# GENETIC RESEARCH IN MODERN SPORT

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**Abstract.** Sport genomics is a comparatively new scientific discipline concentrating on the organization and functioning of the genome of elite athletes. It seems to be the most promising tool for sport selection, individualization of the training process, sport traumatology, and also in illegal 'gene doping'. With genotyping more available, research of gene variants' influence on several phenotype traits related to physical performance have been widely carried out worldwide. This review not only summarizes the current findings of sport genomics study of molecular markers, their association with athlete status and training responses, but it also explores future trends and possibilities. The importance of genetics in modern sport increases every year. However, the recent studies still represent only the first steps towards a better understanding of the genetic factors that influence human physical abilities, and therefore continuing studies are necessary.

**Key words:** sport genetics, polymorphism, physical activity, athlete status

## Introduction

An individual's physical performance is dependent on a combination of numerous environmental and genetic factors. Within the group of genetic components that are believed to play a role in athletic ability, there are gene variants that have a key impact on human body composition and metabolism such as endurance, power, strength, muscle fibre size and composition, flexibility, neuromuscular coordination, temperament and other phenotypes (Ahmetov and Fedotovskaya 2012). In addition, De Moor and co-workers (2007) estimated that the heritability of athletic status is around 66%. The remaining variance is due to the environmental components such as training, nutrition, motivation, lifestyle, and advance in equipment etc.

Sport genomics is a comparatively new scientific discipline concentrating on the organization and functioning of the genome of elite athletes (Ahmetov and Fedotovskaya 2012). It seems to be the most promising tool for sport selection, individualization of the training process, sport traumatology, and also illegal "gene doping" (Sawczuk et al. 2011).

At first, studies were based on the statistical analysis of a given phenotype of mainly structural traits in the population. Initially, family or twin studies were used to investigate the influence of genetic factors on individual characteristics of the human body by using heritability estimates ($h^2$), which shows the population variance in a trait attributable to genes. In 1970s, these indirect methods were carried out by comparing the intra-pair variation between monozygotic (MZ) and dizygotic (DZ) twins (the difference of the variance between DZ and MZ twins is divided by the variance of DZ twins) (Bouchard and Lortie, 1984; Sawczuk et al. 2011; Pitsiladis et al. 2013). Despite the suggestion of important heritable components for a range of sport-related traits, family and twin-based studies do not offer insight into the specific gene variation underlying these heritable traits (Pitsiladis et al. 2013).

The era of sports genomics started in the early 2000s after the development of molecular biology methods, decoding the human DNA structure, and the discovery of the first genetic markers referring to physical performance (Ahmetov and Fedotovskaya 2012). In 1998, Montgomery and co-authors identified a positive association between a genetic variation, the inversion/deletion (I/D) polymorphism of the angiotensin-converting enzyme gene (*ACE*) which is involved in the blood flow regulation, and endurance exercise performance. This paper first determined the role of the gene variation for sport success and was the inspiration for several groups of scientists worldwide to analyze the association of numerous gene polymorphisms with various performance-related phenotypes in continuation studies (Roth 2007; Ahmetov and Rogozkin 2009; Wang et al. 2013).

This review not only summarizes the latest findings of sport genomics studies of molecular markers and their association with athlete status and training responses, but it also explores future trends and possibilities.

## Genes and elite athlete status

Advances in molecular biology methods have enabled researchers to apply genome-wide association studies (GWA study or GWAS) to the field. GWAS, combined with informatics and statistics, allow for the analysis of polymorphic sites of the whole genome to link genetic markers, usually single-nucleotide polymorphisms (SNPs), to physiological phenotypes (Eynon et al. 2011; Kim et al. 2011; Pitsiladis et al. 2013; Wang et al. 2013). GWA study is a promising approach, however, it is not devoid of significant limitations. For example, human height is a very heritable (up to 90% of population variance) as well as stable and simple trait to measure, and while one of the largest studies (n = 183 727) recognized at least 180 loci linked with human height, together these clarified for only 10% of the variation in this trait (Lango Allen et al. 2010). This is related to the small effect size of most of these genetic variants. GWA study is able to identify a lot of loci that implicate biologically related genes and pathways. However, the occurrence of rare variants which are not captured by GWAS may partly explain this limited success in determining the genomics of human height and other complex traits (Manolio et al. 2009; Pitsiladis et al. 2013; Wang et al. 2013).

