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Genes and physical fitness

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The search for genes with that positively affect physical fitness is a difficult process. Physical fitness is determined by numerous genes, and its genetic determinants are modified by environmental factors. The map of candidate genes that can potentially affect physical fitness becomes larger every year, and currently it contains more than 200 genes associated with such aspects as respiratory and cardiovascular stability; body build and composition – especially muscle mass and strength; carbohydrate and lipid metabolism; response to training; and exercise intolerance. The inclusion of the genetic component in physiological and biochemical studies would permit drawing a representation of predispositions for each athlete interested in practicing high performance sports and would be a valuable coaching aid in the process of training individualization.

KEY WORDS: genes, physical fitness.

What this paper adds?

The present article demonstrates the results of studies on the effects of polymorphisms of the angiotensin-converting enzyme (ACE), alpha-actinin-3 (ACTN3), creatine kinase (CKM), mitochondrial NADH dehydrogenase subunit (mtND5), insulin-like growth factor 1 (IGF1) and insulin-like growth factor-binding protein 3 (IGFBP3) genes on maximal oxygen uptake, which is a physiological aerobic capacity index of high heritability.

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Physical fitness

Physical fitness is the body's ability to perform heavy or long-lasting physical efforts using large muscle groups without any significant imbalance of homeostasis. After the completion of such an effort all parameters of the muscles return quickly to their resting levels. Physical fitness includes both long-lasting and short-lasting efforts of high intensity as well as recovery, i.e. replenishment of energy supplies and removal of post-exercise homeostatic imbalance in order to undertake another exercise in a short time. Long-lasting aerobic efforts are in opposition to short-lasting efforts that develop maximal force and are dominated by anaerobic metabolism. The basic energy carrier in both types of efforts is ATP; however, the sources of ATP re-synthesis in the two types of exercise are different.

The ATP stores in muscles are used up a few seconds after the commencement of exercise, thus reactions are activated that replenish the cellular supplies of ATP regardless of the presence of oxygen. They include creatine kinase enzyme reaction and glycolysis as well as myokinase reaction which by increasing the ATP/ADP ratio activates glycolysis. The activation of aerobic sources of energy requires time. Thus the activation of anaerobic ATP sources is crucial in short-lasting efforts of great intensity such as static exercises (e.g. weightlifting) and dynamic exercises (e.g. sprint runs). Apart from energy metabolism the properties of muscles are also significant for short-time exercises. They include the cross-sectional area of the muscle and fiber composition, i.e. the contribution of type II fast-twitch fibers which determine contractile speed and generate considerable

muscle force in a short time. Also the performance of intensive short-time exercises is determined by intramuscular temperature and resistance to fatigue caused by the accumulation of unhealthy products of anaerobic metabolism.

On the other hand long-lasting exercises (from a few minutes to a few hours) depend on the amount of ATP from the oxidation of glycogen and free fatty acids as well as the rate of glucose recovery in gluconeogenesis. The reserves of fatty acids are large enough so their losses during a day-long work are insignificant. On the other hand, the glycogen stores can be become depleted after 90 minutes of intensive exercise. Aerobic energy processes (oxidative phosphorylation based on beta-oxidation of fatty acids and aerobic glycolysis) are determined not only by the presence of the substrate but also by the appropriate oxygen level in muscle cells. This is why individuals with better abilities of oxygen transportation and utilization achieve a higher rate of ATP re-synthesis and tolerate better long-term exercises. The efficiency of oxygen delivery is determined by the function of the respiratory system, including the maximal pulmonary ventilation, diffusing capacity of the lungs and the circulatory system, i.e. more specifically, maximal cardiac output and oxygen capacity of blood, muscular blood flow and vasomotor regulation. The last one is a factor inhibiting the delivery of oxygen to working muscles only in vasomotor neuroses. The respiratory system of healthy persons, unlike the circulatory system, does not inhibit the capacity of oxygen transportation to cells. While the maximal heart rate is similar in people at the same age, the maximal stroke volume is a discriminatory factor, especially in comparisons between healthy and sick individuals or physically active and sedentary individuals. An improvement of the oxygen supply function will depend on the reinforcement of the circulatory system *via* an increase in cardiac output and muscular blood flow, which depends on muscular capillary density. During long-lasting physical exercises it is important to reach the highest level of aerobic metabolism as quickly as possible by limiting the less economical uptake of energy from anaerobic sources.

Apart from the aforementioned functions of oxygen delivery and energy metabolism physical fitness is also affected by the ability of balancing exercise-induced changes in the internal environment and tolerance to fatigue. The former includes the ability of quick removal of harmful metabolites from muscles, i.e. the capacity of buffers in the blood preventing metabolic acidosis, ability of lactate removal from the muscle and the blood, and efficient thermoregulation against overheating. Lactate is converted into glucose in the liver, and in the muscles it is oxidated by cardiac lactate dehydrogenase contained mostly in type I slow-twitch fibers. The effectiveness of gluconeogenesis and composition of muscle fibers determine, therefore, the range of exercise-induced metabolism and the rate of homeostatic recovery. The disturbances of homeostasis are related to tolerance to fatigue, which is difficult to measure since the sensitivity to muscle pain caused by the accumulation of harmful metabolites (e.g. ammonia, AMP, ADP, IMP) and depletion of energy stores is a subjective feeling dependent on psychological factors, e.g. motivation to attain a good sport result.

