BIOMARKERS AND GENETIC FACTORS RELATED TO PHYSICAL ACTIVITY AND ITS HEALTH BENEFITS

DHURATA BOZO and SUELA XHUFI
Department of Physical Activity and Health, Institute for Sport Research, University of Sports, Tirana, Albania

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ABSTRACT

The benefits of physical activity (PA) on health and fitness are well known. Regular physical activity (PA) is associated with a reduced risk for many chronic medical conditions, including depression, cardiovascular disease; type 2 diabetes, obesity, and cancer. Recent studies show that heritability plays a significant role on the health benefits and the reduced risk for both prevention and treatment of chronic medical conditions. The purpose of this minireview is to summarize the existing literature on the role of biomarkers in general and genetic determinants of PA, on biological response and other biological factors on physical activity and its beneficiary effects for human health.Use of biochemical and physiological biomarkers, in conjunction with genetic factors are important and useful indicators to assess the human health status in general and health effects of physical activity and sports, the biological response to physical activity and in the context of the prevention and treatment of diseases arising from sedentary life related or not to biological and physical aging. The use of bio-genetic markers presents limitations related to their sensitivity, the lack of reference values for groups engaged in physical activity and sports, and others. In this context, the exploration of the genetic basis and hereditary factors, in collaboration with the above, takes on special importance for the purposes of this paper. The Human Gene Map for Performance and Health related Fitness Phenotypes considers a number of genes associated with exercise performance and response to exercise training. These genes interact with physical activity and/or exercise to influence multiple physical and physiological traits, biochemical parameters, and hemodynamics. The functions of these genes are consistent with the fitness phenotypes of physical activity and provide insight on how physiologic processes might drive the capacity for physical activity and the relative associations with performance phenotypes and their potentials to be used as markers for talent identification and trainability in sport. However, Physical Activity, biological response and its health benefits and sport performance is a complex multifactorial phenomenon governed by several intrinsic factors such as genetic polymorphism, psychomotor skills, physical fitness that are greatly influenced by a variety of

extrinsic factors such as diet, exercise andtraining, behavioral, social and cultural factors as well.
Keywords: biomarkers, Physical Activity, HGMPH, sport genes, polymorphisms

1. INTRODUCTION

Biomarkers are small molecules widely used for assessing the health status of individuals engaged in physical and recreational activity and for athletes in the context of tracking and monitoring physical and athletic performance. Traditionally, biomarkers started to be used in the field of sports, to assess, monitor and track athletic and training performance and to identify the conditions of training overload of athletes (Lee *et al*., 2017).

Biochemical and genetic markers are used today to assess the physical fitness, the cardiovascular capacity, muscle strength or power, oxidative stress, muscle fatigue, response to exercise, etc. Recently, there has been a growing interest in biomarkers used for assessing health-related aspects, both in individuals who engage in sports activity and those engaged in physical activity for health or recreation (Lightfoot 2013; Palacios *et al*., 2015).

The biological values of biomarkers depend on the health status of individuals, the status and level of physical activity and exercise load, type of sport, intensity and duration of exercise, in addition to other factors such as age group, gender, and special physiological, pathological or nutritional conditions. International studies provide recommendations and biomarkers lists to be used for tracking and monitoring changes in individuals engaged in physical activity and various exercise programs and for athletes of specific types of sports (Lee *et al*., 2017). Biochemical and physiological biomarkers present also some limitations related to their specificity, need to be used in combination with others, lack of reference values in active people and athletes, and others (Gielen *et* al., 2014).

The aforementioned limitations have called the need to explore more about genetic and molecular markers, which are the basis for the production and synthesis of the biomarker molecules themselves. However, it should be noted that the weight of genetic determinants is not absolute, as the fitness phenotype, the biological response to PA and its health benefits, as well as sport performance is a complex multifactorial trait determined by the combination and coordination between intrinsic (genetic polymorphism, psychomotor skills, physical fitness/health) and extrinsic factors (diet, exercise/ training behavior, social/educational/cultural factors) and others (Zhang *et al*., 2018).

Over the last 20 years the genetics of Physical Activity and sports has developed significantly and the obtained results/discoveries are impressive. It has become possible today to discover and identify the location and role of hundreds of specific genes that directly or indirectly encode the traits related to fitness, exercise and sport performance (Lightfoot *et al*., 2018).

