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Are SNIP's still desirable in sports genomics?

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Abstract
A single-nucleotide polymorphism (SNIP) is a variation in a single nucleotide that occurs at a certain position in the DNA. Each variant is, to some extent, present within a population (e.g. > 1%). Due to the correlations of some SNIP's with sport performance and athletic physical capacity, various authors considered their importance in the context of professional sport. Among many SNIP's angiotensin I converting enzyme (ACE) polymorphism is a well-studied example associated with an enhanced physiological response to aerobic exercise. Among other sport-related interesting SNIP's following are highly documented: AMPD1 (C34T) Gln12 Allele, BDKRB2 rs5810761, UCP's and eNOS rs1799983.

KEYWORDS: nucleotide polymorphism, sport performance, genetic predisposition.

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Introduction

In highly professional sports – especially team sports such as soccer, American football, basketball, etc. – the market value of the players is skyrocketing, their value sometimes exceeds 100 million dollars. Such enormous financial funds spent by clubs on the athletes are forcing managers and club administration to collect far-reaching information on the player's psycho-physical profile. People who are responsible for such decisions are also very aware of the numerous potential risks associated with the high loads which are subjected to the athletes during both training and competition. In such environment there is also a big emphasis put on the role of genetic testing in the identification of predisposition to injury or other sudden episodes like Sudden Cardiac Death (SCD) while exercise. The detailed review covering the role of genetic testing in the identification of young athletes with inherited primitive cardiac disorders was prepared in 2016 by Tiziano et al. [1].
However, the question is what makes a champion – nurture or nature? Genes, environmental factors or gene-environment (G × E) interaction? Brutsaert and Parra have tried to answer this question [2]. The authors come up with the evidence to support the genetic basis to athletic performance, with some emphasis on the candidate gene studies. In their review they have definitely stressed environmental factors that influence the athletic performance and highlighting the irreversible environmental effects, i.e., epigenetic effects, fetal programming, or ones occurring during childhood and adolescence. The authors underline the significance of G × E interaction in meaning of understanding variation

in human physiological performance [2]. Genes have a great impact on various athletic performance components such as strength, power, flexibility, neuromuscular coordination, endurance, psychological traits, and other phenotype traits. Athletes' condition is a heritable trait – it depends on sports discipline, but on average 66% of the variance in athletes' condition is explained by additive genetic factors. The residual variance is due to nonshared environmental factors.

The genetic studies related to sport origin from observations that identical twins engaging in competitive sports were significantly more likely to participate in the same sports than pairs of dizygotic twins [3]. The next documented step to identify genetic markers for sports performance relate to the Mexico (1968) and Montreal (1976) Olympic Games, yet the researchers did not generate any strong positive findings [4]. It was until 1998, when, the association between the ACE gene and an aptitude for sport was described by Montgomery et al. [5]. Since then our knowledge about the role of genetics in sports has changed significantly. Among others we have learned about SNIPs (Single Nucleotide Polymorphism's) and major genes (genes with major effect). Although the probability of becoming an elite athlete is very likely influenced by genetic factors only the few of the genes have been yet proven to be associated with motor skills [6, 7]. Nowadays there are many programs, which could be collectively called "Talent Search".

The scientists from the multiple-medal countries put the great expectations in the assessment of sport predisposition on the basis of Performance Enhancing Polymorphism (PEP's) [8]. However are genetic tests currently practical application as expectations are still significant? PEP's are those gene variants (the variants of genes) that may determine the critical for a given sport physiological features such as cell metabolism, muscular structure and even injury susceptibility. PEP's are based mainly on the SNIP's examination.

There are multiple single nucleotide polymorphisms in the human genes, raising the possibility that allelic differences in definite gene might influence physical performance [9], injury susceptibility [10] as well as nociception in the general population [11, 12]. SNIP's may affect levels of transcription, splicing, stability and expression of RNA by altering the amino acid sequence [13, 14, 15]. Are SNIP's still desirable in the study of genetic predisposition in sport? The answer to such question is positive, although the selection of adequate SNIP's remains a big challenge for researchers. In current research the most popular SNIP's are related to: cardiorespiratory capabilities and skeletal muscle potential to exercise at high intensities, structure of muscle cells, aerobic and anaerobic power, injury susceptibility or sensitization to pain. Advanced research on those topics are carried out on a large scale in just a few countries in the world: the US, Russia, China, Australia, Spain, Israel, South Africa, Australia and Poland. Results published up to date have focused on differences in allele frequencies between athletes and non-athlete controls. Among thousands of major genes main interest was located on angiotensin I converting enzyme (*ACE)*, α-actinin-3 (*ACTN3)*, and peroxisome proliferator-activated receptor-γ coactivator 1α (*PPARGC1A)* polymorphisms and on mitochondrial DNA (mtDNA) haplogroup distributions [16].

