in professional soccer players. Br J Sports Med. 2008;42:71–73.

[35] Yang N, MacArthur DG, Gulbin JP, Hahn AG, Beggs AH, et al. ACTN3 genotype is associated with human elite athletic performance. Am J Hum Genet. 2003;73:627–631.

[36] Moran CN, Yang N, Bailey ME, Tsiokanos A, Jamurtas A, et al. Association analysis of the ACTN3 R577X polymorphism and complex quantitative body composition and performance phenotypes in adolescent Greeks. Eur J Hum Genet. 2007;15:88–93.

[37] Eynon N, Duarte JA, Oliveira J, Sagiv M, Yamin C, et al. ACTN3 R577X polymorphism and Israeli top-level athletes. Int J Sports Med. 2009;30:695–698.

[38] Muniesa CA, Gonzalez-Freire M, Santiago C, Lao JI, Buxens A, et al. World-class performance in lightweight rowing: is it genetically influenced? A comparison with cyclists, runners and non-athletes. Br J Sports Med. 44:898–901.

[39] Yang N, MacArthur DG, Gulbin JP, et al. ACTN3 genotype is associated with human elite athletic performance. Am J Hum Genet 2003;73(3):627-31.

[40] Shang X, Huang C, Chang Q, et al. Association between the ACTN3 R577X polymorphism and female endurance athletes in China. Int J Sports Med 2010;31(12):913-6.

[41] Clarkson PM, Devaney JM, Gordish-Dressman H, et al. ACTN3 genotype is associated with increases in muscle strength in response to resistance training in women. J Appl Physiol 2005;99(1):154-63.

[42] Döring FE, Onur S, Geisen U, et al. ACTN3 R577X and other polymorphisms are not associated with elite endurance athlete status in the Genathlete study. J Sports Sci 2010;28(12):1355-9.

[43] Myerson S, Hemingway H, Budget R, et al. Human angiotensin Iconverting enzyme gene and endurance performance. J Appl Physiol 1999;87(4):1313-6.

[44] Papadimitriou ID, Papadopoulos C, Kouvatsi A, et al. The ACTN3 gene in elite Greek track and field athletes. Int J Sports Med 2008;29(4):352-5.

[45] Boskovic D, Badnjevic A. „Opportunities and Challenges in Biomedical Engineering Education for Growing Economies“, IEEE 4th Mediterranean Conference on Embedded Computing (MECO), pp: 407-410, 14 – 18 June 2015, Budva, Montenegro

[46] Badnjevic A, Gurbeta L, „Development and Perspectives of Biomedical Engineering in South East European Countries“, IEEE 39th International convention on information and communication technology, electronics and microelectronics (MIPRO), 30. May to 03. June 2016. Opatija, Croatia

[47] Montgomery HE, Marshall R, Hemingway H, Myerson S, Clarkson P, Dollery C, Hayward M, Holliman DE, Jubb M, World M, Thomas EL, Brynes AE, Saeed N, Barnard M, Bell JD, Prasad K, Rayson M, Talmud PJ & Humphries SE (1998). Human gene for physical performance. Nature 393, 221–222.

[48] Gayagay G, Yu B, Hambly B, Boston T, Hahn A, Celermajer DS & Trent RJ (1998). Elite endurance athletes and the ACE I allele – the role of genes in athletic performance. Hum Genet 103, 48–50.

[49] Myerson S, Hemingway H, Budget R, Martin J, Humphries S & Montgomery H (1999). Human angiotensin I-converting enzyme gene and endurance performance. J Appl Physiol 87, 1313–1316.

[50] Collins M, Xenophontos SL, Cariolou MA, Mokone GG, Hudson DE, Anastasiades L & Noakes TD (2004). The ACE gene and endurance performance during the South African Ironman Triathlons. Med Sci Sports Exerc 36, 1314–1320.

[51] Woods D, Hickman M, Jamshidi Y, Brull D, Vassiliou V, Jones A, Humphries S & Montgomery H (2001). Elite swimmers and the D allele of the ACE I/D polymorphism. Hum Genet 108, 230–232.

[52] Nazarov IB, Woods DR, Montgomery HE, Shneider OV, Kazakov VI, Tomilin NV & Rogozkin VA (2001). The angiotensin converting enzyme I/D polymorphism in Russian athletes. Eur J Hum Genet 9, 797–801.

[53] Rankinen T, Perusse L, Gagnon J, Chagnon YC, Leon AS, Skinner JS, Wilmore JH, Rao DC & Bouchard C (2000a). Angiotensin-converting enzyme ID polymorphism and fitness phenotype in the HERITAGE Family Study. J Appl Physiol 88, 1029–1035.

[54] Taylor RR, Mamotte CD, Fallon K & Van Bockxmeer FM (1999). Elite athletes and the gene for angiotensin-converting enzyme. J Appl Physiol 87, 1035–1037.