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CANDIDATE GENES IN THE FIELD OF EXERCISE GENOMICS

Vladimir Galić*
Department of Physiology
Medical faculty Novi Sad

Abstract

Skeletal muscle is extremely adaptable to various stresses which can be placed upon it. In spite of importance of skeletal muscles, little is known about genetic factors which demonstrate high influence to muscle size, function, strength and adaptation to various environmental factors. Because endurance performance is a multifactorial trait, the list of candidate genes which could account for human variation in related phenotypes is extensive. One of the first characterized and most frequently studied genetic variant is a polymorphism in the angiotensin converting enzyme I gene. The ACTN3 gene is the first structural skeletal muscle gene with a relation between its genotype and elite sprinter' performance. Nevertheless, current genetic testing cannot provide an extra advantage over existing testing methods in determining sports selection in young athletes. The main challenge still remains to identify other, complex polygenetic variants and their interactions with environmental factors which could provide benefit in the sports selection and existing talent identification.

Keywords: exercise genomics, genetic polymorphism, muscle tissue

Introduction

Muscle tissue constitutes approximately 30% of body mass, it is metabolically very active with high turnover of energy and is capable of efficient response to different environmental stimuli. Skeletal muscle is extremely adaptable to various stresses which can be placed upon it. These adaptations can be either positive, such as tissue growth, extreme athletic performance or reparation of an injury, or negative, such as decline in mass and function over the years of disuse or disease. Muscle strength is one of the most important determinants of one's functional ability and can influence some other tissues, like bone tissue by maintaining its

* Corresponding author. Department of Physiology, Medical faculty Novi Sad. Hajduk Veljkova 3, 21000 Novi Sad. E-mail: galic.ns@gmail.com

density throughout a lifetime. In spite of such importance of skeletal muscles, little is known about genetic factors which demonstrate high influence to muscle size, function, strength and adaptation to various environmental factors. Besides that, there is a diversity of information in literature related to heritability of muscle characteristics. According to research of Bouchard and his coworkers, whose main goal was to review all known genetic loci related to physical performance or health-related fitness, there are more than 200 autosomal chromosome genes, seven genes on the X chromosome and 18 mitochondrial genes that have been shown to influence fitness and performance phenotypes (Bouchard et al., 2008). The physical performance human phenotypes include cardio-respiratory endurance, muscle strength and exercise intolerance. On the other hand, the health-related fitness phenotypes could be grouped in several categories: exercise heart rate, blood pressure, body composition, insulin and glucose metabolism, blood lipid and haemostatic factors (Bouchard et al., 2008). Despite all up-to-date published information, majority of studies cannot establish a definitive relationship between genotype and phenotype. The main reason for this uncertainty is small effect of a particular gene on fitness or health-related traits and as a consequence, in order to achieve a significant ratio, it is necessary to have above 1000 cases with as many controls. On the other hand, if the subjects are examined in well-controlled laboratory conditions the sample size could be lower. However, obtained results should be interpreted cautiously until other similar studies confirm initial findings and assumptions.

Heritability of performance and health-related characteristics

One of the first strong evidence for a genetic influence on physical performance was obtained from studies which compared related individuals with unrelated subjects in order to discover heritability for several aerobic and cardiac-related characteristics (MacArthur, 2005). Generally, genetic factors are thought to determine 20-80% of changes in a range of traits related to elite athletic performance (MacArthur, 2007). Researchers estimate that performance related traits have heritability values of approximately 50% for maximal oxygen uptake (VO_2 max), 42-46% for stroke volume and cardiac output during sub maximal exercise, 40-50% for muscle fiber type proportions, and 67% for explosive muscle power (MacArthur, 2004). Considerable genetic effects have been discovered for measures of skeletal muscle strength and performance, such as muscle adaptation to endurance exercise (Hamel et al., 1986) or anaerobic capacity and explosive power (Calvo et al., 2002). Interestingly, heredity of relative proportions of skeletal muscle fiber types is considered to be between 40% and 50% (Simoneau & Bouchard, 1995). These and studies similar to them will initiate more research into the area of human performance genetics in order to discover favorable blend of genes, that are conducive to an athlete's specific discipline (e.g. sprinting or endurance running).

Candidate genes in elite athletes (ACE I/D and ACTN3 R577X polymorphisms)

Specific allelic variants of the ACE and ACTN3 genes are known to produce favorable traits with respect to athletic performance. These two genes were chosen, based on current literature references, because they have opposing effects in the human body; variants of the ACE gene are assumed to express bigger advantage in endurance activities, whereas, variants of the ACTN3 gene are considered to present an advantage to power athletes, who require short surge of intense strength and power.