ACE (I/D)

Angiotensin I converting enzyme (ACE) is a peptidase responsible for the blood pressure regulation, belonging to the renin-angiotensin system (RAS). ACE converts angiotensin I to angiotensin II, which is a very potent vasoconstricting factor [17]. Defective functioning of renin-angiotensin system may be the cause of numerous cardiovascular changes. Insertion-deletion (I/D) polymorphism within the ACE includes the two allelic variants characterized by presence/absence of the *Alu* repetitive 287 bp sequence in 16 intron. Thus ACE gene may have two alleles, distinctly different in their size: shorter – deletion allel (D) and longer – insertion allel (I). The activity of angiotensin I converting enzyme in the blood of individuals with DD genotype is about twice higher than in those with genotype II [18, 19], therefore the genotype II is correlated with a lower risk of cardiovascular disease [20]. Homozygous D/D, which often reveals elevated blood pressure, may be defined as a group under the risk of developing the cardiovascular system disease.

Insertion II genotype (homozygous insertion) has the low angiotensin activity in the tissues [18] and is associated with a better response to aerobic exercise [19]. It allows to maintain a favorable energy balance during the intense and prolonged physical exercise. It has been observed that athletes competing in disciplines with aerobic metabolism predominance, e.g. climbing, long-distance running, long distance swimming, almost never have the D allele in their genotype. In turn, athletes of anaerobic disciplines (with a predominance of anaerobic metabolism) – sprinters, short distance swimmers – are the ones with high levels of ACE and more frequent occurrence of DD genotype deletion [18, 19].

AMPD1 (C34T) Gln12 Allele

AMPD relocates the balance of the myokinase reaction in the ATP production process (2 ADP ↔ ATP+AMP) by transforming AMP to inosine monophosphate (IMP) [21, 22]. This reaction is important because of (i) rapid ATP synthesis (ii) AMP is potent stimulant for glycolysis [23]. AMPD is coded by three independent gene families (AMPD1 – is expressed in skeletal muscles, AMPD2 – is expressed in non-muscle tissue and smooth muscle, AMPD3 – is expressed in erythrocytes) [24]. The activity of AMP deaminase in myocytes is several times higher than its activity in other tissues – this condition is associated with the regulation of purine nucleotide cycle [25]. The AMPD reaction is the preliminary response of the purine nucleotide cycle and plays a central role in the recovery of adenine nucleotides [21]. AMPD, together with myokinase, participates in the ATP restoration in myocytes acting as muscle energy metabolism regulator during high-intensity exercise [26, 27, 28]. Physical exercises change muscle AMPD activity and *AMPD* expression in skeletal myocytes dependent on the fibre types [21, 22, 28]. Especially *AMPD1* is essentially expressed in fast-twitch muscle fibres where anaerobic activity causes a decrease in AMPD activity concurrent with an increase in the proportion of active fast-twitch (type II) fibres. Hence, AMPD expression appears to be influenced by the intensity of physical activity [29]. The nonsense mutation 34C>T (C to T transition in nucleotide 34, Gln12X, rs17602729) in exon 2 of the *AMPD1* gene converts glutamine codon (CAA) into the premature stop codon (TAA), and in consequences appears to be the main cause of AMPD deficiency [26, 27, 29]. Individuals with one normal and one mutant allele are more often engaged in intermediate activities, and those with two AMPD1 normal alleles in high-intensity activities. The *AMPD1* CC genotype was found to be associated with anaerobic performance (Vertical Jump) [29]. Ginevičienė et al. [29] also found that the X allele is an unfavourable factor for athletes in sprint and power-oriented sports categories.

BDKRB2

The renin-angiotensin system (RAS) with its key component: angiotensin I converting enzyme (ACE), plays a fundamental role in circulation and blood homeostasis [30]. While ACE by vasoconstricting influence increases blood pressure, bradykinin (BK) by being a very potent endothelium-dependent vasodilator decreases it. In 1980, over 30 years after bradykinin was discovered by Maurício Rocha e Silva group, Regoli and Barabé proposed that BK acts via specific two cell-surface receptors that are classified as the bradykinin 1 receptor (BDKRB1) and the bradykinin 2 receptor (BDKRB2) [31]. Both receptors are anchored on the plasma membrane of the myocytes and the vascular endothelium [32]. During physical activity BDKRB2 are consequently activated, what results in increased blood flow in the muscles, improved muscle glucose uptake, and thus higher endurance performance [33].
BDKRB2 is encoded by a single-copy gene, located to chromosome 14q32 and expressed in most human tissues. The insertion/deletion polymorphism (–9/+9, rs5810761) in exon 1 is the most commonly investigated polymorphism associated with athletes condition, as well as cardiovascular disease and hypertension [32, 34, 35]. Deletion of a 9 bp (–9) repeat in exon 1 of the *BDKRB2* gene is associated with higher mRNA expression, and increased receptor activity [36, 37]. It is suggested that –9 allele may be correlated with higher skeletal muscle metabolic adeptness and endurance performance [33]. The interesting research was conducted on swimmers with the –9/–9 genotype, who performed better in long distance competitions, than swimmers with other genotypes of the *BDKRB2* gene [30].