Physical fitness is therefore a complex trait and, at the same time, an individual one, depending on sex, age, physical activity level, lifestyle, diet, climate and – first of all – sport or health training. In order to determine the physical fitness of a given person a number of physiological, biochemical and psychological parameters should be examined. Most often, general physical fitness – in particular aerobic capacity – is defined by the maximal oxygen uptake (VO_2max), which is the maximum capacity of an individual's body to use oxygen during incremental exercise in one minute. It can be used as an index of physical fitness since the amount of oxygen one is able to use within one minute is indicative of meeting the oxygen demand during exercise. The more oxygen the body is able to absorb, the more effective aerobic energy processes at the cellular level are. Furthermore, the maximal oxygen uptake is correlated with the aforementioned factors determining physical fitness. A high VO_2max reflects a high efficiency of the respiratory system, circulatory system and metabolic capacity of skeletal muscle. It is a versatile index which can be used for examination of patients with cardiopulmonary diseases, individuals leading a sedentary lifestyle, physically active people and elite athletes.

The maximal oxygen uptake can be most easily expressed in ml/kg/min. The lower limit of VO_2max, which enables independent locomotion, is 15 ml/kg/min. In young healthy individuals the VO_2max values fall between 30 and 50 ml $\cdot$ kg^{-1} $\cdot$ min^{-1}, and in elite endurance athlete practicing such sports as the marathon or road cycling, they can even exceed 85 ml $\cdot$ kg^{-1} $\cdot$ min^{-1} [1]. The VO_2max increases until the age of 18-20 and remains at a relatively steady level until the age of 25 years. After 30 years of age the VO_2max decreases for

10% per each decade of life. Men reach a higher VO_2max than women due to their greater muscle mass, heart size, circulating blood volume and more hemoglobin in the blood in relation to body mass [2].

Factors affecting the maximal oxygen uptake are classified into four groups linked with (i) the respiratory system, (ii) blood circulation, (iii) muscular blood flow, and (iv) muscle metabolism. The first three groups are associated with oxygen transportation to mitochondria, the last one is concerned with oxidative processes inside the mitochondria. Each group of factors can significantly affect the VO_2max; however, the most important determinants include cardiac output, hemoglobin level, muscular capillary density, the number of mitochondria and activity of oxidative enzymes. The results of Blomstrand's study of VO_2max showed that the functional oxygen utilization capacity of mitochondria is significantly higher that the transportation capacity of oxygen. It can be thus deduced that it is oxygen transportation, rather than oxygen utilization in mitochondria which is the main determinant of the individual VO_2max level [3].

Aerobic capacity can be precisely characterized by the aforementioned VO_2max and the anaerobic threshold (AT); however, the former is used more frequently due its greater dependence on the genetic component as opposed to AT which is training-related.

Genetic determinants of physical fitness

Both qualitative and quantitative traits can be genetically inherited. The former, including genetic disorders, are often single gene disorders, e.g. mucoviscidosis (CFTR gene), Duchenne muscular dystrophy (DMD gene), familial hypercholesterolemia (LDLR gene) and many others. If one specific gene is responsible for the incidence of a disease than the inheritance type is called one gene one disorder (OGOD). The OGOD trait inheritance assumes that a single gene is the necessary and sufficient determinant of a trait or a disorder [4]. The qualitative traits are determined by a large unspecified number of genes, i.e. quantitative trait locus (QTL), from which any single gene is not sufficient to cause a trait. Such genes do not lead to the development of a trait to the extent their effects can be only identified on the basis of ontogenetic phenotypic differences. There are, however, cases of genes that exert a larger influence than others. If their effects exceed a double SD, these genes are called major genes. The probability of detection of such a gene depends on the examined population: its size, structure, gene frequency, and chromosome location in relation to the marker. Thus the proper selection of a research sample is highly significant for the successful search for major genes. In practice, however, there would be several genes with minor effects.

Physical fitness is a qualitative trait affected by numerous components and features of large phenotypic variation. It is determined by genetic and environmental factors (lifestyle, nutrition, training). The effect of a genetic and an environmental factor on a given trait is measured by the heritability coefficient h^2. According to its classical definition, heritability is measured by estimating the relative contributions of genetic and non-genetic differences to the total phenotypic variation in a population. In the narrow sense, heritability is a percentage contribution of additive genetic or allelic variation to phenotypic variability. The closer h^2 is to 1 (100%), the more genetically determined a given trait is. The closer it is to 0, the more environmentally determined a given trait is. The heritability of a trait in a given population is estimated by a comparison of the observed covariance among related individuals with an expected covariance based on the degree of their relationship. Valuable sources of information about the heritability coefficient are studies of parents and children, and of monozygotic twins (MZ) and dizygotic twins (DZ). Assuming that the environmental conditions of a pair of twins are the same, and that MZ twins are genetically identical, whereas DZ twins are related to each other to the same degree like any siblings (50% of the same genes), the variability of a given trait will be lower in the MZ pair, proving that the genetic component really does influence the observed phenotypic variation in a population. The difference between the variation in a pair of MZ twins and the variation in a DZ twins can be thus attributed to genetic factors. These types of studies are an important source of data, one must remember, however, that the MZ twins are not entirely identical due to some molecular mechanisms, e.g. imprinting, inheritance of the genome, somatic mutations, etc. and that a combination of determinants of the development of twins can facilitate research, but does not have to be representative for the entire population [5, 6].

