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GENES IN SPORT AND DOPING

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ABSTRACT: Genes control biological processes such as muscle production of energy, mitochondria biogenesis, bone formation, erythropoiesis, angiogenesis, vasodilation, neurogenesis, etc. DNA profiling for athletes reveals genetic variations that may be associated with endurance ability, muscle performance and power exercise, tendon susceptibility to injuries and psychological aptitude. Already, over 200 genes relating to physical performance have been identified by several research groups. Athletes' genotyping is developing as a tool for the formulation of personalized training and nutritional programmes to optimize sport training as well as for the prediction of exercise-related injuries. On the other hand, development of molecular technology and gene therapy creates a risk of non-therapeutic use of cells, genes and genetic elements to improve athletic performance. Therefore, the World Anti-Doping Agency decided to include prohibition of gene doping within their World Anti-Doping Code in 2003. In this review article, we will provide a current overview of genes for use in athletes' genotyping and gene doping possibilities, including their development and detection techniques.

KEY WORDS: gene polymorphism, endurance, muscle mass, muscle force, tendon injury, emotions, gene doping

An athlete's abilities to perform specific physical efforts are determined by the adaptive mechanisms of the circulatory and respiratory system, skeletal muscles and others. The effectiveness of these mechanisms is genetically determined. The presence of specific gene variants decides about the strength of such physical traits as speed and endurance, muscle strength and emotion control.

The DNA profiling of the human genome and development in molecular medicine have made it possible to apply DNA analysis methods in sport diagnostics. The techniques of molecular biology, e.g. *in situ* hybridization, DNA microarray (also commonly known as DNA chip) and polymerase chain reaction (PCR) analysis, enable identification of a variety of DNA sequences in the genome even at the level of a single nucleotide. In a single experiment researchers can measure the expression levels of large numbers of genes simultaneously or genotype multiple regions of a genome.

However, the advances of molecular biology techniques have caused the possibility of using genetic manipulation to enhance athletic performance. In such "gene doping", exogenous genetic sequences are inserted into specific tissues, altering gene activity or leading to the expression of protein products. The exogenous genes most likely to be utilized for gene doping include erythropoietin (*EPO*), growth hormone (*GH*), vascular endothelial growth factor (*VEGF-A* and *VEGF-D*), insulin-like growth factor 1 (*IGF-1*) and myostatin antagonists such as follistatin (*FST*). In 2003, the World Anti-Doping Agency decided to include prohibition of gene doping within their World Anti-Doping Code. According to the 2013 Prohibited List gene doping is defined as the transfer of polymers of nucleic acids or nucleic acid analogues, as well as the use of normal or genetically modified cells.

In this review article, we provide a current overview of genes for use in athletes' genotyping and gene doping possibilities, including their development and detection techniques.

Physical activity genes

Our physical activity is the result of millions of years of evolution and natural selection mechanisms that have led to directed changes in the gene pool of the population, increasing its adaptation to the natural conditions. Physical activity allowed our ancestors to acquire food and to survive. The typical weekly programme of human ancestors included hunting activity for 3-4 days. During a single hunt our

ancestors covered an average distance of 14-19 km. The hunting time was interrupted with rest breaks far from being a state of inactivity. The daily energy expenditure of an early Hominid amounted to 49 kcal/kg, while the daily energy expenditure of a modern human is 32 kcal/kg of body mass [10].

According to Bouchard & Hoffman [12], physical activity is an important factor shaping the human genome during evolution. The first gene linked to human fitness was the angiotensin-converting enzyme gene (*ACE*), discovered by Hugh Montgomery in 1998 [44]. Bray et al. designed a map of gene polymorphisms that may be related to predisposition to physical fitness and sports results. They identified 239 fitness genes: 214 in autosomal chromosomes, 7 in chromosome X, and 18 in mitochondrial DNA [13].