The genetic basis of the response to physical activity for health, recreation and sports is the most explored field especially in the last 10 years. There have been identified and defined genes that affect muscle strength, resistance, 'speed' , the bodily changes in response to exercise, those responsible for glucose and fat metabolism in response to exercise, for energy balance and obesity, including those dealing with interaction with exstrinsic factors. These discoveries enable today the design of special exercise programs for groups, individuals within the various goals of physical activity, to the design of specialized personalized programs and the identification and selection of talents in various sports. These studies and discoveries have also paved the way for the genetic modification techniques and methods that constitute the basis of genetic doping, a critical and much debated issue in the field of sports, directly related to the health of physical exercisers (Dias, 2011; Lee *et al*., 2017).

Given the importance of these markers and the limited knowledge about them and their use, the present paper reviews the current data regarding the types of biomarkers, their importance with a special focus on the genetic markers used to evaluate and asses the health-related fitness phenotypes and the impact of physical activity on human health.

2. MATERIALS AND METHODS

This publication is a summary mini-review on issues and scientific aspects related to the current state of knowledge on biomarkers used in the context of the impact that health activity has on its broad conception of human health, of individuals engaged in physical and recreational activities as well as to guarantee the health of athletes of various sports. The literature references of this mini-review have been selected among those reported during the last 10 years from reliable and reputable sources and publications in scientific journals.

3. RESULTS AND DISCUSSION

Biomarkers for Physical Activity and Health

Biomarkers are useful tools for assessing and monitoring health, training status and performance.

Traditionally, biomarkers have been of interest in sports in order to measure performance, progress in training and for identifying overtraining, to identify the degree of physical fitness, chronic stress, overtraining, cardiovascular risk, oxidative stress and inflammation. In sport, biomarkers are key parameters to assess the impact of exercise on different systems, tissues and organs. During the last years, growing interest is set on biomarkers aiming at evaluating health-related aspects which can be modulated by regular physical activity and sport. Today we can estimate parameters for assessing the degree of fitness, muscle damage, hydration/dehydration, inflammation, oxidative damage, fatigue, overtraining, etc, which facilitate the evaluation of the response of the human body at the different levels of physical activity or training being carried out. Biomarkers can also be used to measure the impact of training on the long term or the acute effect of exercise (Papa *et al*., 2015).

Depending on the purpose of their use and application, they can be classified and grouped into markers that assess and monitor muscle condition, inflammation in general and muscle in particular (including cardiac), muscle strength and strength, metabolic changes such as consequence of exercise, the level of parameters such as glycemia or cholesterolemia as an effect of exercise. In the field of applications in the field of sports they are classified into biomarkers that assess muscle energy status, lactate production rate, hydration status, inflammatory effects of exercise, recovery after exercise, inflammatory and other injuries caused by excessive or poor exercise, etc. (Van der Mee *et al*., 2018).

The value or concentration of a biomarker depends on many factors, as the training status of the subject, the degree of fatigue and the type and duration of exercise, apart from age and gender, among others. Other useful biomarkers are body composition (specifically muscle mass, fat mass, weight), physical fitness (cardiovascular capacity, strength, agility, flexibility), heart rate and blood pressure. Depending on the aim, one or several biomarkers should be measured. It may differ if it is for research purpose or for the follow up of training (Lee *et al*., 2017).

A single measurement of a biomarker does not enable a complete and accurate assessment of an individual's health status. Even when specific molecular and biochemical markers have high sensitivity, their combined use does not always yield accurate and well-referenced data. This is further complicated by the fact that individuals exhibit an extremely wide inter-individual absolute and relative variance even under normal conditions, the more it becomes difficult to interpret and compare in the conditions of PA and sports. Moreover, reference values for biomarker values or concentrations specifically to physically active people and athletes are lacking, which may lead to incorrect interpretation of the results (Palacios *et al*., 2015).