DNA polymorphisms (with 1% or greater frequency in the population) and rare DNA mutations can be classified as genetic markers related to endurance or/and power athlete status. The significance of a given candidate gene is based on numerous criteria such as: biological relevance to the trait of interest, the type of the polymorphism (missense, nonsense, intronic etc.), its impact on the overall function of the gene, its frequency in an examined population, the criteria of selection of athletes and control groups (e.g. sex and ethnic background), as well as a great amount of research with positive or negative results etc. (Eynon et al. 2011; Ahmetov and Fedotovskaya 2012; Pitsiladis et al. 2013). In recent years, "the human gene map for performance and health-related fitness phenotypes" identified over 200 genetic markers potentially linked with some physical performance phenotypes (Bray et al. 2009;

Eynon et al. 2011). However, the latest literature search revealed that about 79 DNA polymorphisms are linked to elite athlete status. These include 59 endurance-related and 20 power-related genetic markers, while 25% of these markers were positively associated with athlete status in at least two studies (Ahmetov and Fedotovskaya 2012). They are located within 40 autosomal genes, mitochondrial DNA and Y-chromosome. Interestingly, almost all chromosomes, except for 13, 16, 18, 20 and X chromosomes, include sport-related genetic markers (Ahmetov and Fedotovskaya 2012).

Differentiation of marker genes is correlated with predispositions to perform different types of effort, which can be divided into two main groups: endurance effort (aerobic character) and power effort (anaerobic character) (Ahmetov and Fedotovskaya 2012). The genes which have been most often discussed in this context are heterogeneous, so we can divide them into four major groups:

1. Genes encoding proteins involved in the regulation of blood pressure, including proteins of the kallikrein-kinin system (e.g. angiotensin-converting enzyme gene – *ACE*, bradykinin B2 receptor gene – *BDKRB2*, endothelial nitric oxide synthase gene – *NOS3*, angiotensinogen gene – *AGT*) and proteins of adrenergic receptors (adrenergic receptor genes – *ADRA2A*, *ADRB1*, *ADRB2* and *ADRB3*).

2. Genes encoding factors associated with the structure of muscle fibers, connective tissues and regulating the development of muscles, myogenesis and muscle angiogenesis (e.g. α-actinin-3 gene – *ACTN3*, myostatin gene – *MSTN*, collagen-related genes – *COL1A1*, *COL5A1*, *COL6A1*, vascular endothelial growth factor A gene – *VEGFA* and VEGF receptor 2 gene – *VEGFR2*, interleukin 15 receptor α gene – *IL15RA*).

3. Genes encoding transcription factors that control the expression of genes involved in the metabolism of cells (e.g. GA binding protein gene – *GABPB1*, hypoxia-inducible factor-1α gene – *HIF-1α*, peroxisome proliferator-activated receptor α, δ, and γ genes – *PPARA*, *PPARD*, and *PPARG*, PPARγ coactivator 1 α and β genes – *PPARGC1A* and *PPARGC1B*, mitochondrial transcription factor A gene – *TFAM*, endothelial PAS domain protein 1 gene – *EPAS1*, calcineurin/NFAT-related genes – *NFATC4*, *PPP3CA*, *PPP3CB*, *PPP3R*) and involved in DNA methylation (5, 10-methylenetetrahydrofolate reductase gene – *MTHFR*, methionine synthase gene – *MTR*, methionine synthase reductase gene – *MTRR*).

4. Genes encoding/participating in important metabolic pathways (e.g. aquaporin-1 gene – *AQP1*, hemochromatosis gene – *HFE*, uncoupling proteins 1, 2, and 3 genes – *UPC1*, *UPC2*, and *UPC3*, potassium inwardly-rectifying channel, subfamily J, member 11 gene – *KCNJ11*); and pathways associated with the release of energy essential in working muscles (adenosine monophosphate deaminase 1 gene – *AMPD1*, muscle creatine kinase gene – *CKM*, mtDNA genes).

These genes have been described by a few teams in the world, mainly from countries such as USA, Russia, Spain, China, England, Australia, Italy. Additionally, in recent years Polish scientists have studied many of them, such as: *ACE* (Eider et al. 2013a), *BDKRB2* (Sawczuk et al. 2013a), *NOS3* (Cięszczyk et al. 2010), *AGT* (Zarębska et al. 2013a), adrenergic receptor genes (Sawczuk et al. 2013b), collagen-related genes (Ficek et al. 2013), *ACTN3* (Cięszczyk et al. 2011a), *VEGFR2* (Eider et al. 2013b), *GABPB1* (Maciejewska et al. 2012), *HIF-1α* (Cięszczyk et al. 2011b), *PPAR genes* (Maciejewska-Karłowska et al. 2013), *MTHFR* (Zarębska et al. 2013b), *AMPD1* (Cięszczyk et al. 2011c), *CKM* (Fedotovskaya et al. 2013), and many others.