The criteria of selection for high-performance sports coupled with high demands and diverse tasks assigned to athletes lead to specialization in sport. A study in world-class athletes revealed that the performance in explosive power specialities such as the 100 m sprint or the long jump is negatively correlated with performance in the more endurance-oriented 1500 m race [61]. This supports the hypothesis of a "trade-off" between spirit and endurance phenotypic traits such that an individual is inherently predisposed toward performance in either sprint/power or endurance events [21]. The differences among individuals are related to genetic variation called polymorphism, i.e. the presence of two or more variants of a given gene differing in one nucleotide (single nucleotide polymorphism, SNP), e.g. α-actinin skeletal muscle isoform 3 gene (*ACTN3*) or a simple sequence length polymorphism (SSLP), e.g. the polymorphism in the angiotensin-converting enzyme gene (*ACE*). Sequential differences can be noted in the non-coding regions, e.g. gene promoters and introns, influencing gene expression; or in coding regions (exons) affecting the structure and functioning of an encoded protein. Gene polymorphisms are examined as genetic markers of predispositions toward a type of sport in general, e.g. endurance-oriented, or a sport speciality in particular (cross-country running marathon and weight-lifting), ethnic differences, e.g. Kenyans and Scandinavians, and abilities of adaptation to external conditions, e.g. high temperature and hypoxia. On some of the polymorphic genes, such as *ACE* and *ACTN3* genes, significant amounts of data have been collected, and mechanisms explaining their effects on athletic ability have been proposed and analysed. In contrast, other genes, such as peroxisome proliferator-activated receptors *α* (*PPARα*), have only received attention in this context fairly recently [37,66]. Table 1 shows four groups of genetic variants associated with physical fitness and described in the article.

Endurance ability

Adaptation to endurance efforts is related to the metabolic activity of mitochondria determined by genes of nuclear and mitochondrial DNA that encode enzymes of energy metabolism. The key regulators of the mitochondria function are peroxisome proliferator-activated receptors α, δ, γ (PPARα, PPARδ and PPARγ). Particularly important is the PPARδ receptor that regulates the expression of hundreds of genes involved in lipid and carbohydrate metabolism, and affects glucose uptake in skeletal muscles [6]. A single nucleotide polymorphism (+294T/C) of the *PPARδ* gene is associated with an increased PPARδ level and predisposition to endurance performance [1,23].

Nuclear respiratory factor 2 (NRF2) together with nuclear respiratory factor 1 (NRF1) induces mitochondrial biogenesis and plays an important role in nucleo-mitochondrial interactions. NRF2 binding sites are found in the promoter regions of several nuclear genes encoding mitochondrial proteins, including cytochrome c, components of all five electron transport chain complexes, mitochondrial import proteins, and haem biosynthesis proteins, regulating the expression of nuclear and mitochondrial genes of elements of the respiratory chain. The *NRF2* intron 3 A/G polymorphism improves endurance capacity in response to training [18,19].

The protein family called hypoxia-inducible factors (HIFs) is responsible for adaptation to hypoxic stress. The HIFs regulate the expression of about 200 genes involved in energy metabolism, glucose transportation, angiogenesis, erythropoiesis, etc. [59]. HIF-1 and HIF-2 are deactivated in normoxia, and activated in hypoxia conditions. HIF-1 is expressed in the majority of tissues while HIF-2 expression is limited to a few tissue types, e.g. endothelial cells. Subunit α of HIF-2 is encoded by the EPAS-1 gene, which is responsible for adaptation of the Tibetans to long-term physical efforts at altitude [62]. A recent study demonstrated that the *HIF-1α* gene polymorphism (Pro582Ser) is strongly associated with endurance training responses [16,42]. However, Cięszczyk et al. [15] suggested that *HIF-1α* gene polymorphism (Pro582Ser) can be taken into consideration as a genetic marker in power-oriented athletes.