UCP's

ATP is produced by energy coupling, proceeding at the level of the electron transport chain in mitochondria. In adipose tissue, this coupling with ADP phosphorylation is only partial, because uncoupling proteins (UCPs) induce a proton leak, releasing the energy stored in ATP as heat [38]. Uncoupling proteins belong to the abundant family of mitochondrial anioncarrier proteins (MCAPs). Two of them may be taken into account as important for physical fitness: UCP2, which is expressed e.g. in muscles, lungs, spleen, heart, kidneys, central nervous system and white adipose tissue and UCP3, found in heart and skeletal muscles [39, 40]. The physiological role of UCP2 is not clear. Numerous studies showed that the most probable function of this protein is mild energy uncoupling, which accelerates metabolism and protects cells against damage by reducing the amount of reactive oxygen species (ROS) [38]. Fleury & Sanchis [39] and Bouchard et al. [41] supposed the UCP2 protein is associated with lipid metabolism and energy balance. Several SNIP's observed in *UCP2*, correlates with metabolic syndrome [42], obesity, BMI, resting metabolic rate [39, 43], or susceptibility to diabetes type 2 [44], but the results of those studies are equivocal. Some UCP2 SNIP's are associated with a higher energy efficiency, thus it is probable that UPC2 affects energy expenditure during physical activity [45, 46].

The decreased UCP3 expression (lower UCP3 mRNA level) was observed in athletes with negative correlation with VO_2max, therefore it is supposed that UCP3 expression may be influenced by strength training [39, 47]. Very regular physical activity or strength training decrease *UCP3* gene expression, and thus may increase energy efficiency in such athletes [39, 48].

Although lipid metabolism seems to be essential for aerobic capacity, so far only few studies have focused on the direct effects of polymorphisms of UCP genes on athletes performance [38, 49]. The authors analysed the association of the maximum oxygen uptake level (VO_2max) with two polymorphisms: insertion/deletion (I/D) in exon 8 of the UCP2 gene and C>T substitution in exon 5 (630 C>T; Y210Y) of the UCP3 gene [38].

NOS

Nitric oxide (NO), the molecule of the 1992 year, is produced by Nitric Oxide synthase (NOS; EC 1.14.13.39) from L-arginine – semiessential amino-acid derived from food, intracellular protein degradation or from endogenous synthesis [50, 51]. The L-arginine amine group is oxidized by molecular oxygen to L-citrulline and NO [52]. There are three isoforms of NOS: neuronal (nNOS or NOS I), inducible (iNOS or NOS II), and endothelial (eNOS or NOS III), which differ in the structure and function [50, 53]. Neuronal NOS is expressed in specific neurons of the central nervous system (CNS). It's action is associated with synaptic plasticity, central control of blood pressure and with penile erection [53]. Expression of the inducible NOS, which is Ca^{2+}-independent, can be stimulated in almost any cell or tissue, so long as there are appropriate inducing agents available – inflammatory mediators (e.g. cytokines) [52]. iNOS exhibit antibacterial effect due to generating the large amounts of NO which interacts with O_2^- leading to the local formation of toxic peroxynitrite ($ONOO^-$). Beside the cytostatic effects excessive NO production by iNOS plays a crucial role in massive arteriolar vasodilatation seen in septic shock [54]. Endothelial NOS is expressed by endothelial cells, cardiac myocytes and cardiac conduction tissue [55]. Endothelial Nitric Oxide is a physiological vasodilator, but it also serve vasoprotective activity: it inhibits the platelet and leucocyte adhesion to the vascular wall and endothelial permeability avoiding the atherogenesis development or the release of platelet-derived growth factors preventing the smooth muscle proliferation.

Moderate exercise leads to an improvement of endothelium function mainly through increment of the NOS activity, generally eNOS. Endothelial nitric oxide synthase (eNOS) is up-regulated by an increase in flow-mediated shear stress associated with physical exercise, due to a complex pattern of intracellular regulations [56, 57, 58]. Investigations conducted on humans and animals have documented that exercise increases eNOS gene and protein expression [59, 60, 61]. Moreover under chronic exercise also the shear stress–induced eNOS phosphorylation occurs, so the ratio of phosphorylated to unphosphorylated eNOS gets higher in the trained individuals compared with the controls [58]. Therefore even without a significant increase in eNOS protein the improvement in functioning of the cardiovascular system may occur [62].

The gene is 21 kb of genomic DNA, 26 exons [63]. The most examined and functionally related common variants of the NOS3 are single nucleotide polymorphisms (SNP): 786T/C (rs2070744), G894T (Glu298Asp, rs1799983), as well as the intron 4 variable number tandem repeat (VNTR) [64]. Numerous studies indicate that –786T/C (rs2070744) and G894T NOS3 SNP's can be associated with several health/fitness, training or exercise response phenotypes e.g. adaptation of parasympathetic modulation response to exercise training, cardiovascular traits such as blood pressure, heart rate, cardio-biochemical parameters and vascular reactivity.

Other genes which still require to be investigated are: ACTN3, EPAS1, HIF1, IGF1, IL1 RN VNTR-86bp, IL-15, IL-6, MCT1, NFATC4, NRF1, PPARD, PPARG, PPP3R1, TFAM, TNF, VEGFA. In conclusion SNIPs are very informative and therefore seem to be useful in sports genomics. As shown in this paper some of them correlate with sport performance and athletes physical capacity.

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