The studies on the contribution of the genetic components to the development of aerobic capacity were first undertaken in the early 1970s. Klissouras in his analysis of 15 pairs of monozygotic twins and 10 dizygotic pairs of twins estimated the contribution of the genotype to maximal aerobic power at about 93% [7]. Another study

from 1991 conducted by Fagard et al. [8] showed a 74-80% contribution of genetic variability to the VO_2max level. Following the adjustment of these data by accounting for anthropometric traits and sporting activity, the VO_2max heritability was shown to be 66%, with 34% of the non-shared environmental factors in the studied individuals [8]. Different results were achieved by Bouchard [9], who estimated the heritability of maximal oxygen uptake at 47%; however, considering the shared environmental factors in a given group the h^2 dropped to 25% of phenotypic variation.

While estimating the coefficient of heritability the assumption of the same environmental determinants in twins should be approached with caution. Howald did not observe the VO_2max genetic variability in his study, and after having eliminated wrongly qualified pairs of twins the heritability coefficient amounted to 68% [10] An important research contribution was made by Lesage, who observed a significant influence of maternal DNA on the VO_2max level in children, while Bouchard estimated this impact at 50% in individuals leading a sedentary lifestyle [11].

Another significant contribution to the knowledge of inheritance of traits related to physical fitness was made by Bouchard et al. in their family research project called HERITAGE (Health, Risk Factors, Exercise Training And Genetics) involving a variety of physiological and genetic tests undertaken by different generations from 130 families. Their findings as well as observations of other researchers led to the creation of The Human Gene Map for Performance and Health-Related Fitness Phenotypes – an annually updated information project on genes that can potentially influence performance abilities [12].

Some traits which are significant in sport depend on genetic factors only to a limited extent. They include maximal isometric force, body fat percentage and reaction time which are largely determined by environmental factors, e.g. training or nutrition. On the other hand, such traits as motor coordination, maximal power output, strength endurance, muscle mass, maximal aerobic capacity and movement speed and precision depend to a smaller or larger degree on genetic factors, and their heritability coefficient is relatively high, i.e. between 0.4 and 0.8 [13] Table 1 presents the heritability of some traits with a contribution to physical fitness. The variability of h^2 for the same trait is due to differences between the studied populations (genetic differences are due to genetic drift or new mutations, and environmental differences with regard to the homogeneity of living conditions).

Gene mapping strategies

The mapping of genes that contribute to the development of VO_2max is not an easy task due to the additive character of the trait and, therefore, due to the accumulative effect of multiple genes with an insignificant effect. One of the most common strategies of seeking candidate genes that can potentially affect a trait is the analysis of association. A positive association of an allele with a studied trait or its frequency must be, however, approached with caution. An association can occur not only when an examined polymorphism affects a trait, but also when it remains in a linkage disequilibrium with the marker affecting the trait, which is located near the studied polymorphism. Linkage disequilibrium is a type of association of two polymorphisms located close to each other on the same chromosome and inherited as a haplotype. If there is then an association of a polymorphism with a trait, it does not functionally affect the development of this trait, but most probably remains in the linkage disequilibrium with another functional polymorphism. An association can be also positive, when the population is heterogeneous. Then any allele common in a subgroup of the population will reveal an association with the studied phenotype in a mixed population [5, 6].

Another mapping strategy known as linkage analysis is used for seeking unknown genes using highly polymorphic DNA markers, equidistantly located in the entire genome (10 cM from one another). This strategy is used to find the loci of markers linked with a given trait in a group of related individuals, most often in the highest possible number of pairs of siblings. Linkage analysis requires the knowledge of heritability type of a given trait. Most often the linkage can be found, if the locus of the polymorphic marker contains more often the same allele in particular pairs of siblings, than it would have been deduced from random inheritance. The markers located in fragments of chromosomes unrelated to the development of a given trait reveal no deviation from random inheritance. This strategy is used for the mapping of quantitative trait loci (QTL) and selection of candidate genes that can potentially affect a given trait. It is also an introduction to the analysis of association [5, 6].

Selected candidate genes and their polymorphisms are discussed below. Their selection was made from among

those described in literature as the most promising in terms of their effects on physical fitness, but not always linked with the VO_2max level.

Angiotensin I-converting enzyme (ACE) gene

Location: 17q23

The ACE gene is one of the most documented genes affecting physical activity in humans. It is an important component of the renin-angiotensin-aldosterone system (RAAS) responsible for the maintaining of homeostatis of the circulatory system, consisting of renin and angiotensins, which regulate blood pressure. Renin is secreted by the kidney and it mediates the conversion of angiotensin I from a non-active angiotensinogene. Through the removal of two C-terminal residues from the decapeptide (angiotensin I) angiotensin I-converting enzyme converts angiotensin I into angiotensin II – one of the most powerful vasoconstrictors – and activate aldosterone responsible for the water-mineral balance in the body. Another function of ACE is degradation of bradykinin – a vasodilator reducing blood pressure. Thus ACE leads to an increase in blood pressure in two different ways [14]. An ill-functioning RAAS is the basis of a number of cardiovascular diseases. ACE, which is a halide-activated exopeptidase, occurs in two isozymes: somatic ACE (sACE), secreted in a number of tissues, e.g. vascular endothelial cells, epithelial kidney cells, Leydig cells and blood plasma; and germinal ACE (gACE) expressed only in sperm [14].