The search for variants of genes predisposing to endurance sports has also revealed many other genes, e.g. haemoglobin β (HBB) is primarily responsible for transferring oxygen from the lungs to respiring tissues**,** erythropoietin receptor (EpoR) regulates erythroblast proliferation and differentiation, skeletal muscle glycogen synthase 1 (GYS1) catalyses glycogen synthesis in skeletal muscles, β-2 adrenergic receptor (ADRB2) activates fat energy sources, cholinergic receptor muscarinic 2 (CHRM2) improves the electrical conduction system of the heart, bradykinin type 2 receptor (BDKRB2) influences bradykinin-dependent vasodilation during angiotensin-converting enzyme inhibition, endothelial nitric oxide synthase (NOS3) generates NO in blood vessels and is involved in regulating vascular function, and the vascular endothelial growth factor (VEGF) regulates blood flow and angiogenesis [12,13,24,25,30,33].

The polymorphism insertion/deletion (I/D) of a 287-nucleotide fragment in an intronic sequence of the angiotensin-converting enzyme (*ACE*) gene is frequently determined in athletes. The ACE enzyme transforms angiotensin I into angiotensin II, a potent vasoconstrictor, as well as other vasoactive peptides. Through this metabolic process, ACE plays a key role in the regulation of blood pressure and also in the development of vascular pathology and remodelling [9]. The I/I genotype is related to low ACE activity in serum and

tissues and it is found in marathon runners, triathletes and rowers [63]. Thompson et al. [58] made some interesting observations in mountaineers. ACE genotype distribution differed significantly between those who had successfully climbed beyond 8000 m and those who had not. The I allele was associated with increased maximum altitudes achieved. There was no statistical difference in *ACE* genotype frequency between those who climbed to over 8000 m using supplementary oxygen and those who did not.

Muscle performance and power exercise

Studies of the *ACE* gene polymorphism in athletes of various sports revealed a higher occurrence rate of the I/D and D/D variants in strength sports and sprinters [63]. On the basis of these research results a hypothesis was formulated that the sequential polymorphism D (deletion) determines the ability to perform efforts requiring speed and strength, whereas variant I (insertion) is associated with endurance efforts. These associations can, however, vary in different

TABLE I. GENE VARIANTS ASSOCIATED WITH ENDURANCE ABILITY, MUSCULAR PERFORMANCE, SUSCEPTIBILITY TO INJURIES AND PSYCHOLOGICAL APTITUDE [12,13,30, 33].

GENE	VARIANT
ENDURANCE ABILITY	
ACE/ *angiotensin-converting enzyme*	ins/del
ADRB2/ *β-2 adrenergic receptor*	46A/G (Arg16Gly)
	79C/G (Gln27Glu)
BDKBR2/ *bradykinin type 2 receptor BE1*	-9/+9 bp
CHRM2/ *cholinergic receptor muscarinic 2*	616A/G
EpoR/ *erythropoietin receptor*	6002G/A
	(Try439Stop)
HBB/ *haemoglobin beta*	16C/G
	551C/T
HIF-1α/ *hypoxia-inducible factor 1*	1744C/T
	(Pro582Ser)
GYS1/ *glycogen synthase 1*	*XbaI restriction*
	Met416Val
NOS3/ *nitric oxide synthase*	894G/T
NRF2/ *nuclear respiratory factor 2*	A/G in intron 3
PPARδ/ *peroxisome proliferator-activated receptor δ*	294A/G
VEGF/ *vascular endothelial growth factor*	2578A/C
	1154G/A
	634G/C
MUSCLE PERFORMANCE AND POWER EXERCISE	
ACE/ *angiotensin-converting enzyme*	ins/del
ACTN3/α-actinin 3	1747C/T
	(R577X)
AMPD1/ *adenosine monophosphate deaminase*	G34A/A
CK-MM/ *muscle creatine kinase*	*NcoI restriction*
	214A/G
IGF-1/ *insulin like growth factor 1*	CA *dinucleotide repeats*
SUSCEPTIBILITY TO INJURIES	
COL1A1/ *collagen type 1α1*	2046G/T
COL5A1/ *collagen type 5α1*	401C/T
MMP3/ *matrix metallopeptidase 3*	301A/G
TNC/ *tenascin C*	GT *dinucleotide repeats*
PSYCHOLOGICAL APTITUDE	
5HTT/ *serotonin transporter 5*	-44/+44bp
BDNF/ *brain-derived neurotrophic factor*	196G/A
5HTT/ *serotonin transporter 5*	-44/+44bp

populations. A 2007 study on the *ACE* gene polymorphisms among Israeli athletes showed that the D/D genotype was more frequent in long-distance runners than in sprinters [4]. Genetic research on populations of Jamaican, Ethiopian and Kenyan athletes excluded the association of the *ACE* gene polymorphism with sprint or endurance athlete status [3,53,54].