At present, population-based case-control studies are the most popular research designs in sports genomics. They usually involve determining whether the allele or genotype of a particular DNA sequence (gene or non-coding DNA region) is more common in a group of examined athletes than it is in the control group, thus implying that the

allele or the genotype improve physical performance (Ahmetov and Fedotovskaya 2012). These common studies usually involve the analysis of a single genetic marker. However, elite performance is a polygenic trait, thus the effect of one gene variant is presumably quite small. As a result, there is a need to use more comprehensive approaches to identify the "optimum" genotype profile for endurance and power-oriented phenotypes (Ruiz et al. 2009; Rankinen et al. 2010; Eynon et al. 2011). To date, few authors have attempted to describe the complicated impact of combination of polymorphisms within one gene (haplotypes) or multiple genotype combinations that influence human physical performance (Ahmetov et al. 2009; Ficek et al. 2013; Maciejewska-Karłowska et al. 2013). For example, Ahmetov and co-workers (2009) analyzed the combination of 10 genetic markers (*NFATC4*, *PPARA*, *PPARD*, *PPARGC1A*, *PPARGC1B*, *PPP3R1*, *TFAM*, *UPC2*, *UPC3*, *VEGFA*) on endurance athlete status of 1432 Russian professionals and 1132 controls. Finally, they confirmed that the likelihood of becoming an elite endurance athlete depends on the carriage of a high number of endurance-related alleles (Ahmetov et al. 2009).

Another type of recently popular research are cross-sectional association studies. They examine whether individuals with one allele or genotype of a chosen DNA sequence show different measures of a particular trait e.g. maximal rate of oxygen consumption ($VO_{2max}$), body mass index (BMI), strength measure, muscle creatine kinase (CKM) level etc. compared to the rest of the sample (Montgomery and Safari 2007; Ahmetov and Fedotovskaya 2012). For example, it has been described that *ADRB2* Gly16 polymorphism carriers have a significantly greater BMI increase compared to Arg16 homozygotes (Ellsworth et al. 2002).

However, it should be emphasized that most of the case-control and association studies have involved too small sample sizes and have not been replicated in independent samples (Ahmetov and Fedotovskaya 2012; Pitsiladis et al. 2013; Wang et al. 2013). The major problem in these studies is the limitation of the number of genetic cohorts of elite athletes from a variety of countries and sports disciplines with extensive physical performance phenotypes (Pitsiladis et al. 2013). Therefore, cooperation between teams around the world have become more popular nowadays. More numerous groups of carefully selected athletes and controls from many countries possess sufficient statistical power for meaningful analysis and interpretation. A good example is the combination of three groups of elite European athletes from Poland, Russia and Spain in the articles described by Eynon and co-authors (2012; 2013a; 2013b).

## Genes and response to training

Decades of physiological research in sport has resulted in relatively good knowledge of the functional response of the human body to physical activities. Regular exercises bring about a variety of metabolic and morphological changes including mitochondrial biogenesis, muscle fiber-type transformation, substrate metabolism, and improvements in circulatory system (Adhihetty et al. 2003; Maeda et al. 2006). Although the physiological reactions in the human organisms after regular exercises are quite well described, the genetic background of the reactions still remains mostly unknown. An understanding of the genetic determinants will allow to clarify the criteria of physical activities for individuals, especially athletes. In the future, this knowledge should contribute not only to more efficient and safer sport training (thanks to the increased effectiveness of implemented training regimes, preventing injuries, cardiomyopathies, sudden death etc.) but also better athletic recovery, traumatology, medical care and many other areas (Maeda et al. 2006; Ahmetov and Rogozkin 2009). The process of exercise-induced adaptation in human body involves a number of signalling mechanisms, initiating replication of specific DNA sequences, enabling its following translation, and finally generating new proteins. The physiological effects of these adaptations

are determined by volume, intensity and frequency of physical activity (Coffey and Hawley 2007). It is well known that individuals vary in their responses to similar training: from a lack of adaptive response to extreme overload. Current studies have shown that people with the same genotypes respond similarly to exercises in comparison to those with different genotypes, indicating that some genes play a key role in determination of individual differences in response to physical activities.