ACE I/D polymorphism

Because endurance performance is a multifactorial trait, the list of candidate genes which could account for human variation in related phenotypes is extensive. One of the first characterized and most frequently studied genetic variant is a polymorphism in the angiotensin converting enzyme I gene (ACE) (MacArthur & North, 2005). Specific allelic variants of the ACE gene are known to produce favorable traits with respect to athletic performance. ACE is a

part of renin-angiotensin system which represents a hormonal cascade that regulates cardiovascular function (Baudin, 2002). This pathway starts with the production of renin, in kidneys, which transforms inactive angiotensinogen to angiotensin I. Second step is related to the effect of ACE on angiotensin I and the result is generation of biologically active angiotensin II, which is a strong vasoconstrictor and, in addition, it stimulates renal sodium reabsorption and aldosterone production (Pescatello et al., 2006). A functional polymorphism of gene that codes ACE is the insertion (I) and deletion (D) polymorphism which depends on the presence or absence of a 287 amino acid base pairs on autosomal chromosome 17 (Pescatello et al., 2006). This variation has given three ACE ID genotypes: II, ID and DD and their distributions in a white people population are approximately 25% for II, 50% for ID and 25% for DD genotype (Barley, Blackwood & Carter, 1994). The D allele of this polymorphism is related to higher serum and tissue ACE activity which can result in greater production of angiotensin II and aldosterone as well, increased sodium reabsorption and increased vascular smooth muscle growth (Williams et al., 2005; Williams et al., 2004; Myerson et al., 1999). This allele is more common in muscle strength and power athletes and it is associated with a superior muscle size and strength response to exercise training (Hagberg et al., 1998; Montgomery et al., 1999). The I allele is more present in endurance athletes, such as distance runners, rowers and mountaineers and is associated with a prolonged cardiovascular response to endurance training. Lower ACE activity in both serum and tissues is present in people with the I allele compared to the D allele (Danser et al., 1995; Rigat et al., 1990). Several other studies have shown a significant association between ACE genotype and elite athlete status. Montgomery et al. reported an increased frequency of the I allele in 25 British mountaineers compared to 1906 sedentary controls (Montgomery et al., 1998). On the other hand, higher frequency of the D allele was found in 35 elite short-distance swimmers and such findings suggested that these two alleles of ACE I/D polymorphism have dissimilar effects on performances of elite athletes (Woods et al., 2001). On the contrary, Rankinen and coworkers (2000) published results of 192 males elite endurance athletes compared with 189 sedentary controls and there was no difference in genotype frequencies between these two groups. In addition, one more study has shown the lack of physiological explanation for any association between the endurance-related cardiorespiratory phenotypes and the ACE polymorphisms. In summary, data from the HERITAGE Family Study do not support the concept that genetic variation at the ACE locus is a major contributor to the cardiorespiratory endurance-related phenotypes in the sedentary state in healthy Caucasian people (Rankinen et al., 2000).

Relation of genetic variants of ACE gene with athletic performance

Several mechanisms could explain how ACE expression might influence athletic performance. Generally, cardiorespiratory function, with maximal oxygen uptake which is a solid predictor of endurance performance, is related to the effect of ACE genotype. As previously mentioned, a person with the I allele has reduced ACE serum and tissue levels and its activity. This allele is thought to be a favorable mutation because lower ACE activity leads to less vasoconstriction and thus an increased delivery of oxygenated blood to the working muscles. Moreover, individuals with the I allele or the II (homozygote) genotype have greater advantage in endurance activities, such as running, cycling, and swimming, where demand for oxygen is crucial. A feasible explication for such findings comes from a study by Zhang and coworkers, who showed that the ACE I allele is related with higher mass of type I (slow twitch) muscle fibers in a person (Zhang et al., 2003). Slow twitch fibers acquire energy for their metabolism from aerobic sources and they are fatigue-resistant at relatively low velocities of contraction. On the other hand, the D allele is associated with the expression of type IIa and IIb (fast twitch) fibers which are more efficient in power and strength performance and less fatigue resistant. Nonetheless, there is some contradictory evidence regarding the effect of the ACE gene on endurance and power performance. In some studies, researchers have shown that in older adults

there was no association between ACE gene and physical characteristics as yet (Rankinen et al., 2000; Frederiksen et al., 2003).

In spite of all confusing results, the ACE gene continues to be the most extensively studied of any gene related to athletic performance, with huge amount of articles examining the effect of I/D polymorphism on fitness and performance features. The opposite findings amid many studies illustrate the complexity of genetic studies of complex characteristics. Literature results must be observed thoroughly before one can certainly conclude about the effect of ACE variations on performance phenotypes. For a research to be successful, it is of the utmost importance to have collaborative effort through data sharing among multicenter research facilities.