Another gene polymorphism that is related to muscle performance is the α-actinin skeletal muscle isoform 3 (*ACTN3*) gene, which binds actin filaments in muscle cells in the line of Z sarcomeres and participates in fast-twitch contractions. Genotypes X577X and R577X reduce the level of synthesis of α–actinin 3, which is substituted by α–actin 2 [33]. An Australian study of sprinters showed that athletes demonstrated a frequent RR genotype (ACTN3 synthesis) and very rare XX genotype (6%) [65]. Italian researchers noted that the XX genotype was also extremely rare (2.8%) in female gymnasts [40]. Holdys et al. [27] observed the predominance of the RR genotype in a group of individuals practising speed and power sport disciplines. On the other hand, an American study revealed rare occurrence of genotype XX in white weight-lifters, but not in black weight-lifters [49]. It can be assumed that the association between the polymorphism of the *ACTN3* gene and the ability to perform a specific physical effort may vary in different populations, as in the case of ACE. Ma et al. [36] analysed the associations of *ACE* I/D (366 articles) and *ACTN3* R577X (88 articles) with sport performance by means of meta-analysis. The authors summarised that the genetic profiles might influence human physical performance.

The creatine kinase isoenzyme MM (CK-MM) is responsible for ATP resynthesis through transfer of the phosphate group from creatine phosphate to ADP. It was observed that the NcoI A/G polymorphism in the 3' untranslated region of *CK-MM* reduces the force of muscle contraction during a 60 s test after a 90-min exercise [11]. Subsequent studies did not confirm the association between *CK-MM* gene polymorphism and muscle performance [34,48]; however, they revealed a relationship between the NcoI A/A genotype and exercise rhabdomyolysis [26].

Muscle performance is also related to polymorphisms of adenosine monophosphate deaminase 1 (AMPD1) and insulin-like growth factor 1 (IGF-1) genes. AMPD1 enzyme catalyzes the conversion of adenosine into inosine with increasing AMP during exercise. The subjects with the TT genotype at 34C/T of the AMPD1 gene demonstrate a higher susceptibility of muscle to damage and fatigue [33]. IGF-1 increases muscle mass and strength. The presence of an extra sequence (16 and 22 CA repeats) in the promoter region of the *IGF-1* gene enhances the force of muscle contraction compared in the elderly [32]. Another study showed that polymorphism of the *IGF-1* gene is related to the mass of the left ventricle of the heart in male athletes but not in female athletes [31].

Tendon susceptibility to injuries

Genetic predisposition and increased risk for tendinopathies and tendon sports related injuries is conferred by genetic variants of the ABO blood group genes, collagen I (*COL1A1*), collagen V (*COL5A1*), matrix metalloproteinase-3 (*MMP3*) and tenascin C (*TNC*) [43, 46,47,56]. The polymorphisms of *COL*, *MMP3* and *TNC* genes are associated with Achilles tendon injuries in a physically active population. COL is the main structural component of tendons and ligaments while MMP3 and TNC affect the interaction between the tendons and extracellular matrix [14,43].

Psychological aptitude

Resistance to stress and displaying emotions are to some extent genetically determined. There is evidence that polymorphisms in the 5'-flanking regulatory regions of the serotonin transporter (*5HTT*) gene encoding for long (L) or short (S) alleles might be associated with ability to control emotions. A psychological study of female athletes with the SS genotype revealed that their irritation and pessimism levels were lower than in female athletes with the LS and LL genotypes [33,39].