The search for genetic markers of functional response of human body to physical activities will certainly be more productive than the popular so far case-control and cross-sectional association studies (Bouchard et al. 1997). Actually, there are at least 29 genetic markers that have been shown to be associated with endurance phenotypes in response to sport training. They are located within 12 autosomal genes and mtDNA. Within the group of the genetic markers, there are genes mentioned above, such as *ACE*, *AMPD1*, *CKM*, *GABPB1*, *HIF1α*, mtDNA loci, *PPARD*, *PPARGC1A*, *VEGFA*, *ACTN3*, *IL15RA*, *PPP3R1*, and the new ones such as *APOE* (apolipoprotein E gene), *ATP1A2* (ATPase, Na+/K+ transporting, alpha 2 polypeptide gene), *HBB* (hemoglobin β gene), and *RETN* (resistin gene) (Ahmetov and Rogozkin 2009). To date, only few authors have attempted to describe the fact that heterogeneity in individual response to training stimuli is at least in part determined by genetics. Evidence for genetic influence on pre-training performance have been shown in the case of the *ACTN3* R577X polymorphism; the alpha-actinin-3 deficient mice (genotype XX) had a pre-training lower grip strength (lower muscle strength) and were able to run 33% further on a treadmill when run to exhaustion (improved endurance performance) than their Wild-Type (genotype RR) littermates (MacArthur et al. 2007; 2008).

Additionally, some candidate genes, such as *GSTP1* (glutathione S-transferase P1 gene) and mentioned before *AGT* and *MTHFR*, are believed to explain some of the inter-individual response to exercise training (Zarębska et al. – unpublished data). Recently, the association between the *GSTP1* c.313A>G polymorphism and changes in cardiorespiratory fitness following 12 weeks of supervised aerobic dance training in 66 Polish Caucasian women have been examined. The results confirmed that the *GSTP1* G allele (Val105) was associated with the increase in $VO_{2max}$, and $V_{Emax}$ in response to training. A significant difference in baseline $VO_{2max}$ between GG+AG and AA genotypes was also noted; individuals with the G allele had greater $VO_{2max}$ than the AA homozygotes at baseline (Zarębska et al. – unpublished data).

## Conclusions

World-class athletic performance is a complex multifactorial phenotype which have well confirmed strong genetic basis. However, the main problem is in defining the exact genes and DNA variations that are involved, and describing by which mechanisms and pathways they exert their effect (Ahmetov and Fedotovskaya 2012). In view of the fact that gene variants do not completely explain the heritability of athlete status, other forms of variation, such as rare mutations and epigenetics (modulating gene expression, mainly DNA methylation and histone modifications, which leads to persistent effects on the availability of DNA for transcription) as well as proteomic profiling, must be considered (Sharp 2010; Ahmetov and Fedotovskaya 2012; Ehlert et al. 2013). Nowadays, numerous studies which have tried to solve this question still represent only the first steps towards a fuller understanding of the genetic factors that influence human physical abilities, and continuing studies are necessary. In the near future, more research should be also focused on identifying genetic markers referring to other sport-related traits e.g. resistance to stress and pain, coordination, flexibility, as well as temperament of athletes (Ahmetov and Fedotovskaya 2012;

Pokrywka et al. 2013). What is more, the new molecular biology technologies and bioinformatics will be applied to analyze the genetic effects on physical performance.

Sport genomics could provide new opportunities for sports clubs as well as individuals. Understanding the genetic background of physiological processes should contribute not only to sport selection, more efficient and safer sport training but also better athletic recovery, traumatology, medical care, diet, suplementation and many other areas (Maeda et al. 2006; Ahmetov and Rogozkin 2009). Knowledge of athletes' genotypes also provides information about the metabolism of performance enhancing substances, and may help in detection of prohibited substances in sport (Pokrywka et al. 2013).

Nevertheless, the development of sport genomics poses a risk of using genetic manipulation to enhance athletic performance i.e. illegal "gene doping" understood as "the non-therapeutic use of genes, genetic elements and/or cells that have the capacity to endurance athletic performance" (Pokrywka et al. 2013).

In summary, the importance of genetics in modern sport increases every year. Therefore, it is important to discuss the achievements, hopes and fears connected with the rapid development of molecular biology in sport.

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