The ACE gene was isolated in 1956. It comprises 26 exons, i.e. 16% of the entire gene of the estimated size of 21 kbp. The somatic isoform of ACE consists of two homologous domains containing exons 1-12 and 14-26, respectively. This means that the gene was probably the result of duplication of an earlier gACE form transcribed from exons 13-26 [15].

In 1992 Rigat et al. identified an insertion-deletion polymorphism (I/D) in the ACE gene and observed its close relationship with the amount of free ACE in blood [16]. This polymorphism features the presence of two allelic variants of different length – short D and long I, which can form the following genotypes in the human genome: II – insertion homozygote, ID – insertion-deletion heterozygote and DD – deletion homozygote. The allelic differences result from the presence of a fragment of 287 bp in the 16 intron of the gene.

After their findings of the influence of the I/D polymorphism of the ACE gene on such cardiovascular diseases as high blood pressure, myocardiac infarction or left ventricular hypertrophy, Jones et al. examined the effects of ACE gene variants on human physical fitness [17, 18]. The first analysis of the ACE gene polymorphism was aimed to determine whether a specific allele is more frequent among athletes as compared with the control group. In 1996 Gayagay et al. confirmed a higher frequency of II and ID genotypes in a group of Australian rowers, who displayed a very high level of aerobic capacity [19].

The insertion genotype (II), which features a low activity of ACE in the tissues, allows maintaining a positive energy balance during intensive and long-lasting exercise. It was noted that athletes practicing sports dominated by aerobic energy processes such as mountain climbing, long-distance running and long-distance swimming, almost never have the D allele in their genotype. On the other hand, athletes of sports dominated by anaerobic metabolism, e.g. sprinters or short-distance swimmers, feature a high level of ACE and a more frequent DD genotype. The ACE activity in the blood of individuals with the DD genotype is twice as high as in individuals with the II genotype [16, 20].

Montgomery et al. studied the effects of I/D polymorphism of ACE gene on aerobic endurance in two parallel experiments: on a group of mountaineers climbing the height of 7,000 m without oxygen respirators, and on a group of British Army recruits. The results of the study of 25 elite mountain climbers showed that their allelic distribution was visibly shifted towards the insertion allele I as compared with non-training men without any cardiorespiratory conditions. Genotype II was found in 50% of the mountaineers, ID in 40% and DD in 10%, while the theoretical normal distribution of the genotypes would have been 25% : 50% : 25%, respectively [21].

A study of British Army recruits (n = 123) revealed an association between the polymorphism of ACE gene and reaction to training consisting of performing the maximal number of elbow bends with a 15 kg load in a specified time. Before the commencement of training the number of repetitions was similar in all participants. After the completion of the training cycle a significant increase in the number of repetitions was observed in the specified time in 66 participants with the II and ID genotypes. The increase was not observed in 12 subjects – deletion homozygotes (DD) – as regards the ACE gene [21].

A 2000 study by Williams et al. [20] found that the presence of the insertion allele of the ACE gene signifi-

cantly increased the mechanical performance of skeletal muscle compared with individuals with the deletion allele in their genotype. This was observed after ten weeks of endurance training [20]. Similar conclusions were reached by Jones, Montgomery and Woods, who noted that the I allele of the ACE gene was linked to a lower activity of angiotensin I converting enzyme, and was particularly frequent in elite long distance runners, rowers and mountain climbers [22]. On the other hand, Thomson noted an increase in the frequency of allele I along the increase of Olympic running distances covered by the athletes [17].

Some authors claim that the insertion-deletion polymorphism of the ACE gene can be a factor positively affecting physical fitness, but not through oxygen consumption or heart rate regulation [23]. Zhang et al. even stated that the presence of the insertion allele of the ACE gene is linked to the increase in the size of type I slow-twitch muscle fibers [24]. They suggested that this phenomenon lies at the basis of the link between the presence of insertion alleles in the genotype of ACE gene and high level physical fitness. However, an association was observed between the D allele and a higher contribution of type II fast-twitch fibers [24], greater force of the quadriceps in response to training, better anaerobic fitness and improved aerobic fitness in short-time exercise [25].

Thompson and Binder-Macleod provide two probable mechanisms of association of the ACE polymorphism with physical fitness. The first is the aforementioned mechanism of better cardio-respiratory capacity connected with the function of angiotensin I converting enzyme. The other is the influence of the ACE polymorphism on metabolic capacity. Montgomery & Katsuya noted an association of the I allele with fat mass and greater anabolic reaction to exercise. Thus the II genotype can have a beneficial effect on metabolic capacity by way of maximal utilization of aerobic sources of energy [17].

A number of authors did not find any associations between the ACE genotype and physical fitness [26, 27]. Rankinen et al. carried out a study of a group of male athletes (n = 192) practicing endurance sports such as cross-country skiing, biathlon, the Nordic combined, long- and middle-distance running and road cycling. They observed that the I allele was not over-represented among athletes reaching the highest oxygen uptake level (above 80 ml/kg/min), which can suggest no effects of the ACE gene polymorphism on cardio-respiratory fitness [28]. Also a study of an ethnically heterogeneous population undergoing basic physical training, i.e. US Army recruits [29] and twins undergoing strength training [30] did not confirm the association of D allele with a greater muscle strength. No relationship was revealed either with the athlete elite status among 291 elite Kenyan athletes of endurance sports [31]. Quite contrasting are the results by Zhao et al., who observed higher levels of maximal oxygen uptake in a group of 67 non-training Chinese men with the deletion DD genotype [32] or even a greater increase in VO_2max in reaction to 20-week training in individuals with the DD genotype as compared with ID and II genotypes [28].