Brain-derived neurotrophic factor (BDNF) is a part of the neurotrophic family and is responsible for the viability and functioning of a variety of neuronal subtypes within the brain. Recent studies have shown that BDNF expression is not only present in neurons but also in skeletal muscles [28,45]. In the brain, BDNF is responsible for enhancing progenitor cell proliferation and differentiation, neuronal process growth and regeneration, neuronal survival, and long-term synaptic remodelling and plasticity [28]. Training increases the BDNF level in the brain and is maintained for 2 weeks after the cessation of exercise while overtraining reduces the BDNF level, which is accompanied by discouragement, anxiety and irritation [8]. Polymorphism of the *BDNF* gene (G/A substitution at nucleotide 196) affects the psychological response to stress and also motivation for exercise. In particular, it has marked effects on the individual's positive/negative thinking during competition. Thus, an athlete can be guided more appropriately and efficiently for better emotions and stress management to achieve optimal performance [30].

Genotyping in sport practice

The genetic diversity of individuals influences the metabolism of performance enhancing substances, and in some cases may hinder the detection of prohibited substances in sport. Research shows that the copy number variation (CNV) of the *UGT2B17* gene may affect the efficiency of anti-doping tests aimed at detection of testosterone abuse. The *UGT2B17* gene encodes UDP-glucuronosyltransferase 2B17 that catalyses the addition of UDP-glucuronide to testosterone. It practically does not catalyse an analogous reaction of addition of UDP-glucuronate to epitestosterone (testosterone epimer) [55]. Testosterone abuse is detected in anti-doping tests by determining the ratio of testosterone to epitestosterone in urine (T/E ratio; equivalent to the glucuronide). Testosterone is not converted to epitestosterone. Moreover, following testosterone administration, its synthesis *de novo* is inhibited and its level in urine is reduced. That is why the T/E ratio rapidly increases after testosterone administration. The World

Anti-Doping Agency (WADA) established that a T/E ratio above 4 may indicate abuse of testosterone, which entails additional anti-doping tests with the use of isotope ratio mass spectrometry [38]. In individuals without any copy of the *UGT2B17* gene (genotype del/del) testosterone is excreted in urine only to a slight extent in the form of glucuronide, unlike epitestosterone, which, in fact, is fully excreted in urine. The mean T/E ratio in urine in individuals with the del/del genotype is 0.14, in individuals with one *UGT2B17* copy (ins/del) it is 1.4, and in those with two copies (ins/ins) it is 2.9. After the administration of a single 500 μg dose of testosterone enanthate a much lower sensitivity of a T/E ratio test was noted in individuals with the del/del genotype: from 5.9% on the second day after administration to 58.8% on the sixth day, as compared with individuals with the del/ins ins/ins genotypes: from 62.5 % on the second day to 100% on the sixth day [52]. Studies on various populations point to significant differences in the number of copies of the *UGT2B17* gene. Its deletion occurred rarely in African and European populations (e.g. 14% in the Yoruba population), but frequently in East Asian populations (e.g. 92% in the Japanese population) [64]. These results indicate that athletes from East Asia might be tempted to abuse testosterone with impunity to a greater extent than European or African athletes. To solve this problem a *UGT2B17* (del/ins) genotyping method was developed using standard urine samples collected for standard anti-doping tests [2]. Also the application of an individual T/E threshold established on the basis of the *UGT2B17* genotype and earlier results of the same athlete enabled a significant increase of testosterone detection sensitivity in individuals with the *UGT2B17* (del/del) genotype [51]. Some data also point to the potential contribution of the promoter polymorphism of the cytochrome *CYP17* gene (homozygous in variant A1) to the natural (endogenous) T/E ratio values above 4 [51]. Naturally, the testosterone level, through inhibition of the UGT2B17 activity and reduction of glucuronide excretion, can be elevated by some dietary components such as phenol agents, but not by ethyl alcohol in red wine [29]. There was also a suggestion that concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) and a single dose of testosterone enanthate would affect the T/E ratio. Recently, Lundmark et al. [35] demonstrated that the concomitant use of NSAIDs and testosterone esters slightly increases testosterone glucuronide excretion while epitestosterone glucuronide excretion is less suppressed compared to testosterone use only. The T/E ratio did not differ between the UGT2B17 genotype groups. The outcome of testosterone doping tests does not seem to be affected by the use of NSAIDs.