ACTN3 R577X polymorphism

The ACTN3 gene and is nonsense R577X polymorphism has generated noticeable interest in the past few years. This is the first structural skeletal muscle gene with a relation between its genotype and elite sprinter' performance (MacArthur & North, 2007; Yang et al., 2003). The alpha-actinins are a family of actin-binding proteins which play a main role in the maintenance and regulation of the cytoskeleton inside a muscle fiber (Blanchard et al., 1989). In mammals, there are four alpha-actinins. Skeletal muscle has highly expressed alpha-actinin-2 and alpha-actinin-3 as major structural parts of the contractile elements at the Z-line, which is an important structure within the sarcomere and its function is to provide structural support for the transmission of force when the muscle fibers are activated. (Virel & Backman, 2004; Dixson et al., 2003; Beggs, Byers & Knoll, 1992). The function of alpha-actinins is to connect with actin filaments, sustain the order of myofilaments and coordinate myofilament contraction by stabilizing the contractile apparatus (Yang et al., 2003). Alpha-actinin-3 is expressed only in fast glycolytic skeletal muscle fibers (Mills, Yang & Weinberger, 2001). Researchers believe that alpha-actinin-3 may be optimized in order to decrease the damage which could be induced by eccentric muscular contractions (Yang et. al, 2003). This is extremely important during forceful contractions, which are abundant in fast twitch muscle fibers. Astonishingly, an estimated one billion humans worldwide are completely deficient in alpha-actinin-3, because of homozygosity for a common nonsense polymorphism (R577X) in the ACTN3 gene (MacArthur et al., 2007; North et al., 1999). The absence of this protein is not related to a disease phenotype, since other proteins can counterbalance, although not completely, its lack in fast twitch skeletal muscle fibers. Moreover, the absence of this protein structure in skeletal muscles has been suggested to block the performance of fast twitch fibers, which are important for rapid, powerful contractions.

A usual genetic variation in the ACTN3 gene results in the replacement of an arginine (R) with a stop codon (X) at amino acid 577 (R577X). The R577 allele is the normal allele with functional alpha-actinin-3, whilst the 577X allele has an amino acid sequence change which produce nonfunctional protein alpha-actinin-3. This polymorphism results in the XX, RX and RR genotype. Representation among healthy white subjects is 18, 52 and 30%, respectively (Yang et al., 2003). It has been noticed that the recurrence of the ACTN3 577RR genotype was higher among elite sprinters when comparing with endurance runners or control participants (Niemi & Majamaa, 2005). This finding can suggest that the presence of 577RR allele might have a beneficial effect on skeletal muscle function during powerful contractions.

According to the literature suggestions, that alpha-actinin-3 performs important functions in fast twitch muscle fibers, it was expected to predict that there might be fine differences in skeletal muscle function among humans with different ACTN3 R577X genotype. Two alleles of ACTN3 gene may provide usefulness for different type of muscle performance. The R allele, which generates a functional alpha-actinin-3 protein, appears to favor strong muscle contraction, while on the other hand, the X allele might somehow provide advantage for slow and efficient muscle performance.

Future perspectives and research activities

During last two decades, an increasing level of competition in different sports has caused athletes to strive to sport results and success at no cost. Studies of the importance of genomic factors in the responses and adaptations of performance and health-related traits to exercise have increased during period of last 10 years (Bouchard et al., 2008). Unfortunately, along with recent developments in gene manipulation, there is a growing concern that researchers and elite athletes could be able to abuse this innovative technology in order to "engineer" individuals who could permanently express desirable genes for a peak athletic performance. Moreover, everyone is worried that "gene doping" would become a reality one day and, as a result, sports competitions could lose their true meaning and significance among athletes. However, successful identification of genes, which control physical performance characteristics, could benefit researchers to determine whether an athlete's genotype has been artificially changed in order to express advantageous genotypes with increased endurance capabilities or muscular strength.

Furthermore, the process of supreme talent identification could be possible by the discovery of genetic variants which has strong effect on athletic performance. A routine genetic analysis could be added to the existing set of physiological, biochemical and psychological tests which are the current basis for selecting skillful young athletes for further training. However, there is still no solid evidence that any of these variants have predictive value for prospectively identifying potential elite athletes. Only relying on large and prospective cohort studies, researchers could be able to evaluate the true values of genetic testing. Several genetic factors, for which positive associations have been reported in elite athlete cohorts (including the ACE I/D and the ACTN3 R577X polymorphisms), are not sufficient to tell if someone can become an elite athlete. However, genomic factors may influence in which sport an elite athlete can compete successfully. In the case of ACE and ACTN3, one allele combination appears to favor performance in sprint or power events (the ACE D and ACTN3 R allele), whereas the other benefit the ability to strive in endurance sports (the ACE I and ACTN3 X allele). This can lead to conclusion that some genetic factors might not be useful in predicting if a young, amateur athlete has elite potential. On the contrary, it may help to guide the choices of young athletes and their coaches in determining appropriate event and training which would be best suited for them.

Nevertheless, current genetic testing cannot provide an extra advantage over existing testing methods in determining sports selection in young athletes. The main challenge still remains to identify other, complex polygenetic variants and their interactions with environmental factors which could provide benefit in the sports selection and existing talent identification.

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