The research results discussed above indicate that the impact of different alleles of the ACE gene on the level of maximal oxygen uptake is ambiguous, however, undoubtedly, the function of the ACE gene is significant for cardio-respiratory capacity. Similar research on Polish athletes seems thus purposeful.

Alpha-actinin-3 (ACTN3) gene

Location: 11q13-q14

Alpha-actinins are cytoskeletal proteins belonging to the superfamily of spectrins feature a considerable evolutionary conservatism [33]. Four actinin-coding genes have been identified in humans: ACTN1, ACTN2, ACTN3, ACTN4. The ACTN1 and ACTN4 genes are extramuscular isoforms, whereas the ACTN2 and ACTN3 genes are expressed in myocytes, localized to the Z-disc, where they help anchor the myofibrillar actin filaments. The ACTN2 gene is expressed in all skeletal muscle fibers, whereas the ACTN3 gene is expressed only in fast-twitch fibers utilized in short-time exercise of high intensity [34]. Apart from their mechanical functions ACTN2 and ACTN3 take part in many metabolic pathways and signal transmission [35].

In 1999, North et al. [35] identified a nonsense mutation - C > T substitution at 1747 (C1747T) in the exon 16 of the gene, resulting in a stop codon (X) at the arginine locus (R) at the 577 bp of the protein chain, which led to a break in the translation and emergence of an inactive protein form. Individuals with the genotype 577XX do not have actinin-3 in fast-twitch fibers. According to North, about 16% of the world population (from 25% of Asian population, 18% of European population to less than 1% of Bantu population in Africa) is deprived of this protein in muscles. Since this does not entail a phenotypic effect in the form of a disorder, it was assumed that the protein did not play any crucial role [36]. In 2003,

Yang et al. proposed a hypothesis of the compensatory effect of actinin-2 in individuals with the 577XX genotype. However, the high evolutionary conservatism of the ACTN3 gene may suggest its survival in the genome due to a different function than that of ACTN2 [37]. The genotyping of ACTN3 in non-ape primates showed that most probably the R577X mutation occurred first in humans [33], and that the genome region around the 577X allele features a low level of genetic and recombination variability in individuals of European and East Asian origin as well as strong selection. A hypothesis was proposed about the positive selection of the 577X allele due to its effects on the metabolism of skeletal muscles in some human populations [38].

The opposition between speed-strength capacity and endurance capacity imposes significant limitations on the development of exercise abilities [39]. It can be seen in the decathletes whose results of events requiring great muscle force, e.g. 100 m dash, shot put, long jump or 110 m hurdles are negatively correlated with the results of the 1,500 m run requiring great aerobic capacity and involvement of muscles resistant to fatigue [40].

An analysis of the frequency of the R577X polymorphism of ACTN3 gene among athletes from the Australian national team representing various sports revealed its significant correlation with the elite athlete status (international and Olympic level) and with the character of practiced sport. Australian sprinters of both sexes had the R allele in their genotype more frequently than the controls. This points to the significant role of actinin-3 in the function of fast-twitch fibers, which seems evolutionarily advantageous to this type of physical effort. Female sprinters featured a higher than expected frequency of the RX genotype, while a lower than expected frequency of the RX genotype was noted in female athletes representing endurance sports. The lack of a similar relationship in men suggests that the ACTN3 genotype affects performance fitness in a different manner in male athletes than in female athletes. In men the role of androgens in reaction to training may reduce the effects of actinin-3 on muscle force development. Furthermore, a different effect of the ACTN3 genotype in the "endurance" type athletes and "speed" type athletes suggests that the polymorphism remains in the human population by way of equilibrium in natural selection [37].

Also the study of Niemi and Majamaa on a group of elite Finnish endurance athletes and sprinters showed a greater frequency of the 577RR genotype in sprinters, unlike the XX genotype, which was more frequent in endurance athletes. None of the examined elite sprinters represented the XX genotype [41].

The association of the R577X polymorphism with the elite athlete status and performance fitness shows that the lack of actinin-3 affects the function of fast-twitch muscles. MacArthur et al. noted that the lack of ACTN3 in mice without this gene brought about significant changes in their fast-twitch fibers: decreased cross-sectional area, increased activity of multiple enzymes of the aerobic metabolic pathway, changes in contractility, faster fatigue reduction, i.e. a shift towards the properties of slow-twitch fibers featuring aerobic metabolism and resulting in better endurance fitness [38].

Zanotelli et al. in their analysis of the composition of the *Vastus lateralis* in six marathon runners consented to the compensatory effects of ACTN2 on the muscle function and to an insignificant role of actinin-3 [42]. They observed the normal function and a high performance level of muscles in the examined athletes in whom actinin-3 was present in 21-46% of type II fibers, whereas in one case, the presence of functional actinin-3 was not found [38]. The lack of actinin-3 in the muscles of an elite athlete is surprising, but it lends support to MacArthur's observations, since different muscle properties and types are significant for the marathon runs and for sprint runs [38]. Also Vincent et al. analyzed the composition of muscle fibers and they showed that in individuals with the RR genotype the number and area of type II glycolitic fast-twitch fibers is much greater that in the XX genotype individuals, which may point to an association between the R577X polymorphism of ACTN3 with the regulation of proportion of muscle fibers [43].