Gene doping

The rapid development of biological sciences and increasing knowledge about gene variants that may predispose individuals to practise sports pose a risk of using this knowledge for the purpose of illegal doping. This knowledge can be applied by technologies of genetic material transfer capable of genetic modification of humans. Such technologies are developed for treatment of genetic diseases. Most often they involve the injection of a functional copy of a gene to treat the causes of a disease [5]. Other gene therapy strategies lead to the suppression of expression of specific genes with the use of small interfering RNA or antisense nucleotides [17,20].

In 2012 Glybera was approved in the EU as the second gene therapy drug in the world. It contains the normal variant of lipoprotein lipase – one of the enzymes participating in lipid metabolism – and is used for treatment of lipoprotein lipase deficiency (LPLD). Also, in January 2013, the US Food and Drug Administration approved Kynmaro, a drug used for treatment of homozygous familial hypercholesterolaemia. It is a gene therapy based on gene expression silencing by siRNA [41]. Moreover, a number of gene therapy drugs are at the level of clinical examination, which indicates that gene therapy will be more and more frequently used in the near future. Genes whose transfer might be used for illegal doping are genes encoding peptide hormones, e.g. erythropoietin (EPO), growth hormone (GH), and growth factors (VEGF and IGF-1). These peptides are on the WADA List of Prohibited Substances and Methods [http://www.wada-ama.org]. In case of application of a successful gene therapy an organism increases the production of these peptides, which improves performance and/or muscle strength. Also gene expression silencing techniques (siRNA, antisense nucleotides) can be used to silence, for example, the expression of the myostatin gene, whose product inhibits muscle growth [22].

As early as 2003 the International Olympic Committee and WADA placed gene doping on their common prohibited list. Gene doping was then defined as the non-therapeutic use of genes, genetic elements and/or cells that have the capacity to enhance athletic performance. In view of dynamic developments in tissue engineering and stem cell transplantation techniques, currently part of the WADA list regarding gene doping reads as follows: "The following, with the potential to enhance sport performance, are prohibited: 1. The transfer of polymers of nucleic acids or nucleic acid analogues; and 2. The use of normal or genetically modified cells." It means that an athlete who received directly an *in vivo* gene transfer e.g. into the bloodstream or locally to specific tissues, intracutaneously, intramuscularly, or genetically modified cells *ex vivo* is automatically disqualified. In *ex vivo* transfer cells that can be easily sampled and cultured outside an organism are, for example, hematopoietic cells.

In the years 2004-2007 the WADA coordinated 21 projects in the areas of genomics, transcriptomics, proteomics, metabolomics, virology and bioinformatics [http://www.wada-ama.org/] aimed at identifying genes and their variants that might be of potential interest to athletes. Two major scenarios of gene doping are described with one being the abuse of "classical" gene therapy, i.e. introduction of synthetic DNA sequences via viral vehicles into the organism, and the other being based on RNA interference strategies [60]. Between 2010 and 2011 the WADA coordinated two projects aimed at the development of gene doping detection methods. According to published data, doping using genes encoding erythropoietin (EPO), insulin-like growth factor 1 (IGF-1), vascular endothelial growth fac-

tor (VEGF-A and VEGF-D), human growth hormone (hGH), follistatin (FST) and regulators of transcription factors is detectable. The detection strategy of gene doping using the mentioned growth factors involves direct detection of cDNA sequences [7,57]. There is no doubt that anti-doping laboratories must constantly incorporate new detection capabilities in order to maintain a harmonized approach to detecting doping substances and methods across the anti-doping system on a worldwide scale. However, taking into consideration specific equipment and knowledge, it is possible that not all WADA accredited laboratories will be requested to implement gene doping detection [50].

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