A research about the hematological biochemical parameters of a target groups of athletes of different sports has been carried out at the Institute for Sport Research, University of Sports, Tirana, Albania, and the results reported that the reference values used as a basis for evaluation or comparison are different and variable. In addition, it is known that individuals engaged in regular physical activity and athletes may have biomarker values / concentrations which would be considered in the range as pathological in untrained people, as observed in the hematological and biochemical parameters of routine in laboratory analysis. Therefore, it is important to adjust the reference values as much as possible and to regularly check each item to set its reference rate. In order to avoid this limitation of biomarkers as much as possible, in addition to continuing studies in this field, our research team is currently elaborating a set of reference values for some biochemical and hematological indicators specially adapted for the assessment of health status and the athletic performance of athletes of various sports (Bozo and Lleshi 2012; Della Valle, 2013).

Another several-year study in female volleyball players, showed abnormal variations in a number (7 out of 13) of critical biochemical-hematological parameters, most of them related to red blood cells, haemoglobin, iron status, etc. These call for special attention to anemia problems within the teams and medical care as a matter to be seriously addressed by the coaches, as one of the main female triade health issue in sports (Della Valle and Haas 2013; Bozo and Lleshi, 2014).

Genetic determinants related to physical fitness and health

Although it is aleady known that there is a considerable genetic component, PA is such a complex phenotype quantification and clear understanding still remains a challenge for future studies (Karvinen *et al*., 2015).

Current understanding of the genetic architecture contributing to PA is limited, especially compared with other phenotypes like height, and genetic diseases like obesity and diabetes. As the ultimate level of PA is an interaction between the genes and the environment, it is more correct to state that genetics influences a predisposition to engage in activity, which is then expressed or not in relation to environmental factors (Aaltonen *et al*., 2013).

Family studies show that genetic factors contribute to variation in PA with heritability estimates ranging from 9% to 57%. A number of family studies suggest that it is difficult to disentangle the effects of genetics from shared environmental effects. Twin studies may address better this issue and reported that heritability of PA is between 43% to 52% in adolescents, 30% in young adulthood and no uniparental heritability was found (Bouchard, 2011; De Vilhena et al., 2012).

Genome-wide linkage studies (GWAS) use association-based candidate-gene methods to provide additional insights into the genetic architecture underlying human PA (Kim et al., 2011; Dias, 2011).

GWAS enables also a more precise location of the potentially causal genes involved in the PA phenotype (Church *et al.*, 2011; Stenholm *et al*, 2014; Pedersen and Saltin 2015).

Thanks to these modern techniques and methods, hundreds of candidate genes have been identified as directly or indirectly related to Physical Activity and its health impact and for the treatment of health conditions, physical fitness and sport performance (De Vilhena *et al*., 2012; Gielen *et al*., 2014; De Geus *et al*., 2014;).

Physical Performance and Health-related Fitness Genes

The human gene map for performance and health-related fitness phenotypes (HGMPHFP) contributed significantly to the identification and gene mapping of physical performance and health-related fitness phenotypes. A total of 239 genes and markers with evidence of association or linkage with a performance or a fitness phenotype are positioned on the map of autosomes (214), X chromosome (7) and mitochondrial DNA (18). The map is continuously growing in number and complexity (De Geus *et al.*, 2014; Diego *et al*., 2015; Lighfoot, 2018; Zhang and Speekman, 2018;).

Physical performance and health-related fitness phenotypes genes are classified based on different criteria and depending on the study or the purpose of use use.

Endurance / resistance genes.

These group of genes encode for molecules that define or influence human structures and functions, increase endurance and muscular endurance and in turn promote the increase of muscle mass. They affect contraction power, blood flow, aerobic fitness, insulin sensitivity, response to hypoxia and other traits, related directly or indirectly to physical activity/sports and health benefits (Lee *et al*., 2017; Dias 2011).

ACE gene is responsible for the production of the Angiotensin-Converting Enzyme, which catalyzes the conversion of angiotensin I to its active form, II. ACE has multiple effects as a vasoconstrictor, regulator of salt and water homeostasis, of inflammatory reactions, erythropoiesis, tissue oxygenation, and skeletal muscle efficiency. Of the two alleles (I and D), the D allele produces a more active enzyme, associated with physical and sports traits common in power sports athletes: I allele associates to anabolic response in bursting power sports. These results makes ACE an important gene to track PA and health benefits outcome (Gielen *et al*., 2014; Bruneau *et al*., 2017; Lightfoot *et al*., 2018).

PPAR-delta (Peroxisome-proliferator Activator Receptor**) gene** regulates the expression of several other genes that promote the further proliferation of slow muscle fibers, increasing the slow and fast muscle fibers, thus affecting speed and endurance and fat breakdown activity in adipose tissue (De Vilhena *et al*., 2012).