Since 2003 various studies have been carried out on the effects of the R577X polymorphism in the ACTN3 gene on differences between athletes representing sports of different energy metabolism, on differences between athletes and non-training controls as well as on relationships between this polymorphism and high sports results and reaction to training [44, 45, 46, 47, 48]. Currently, there is a growing interest in the significance of the R577X polymorphism of ACTN3 in aging and degenerative diseases of the muscles [49, 50].

Muscle creatine kinase (CKM) gene

Location: 19q13.2-q13.3

Creatine N-phosphotranspherase, more often known as creatine kinase (CK) or creatine phosphokinase (CPK)

plays a crucial role in the homeostasis of cellular ATP by catalyzing the conversion of creatine and consuming adenosine triphosphate (ATP) to create phosphocreatine and adenosine diphosphate (ADP). A high level of creatine kinase in cells with high energy demand, e.g. in striated and non-striated muscles, permits a quick regeneration of ATP, which is the most fundamental source of energy in biochemical processes.

CK is found in large volume in muscle cells. Its blood level is indicative of damage of muscle cells – exercise-induced or due to myacardial infarction or ablation. During exercise microleaks and microdamages occur in the myocellular membrane, through which the enzyme enters the bloodstream. The accepted normal level of CK in the blood amounts to 26.0 – 174.0 U/L.

In humans four genes encode subunits of five known types of CK isoenzyme. The muscle type subunit CK-M and the brain type subunit CK-B form CKMM and CKBB homodimers or CKMB heterodimers. Their expression is tissue-specific and their activity depends on the demand of individual structures in the cytoplasm: CKMM and insignificant amounts of CKMB are found in muscles; while CKMB is most active in the heart muscle, while CKBB is active in the brain and to some extent in muscle [51, 52]. There are also octameric forms of mitochondrial CK (mt-CK): sarcomeric CK (Scmit-CK) in muscle as well as ubiquitous CK (Umit-CK) expressed in several tissues, e.g. the placenta, retina or sperm. Mitochondrial CK can be found in the intramembrane space of mitochondria and they are responsible for the replenishment of ATP from phosphocreatine from oxidative phosphorylation [53].

The genes encoding particular subunits are located on different chromosomes: CKB on 14q32, CKM on 19q13.2-q13.3, Scmit-CK gene on 5q13.3, and Umit-CK on 15q1 [53].

CKMM is specifically linked to the sercomere M-line – one of heavy meromyiosins near myosine ATPase and the external membrane of the sarcolasmatic reticulum and vesicles. Large amounts of ATP generated near the myosin heads are due to the CKMM activity [54, 55].

Several studies confirm the hypothesis of the CKMM gene being a promising candidate gene affecting the development of endurance fitness. The muscles of endurance athletes contain more type I fibers and feature a high activity of marker enzymes involved in aerobic metabolism. Considering the fact that the activity of CKMM in type II fast-twitch fibers is twice as high as CKMM activity in slow-twitch fibers, a low activity of this enzyme will be another trait of an "endurance" type athlete. This was confirmed by studies of skeletal muscles of knockout mice without the CKM gene. They showed that in consequence of lower CK activity an improvement of post-exercise endurance parameters can be observed consisting of repeated muscle contractions [53]. It can be assumed that the genetic predisposition to low CKMM activity will be advantageous for the development of the endurance pheonotype.

So far studies on variants of the CKM gene have indicated the presence of multiple polymorphisms, from which two (RFLP) for the NcoI and TaqI endonucleases were examined with regard to their association with physical fitness. Both polymorphisms are located near the poly(A) tail at 470 bp and 1119 bp, respectively. The TaqI polymorphism is in codon 463 and does not cause changes to the amino acid sequence [56]. A more frequent allele here is the wild-type NcoI+ with a restriction site. Rivera et al. carried out an analysis of association of the restriction site polymorphism at 1449 of the 3'UTR region of the gene recognized by NcoI, resulting from A>G substitution, with the improvement of cardiorespiratory fitness estimated with VO_2max after a 20-week training. They noted that in homozygotic individuals there is a smaller change in the maximal oxygen uptake as regards the NcoI- allele in comparison with other genotypes, and thus a worse reaction to endurance training. They also estimated the contribution of the NcoI-/- (GG) genotype to the VO_2max variability post-exercise at 9% [55]. On the other hand, Zhou et al. in their study of volunteers undergoing an 18-week endurance training noted the greatest changes of respiratory parameters (inspiratory capacity, resting oxygen consumption) in reaction to training in individuals with the NcoI+/– genotype [57]. Although they did not estimate the maximal oxygen uptake, the changes of other spirometry parameters can confirm the contribution of the CKM polymorphism to the development of endurance fitness.

Mitochondrial NADH dehydrogenase subunit 5 gene (mtND5)

Location: H: 12337 – 14148

In their evolution, mitochondria have become cellular power centers. These organelles are the sites for the most crucial life processes and thus for abilities to undertake physical efforts.

Traditionally, existing individual differences in endurance capabilities are thought to be determined by the metabolic properties of muscles, in particular, by

their oxidative potential. The polymorphisms affecting well-coupled oxidative phosphorylation with large ATP production and small losses of distributed heat – allow muscles to use their capabilities to the maximum, but are inevitably linked with intensified degenerative diseases, early aging and obesity in individuals leading a sedentary lifestyle [58]. The first reports on the effects of the mtDNA sequence on the VO_2max level were published in 1991 by Dionne et al. who found polymorphisms in mtDNA after an analysis of RFLP with the use of 22 restriction enzymes. A significantly smaller change in the maximal oxygen uptake was observed post-exercise in individuals with the polymorfism of NADH dehydrogenase subunit 5 gene [59].

The NADH dehydrogenase NADH subunit 5 gene is one of seven mtDNA-coded subunits, which contains about 41 polypeptides of the respiratory complex I. The MtND5 is encoded by an H-strand of mitochondrial DNA rich in guanine, located at 12337-14148 bp. The gene comprises 1811 base pairs of uninterrupted coding sequence within the polycistronic H-strand transcript, and 521 base pairs of noncoding sequence at the 3' end, ended with a polyadenylation signal [60, 61, 62].

Complex I is the first link of the respiratory chain. It receives electrons from NADH and transfers them to ubiquinol (CoQ10) via a series of transmitters: flavin mononucleotide (FMN) and six iron-sulfur clusters (Fe-S). Complex I can be divided into three fragments: flavoprotein fragment, iron-protein fragment and hydrophobic fragment in which ND5 is located [63].

Studies following Dionne [59] analyzing the frequency of two polymorphisms in the mtND5 and one polymorphism within the D-loop in athletes and non-training controls did not confirm the existence of differences in the distribution of genotypes between the studied groups, did not observe any influence of mtDNA polymorphisms of the level of maximal oxygen uptake (VO_2max) nor reveal differences in their distribution [64]. On the other hand, Chen et al. [65] in their study of Chinese elite endurance athletes and non-training controls indicated differences in the frequency of D-loop polymorphisms. Ma et al. [66] noted differences in the maximal oxygen uptake for three polymorphisms studied by Chen et al. (2000). Such divergent results can be related to different ethnicities in the studied samples, i.e. representations of different mtDNA haplogroups [64].

Due to their role in respiratory processes, mtDNA polymorphisms can be significant for determining differences in the maximal oxygen uptake levels and responses to endurance training.

Insulin-like growth factor 1 gene

Location: 12q22-q24.1

IGF-1 is a protein from the family of growth hormones, with multiple physiological functions, acting in an endo, para- and autocrine fashion. Its molecular structure

Table 1. The coefficient of heritability (h^2) of most significant traits of physical fitness – on the basis of Rupert 2003 [6], Buenen & Thomas 2004 [5]

Parameter	Heritability (%)	Source
Submaximal aerobic capacity:		
Baseline Exercise-induced	48-74 25-37	Perusse et al. 2003 [93]
Maximal aerobic capacity	35-40	Lortie et al. 1982 [94]
VT: in sedentary individuals exercise-induced	58 (w) 54 (b) 22 (w) 51 (b)	Gaskill et al. 2001 [95]
VO_2max	59-87	Klissouras et al. 1997 [96]
VO_2max in sedentary individuals	< 50	Bouchard et al. 1998 [97]
LT	55-80	Klissouras et al. 1997 [96]
Anaerobic threshold	31-86 62-85	Klissouras et al. 1997 [96] Calvo et al. 2002 [98]
Static strength	27-58 (FS) 14-83 (TS)	Buenen and Thomas 2004 [5]
Dynamic strength	22-85 (TS)	Buenen and Thomas 2004 [5]
Muscular fitness	4-74 (FS)	

VT – ventilatory threshold, LT – lactate treshold, w – white, b – black, FS – family studies, TS – twin studies

resembles proinsulin. IGF-1 consists of 70 amino acids in a single chain. It is produced in the liver and is one of mediators of the activity of growth hormone (GH). Circulating IGF-1, produced as an endocrine hormone affected by GH, is responsible for correct growth and development. IGF-1 produced in target tissues is independent of GH and functions as a growth factor in these tissues [67, 68].

Epidemiological studies indicate a large variability of the IGF-1 level in the blood serum of healthy individuals and between ethnic groups, regardless of the GH level [69]. The IGF-1 phenotype is a complex hereditary trait affected by many genetic determinants, some of which may depend on growth hormone [70]. The contribution of the genetic component to the IGF-1 blood level was estimated at 38-63% by various research teams in studies of adult twins [71, 72, 73].

The level of IGF-1 circulating in the blood decreases with age and it is supposed it might be responsible for the decline in body mass and muscle strength. Studies on animals revealed an influence of IGF-1 on the activation of myosatellite cells. A more significant role is attributed to the isoforms produced in muscle tissue [74, 75].

The IGF1 gene consists of 5 exons, the first two of which form the untranslated region with sgnaling proteins. Exon 3 is the remaining sequence for the signaling protein and a part of domain B, while exon 4 is a part of domain B, C, A and D. The IGF1 has two promoters at the 5' ends of exon 1 and 2. The transcripts starting from exon 2 are GH dependant and are produced in the liver, whereas transcripts from exon 1 are produced outside the liver and are subject to alternative splicing. It results in three different peptides E with a mutual N-terminus sequence but different C-terminuses: IGF1Ea, IGF1Eb, IGF1Ec (MGF). The overexpression of the first of these isoforms in mouse muscles leads to hypertrophy and protects muscles against mass loss. Together with the third isoform they are expressed in muscles following mechanical stimulation, i.e. physical activity [67].