PPARGC1A (peroxisome proliferators-activated receptor g coactivator 1a**) gene** produces an PPAR activator enzyme that controls the glyco-lipid metabolism and conversion of fats into sugars for immediate energy use, thus promoting the increase of muscle fibers and the mitochondrial biogenesis. Two alleles (A and G) are known to correlate with opposite features of muscle performance, speed or resistance (Lee *et al*., 2017).

Genes that affect muscle performance

This category includes candidate genes that influence muscle structure, strength and speed and other properties related to physical and athletic performance.

MSTN (myostatin) gene codes for myostatin, a protein which acts as a negative regulator of skeletal muscle growth, whose inactivation promotes abnormal increase of muscle mass. MSTN is a candidate gene for the treatment of atrophy and muscular dystrophy and subject to doping in sports. Myostatin inhibitors are used as doping agents and listed among the limited inhibitors by the World Anti-Doping Agency (WADA) (Bouchard 2011).

ACTN3 gene: produces Alpha-Actinin3, the binding protein of actin fibers in fast fibers of scheletal muscle, where its presence in high amounts causes a fast explosive powerful muscle contraction. Of the two R and X alleles of ACTN3, R (rapid) determines the increased amount of actin-3 in fast muscle fibers. Variants containing the R allele are very common (about 85%) in the population of Jamaica while in other population it doesn't exceed 14-20% (Lee et al., 2017; Gielen et al., 2014).

CK-MM gene is responsible for the synthesis of Creatine-kinase (CK), which catalyses the conversion of creatine into phosphocreatine (PCr), expressed by various tissue cells, In tissues that consume ATP rapidly, i.e. skeletal muscle, PCr serves as an energy reservoir for the rapid regeneration of ATP. The CK-MM isoenzyme is found in the skeletal and cardiac muscle and increases in cases of muscle damage/injury (Kleiner *et al*.; 2013; Koch *et al*., 2014).

Currently, the Institute of Sports Research, at the University of Sports of Tirana is investigating on a set of biochemical and genetic (ACE, ACTN3, MSTN and CK-MM) in a group of Albanian athletes.

Genes that affect cardiac and respiratory functions

NRF (nuclear respiratory factors) **genes** affect cardiac and respiratory functions, studied in the context of the genetic and biochemical basis of increased cardiac / respiratory capacity, and the ability to respond to long-term adaptation to exercise (Bruneau, *et al*., 2017).

The three types of NRF genes (NRF1, NRF2 and NFE2L2) play a special role in adaptation to exercise. The various genotypes (GG, AA, GA) affect cellular energy economy, increase mitochondrial density in muscles, activate of oxidative phosphorylation (aerobic) and translation of biochemical signals into physiological adaptive responses and increasing endurance and resistance to PA/exercise (Church *et al*., 2011).

Endotelin1 gene produces a protein expressed in vascular endothelium, acts as a vasoconstrictor regulating (increasing) blood pressure and is higly tempered by activity level, cardiac fitness and adaptation. The G allele is associated with increased cardiorespiratory fitness, while T allele with increased hypertension and pulse pressure response to training (Zhang and Speakman, 2019).

The Nitric oxide synthase gene (NOS) produces endothelial nitric oxide (NO) acting as a vasodilator and increasing the blood flow to the skeletal muscle. The NOS3 variant might be a candidate for the adaptive cardiac capacity in elite endurance athletes (Gielen *et al*., 2014).

- ***Training response genes***

Under this group are considered a number of genes that direct and control important enzymes in the metabolism of nutrients and energy, responsible for the metabolism of glucose and fats in response to exercise, etc. Instead than single genes, is the combination, integration and interaction of multiple genes and extrinsic factors that affect performance, determine the individual variation of the response to exercise, make an individual/athlete fit and respond better by increasing physical and athletic performance while maintaining a healthy state (Church *et al*., 2011; Stenholm *et al*., 2014).

This group includes also 127 genes considered as candidate genes associated with obesity and the impact of exercise. These include genes that respond to different traits and functions, that affect energy balance, the body weight, metabolism according to diet, predisposing to weight/obesity, and others (De Vilhena *et al*., 2012; De Geus *et al*., 2014).

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