Some cross sectional studies showed the mean levels of circulating IGF-1 to be positively correlated with physical fitness or intensive physical activity [76, 77, 78]. Other authors found no correlations between the IGF1 level and physical activity and aerobic fitness either in young or elderly persons [79]. The results of studies on the effects of training on the IGF1 level vary. A five-week dynamic endurance training leads to a decrease in IGF-1 in young women [76] and men [79] despite the increase in the circumference of thigh muscle. A similar decreasing impact on circulating IGF-1 is also exerted by low calorie diet without exercise [80]. Other studies indicated no effects of a 6-month endurance training on the baseline IGF1 [81]. Also a 12-month strength training in elderly men and women, despite a significant improvement of either maximal oxygen uptake or muscle force, did not affect the level of IGF1 [82]. Some authors, however, observed, an increase in the IGF1 level after 2-8 weeks of dynamic training that was positively correlated with the increase in the maximal aerobic capacity [83, 84]. Therefore, training intensity and fat mass may influence the changes in the level of circulating IGF-1.

Studies on polymorphisms in the IGF-1 gene are very few and have been usually conducted in the context of lesions caused by lower concentration of the IGF-1. One of the studied polymorphisms described by Rosen et al. was the polymorphism of cytosine-adenine dinocleotide repeat in a microsatellite sequence at the distance of about 1 kbp before the site of the onset of transcription of the IGF1 gene. The IGF1 concentration in blood plasma differed between the genotypes. Among seven alleles (16-22 CA repeats), the most frequent one was the 19 CA allele at 192 bp [71]. So far the studies have focused on the relationships between endocrine – but not tissue – secretion with the polymorphism in the promoter. It was observed that individuals without the allele at 192 bp are significantly shorter, have a lower IGF-1 level in the plasma (18%) and are also more susceptible to ischemic heart disease and type II diabetes [85]. On the other hand, in a group of healthy men and women examined by Rosen et al. the 192/192 genotype featured the lowest IGF1 blood level [70]. Arends in a study of SGA babies noted the presence of ten alleles with the most frequent one being the allele at 189 bp, and the most frequently inherited was the one at 191 bp linked with the lowest IGF1 blood level [86].

The present study attempts to examine this polymorphism in the context of its potential influence on aerobic capacity with regard to the character of the activity of insulin-like growth factor 1 manifested by, inter alia, mobilization of energy substrates (e.g. enhanced transportation of acrbohydrates and amino acids to muscle cells), intensified gloconeogenesis in the liver and oxidation of fatty acids. It does than affects energy supply during exercise, and also perhaps indirectly, the VO_2max level.

Insulin-like growth factor-binding protein 3 (IGFBP3) gene

Location: 7p14-p12

Insulin-like growth factor-binding proteins, such as insulin-like growth factors and their receptors play a key role in the regulation of cell proliferation and apoptosis. IGFBP3 fulfills many functions with the most important ones being maintaining of IGF1 and IGF2 in the blood, modulating their bioactivity and direct inhibition of growth in extravascular tissue compartments, where the expression of IGFBP3 takes place in a controlled fashion [87]. In vivo, IGF1 and IGF2 always form a complex with one of 6 IGF binding proteins (IGFBP1-6). In the blood serum 80-85% of insulin-like growth factor-binding proteins remain in a complex of 150 kDa consisting of three components: one IGF molecule, IGFBP3 and acid-labile subunit (ALS) which is present only in the serum. ALS maintains the IGFBP3/IGF in the blood vessels and prolongs the half-life of IFG in blood circulation. Its synthesis is stimulated by growth hormone.

IGFBP3 has both an inhibitory and growth-inducing influence on cells, independent of IGF, and affects specific binding proteins or IGFBP3 surface receptors on the cytosol side or in nuclear compartments and the extracellular matrix [88].

The IGFBP3 gene consists of 5 exons with the distance of 8.9 kbp and its product is a 264-amono acid protein chain with the mass of 28.7 kDa [89]. In 2001 a few SNP type polymorphisms were identified in the promoter region of the IGFBP3 gene. The most significant one - A>C substitution in locus –202 – was strongly correlated with the level of circulating IGFBP3 in 478 men. An in vitro experiment confirmed a greater activity of the promoter with the presence of variant A in locus –202, compared with variant C [90, 91]. A cross-sectional study on a multiethnic population (African Americans, Hawaiians, Japanese Americans, Hispanics, Caucasians) was also conducted to determine the effects of the polymorphisms in the IGF1, IGFBP1 and IGFBP3 genes on the levels of their corresponding proteins in blood. Five SNP polymorphisms (rs3110697, rs2854747, rs2854746, rs2854744, rs2132570) in the IGFBP3 gene were strongly correlated with the protein blood level [91].

A study of the effects of the polymorphism in the IGFBP3 promoter (–202 A/C) (rs2854744) on the IGFBP3 blood level in response to recombinant growth hormone therapy in children with growth hormone deficiency, revealed a higher IGFBP3 level and faster increase of body height in children with the AA genotype than with AC and CC genotypes [92].

Conclusions

The list of genes that can potentially affect various components of physical fitness is long and grows dynamically. The available research results constitute a large database which must be systematized before implementing genetic profiling in sport. These results must also contain results of studies on Polish athletes representing various sports.

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