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Genetic influence on athletic performance

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Abstract

Purpose of review—The purpose of this review is to summarize the existing literature on the genetics of athletic performance, with particular consideration for the relevance to young athletes.

Recent findings—Two gene variants, *ACE I/D* and *ACTN3 R577X*, have been consistently associated with endurance (*ACE I/I*) and power-related (*ACTN3 R/R*) performance, though neither can be considered predictive. The role of genetic variation in injury risk and outcomes is more sparsely studied, but genetic testing for injury susceptibility could be beneficial in protecting young athletes from serious injury. Little information on the association of genetic variation with athletic performance in young athletes is available; however, genetic testing is becoming more popular as a means of talent identification. Despite this increase in the use of such testing, evidence is lacking for the usefulness of genetic testing over traditional talent selection techniques in predicting athletic ability, and careful consideration should be given to the ethical issues surrounding such testing in children.

Summary—A favorable genetic profile, when combined with an optimal training environment, is important for elite athletic performance; however, few genes are consistently associated with elite athletic performance, and none are linked strongly enough to warrant their use in predicting athletic success.

Keywords

Genomics; endurance; fitness; sport

Introduction

Both the scientific and sporting communities acknowledge that genetic factors undoubtedly contribute to athletic performance. As of 2009, more than 200 genetic variants had been associated with physical performance, with more than 20 variants being associated with elite athlete status (1). Although few studies have examined the link between genetic factors and athletic performance in children or adolescents, this area of research is highly relevant to a pediatric population; the idea of predicting future athletic success through genetic testing in children is becoming increasingly common. The present review will provide an overview of the genetics of athletic performance and will focus on the relevance to young athletes.

Components of Performance

A primary challenge when attempting to describe the influence of genetic factors on athletic performance is its multifactorial nature. Every sport has unique physical requirements and these requirements can be dramatically different between sports. Therefore, any study of the genetic influence on performance must consider the performance components most appropriate for the sport of interest.

Considering the number of body systems that must interact (musculoskeletal, cardiovascular, respiratory, nervous, etc.), athletic performance is one of the most complex human traits. Perhaps the first noticeable difference between athletes of different specialties is in body morphology (i.e., height and body composition), with specific body types naturally suited to specific sports. Beyond body morphology, endurance, strength, and power are primary factors underlying athletic performance.

Aerobic endurance is the ability to sustain an aerobic effort over time, such as distance running or cycling. At the most basic level, aerobic endurance requires the ability of the cardiovascular system to deliver oxygen to the working muscles and the ability of the muscles to utilize that oxygen. The most common quantification of endurance is the maximal rate of oxygen uptake (VO_{2max}). However, VO_{2max} does not perfectly correlate with endurance performance (e.g. marathon running), as other factors such as economy and ventilatory threshold also influence performance.

Muscular strength is the ability of the muscle to generate force. Muscular strength is generally quantified by the one repetition maximum. Muscle power is the interaction between the force and velocity of a muscle contraction (e.g. an explosive movement such as vertical jump). Muscle strength and power are critical in athletic events such as sprinting, jumping, and weightlifting.

Additional components of athletic performance include cognitive factors and injury susceptibility. It is critical to remember that the environment (e.g., training, nutrition) also influences many of these traits. An individual's "trainability," or response to exercise training, is also partially dependent on genetic factors, as recently reviewed by Bouchard (2). The relative importance of environment versus genetic factors on athletic success likely varies widely between sports as well (i.e., gymnastics vs. 100m sprint). Elite athletic status, therefore, results from the interaction of an optimal combination of genetically driven physical and mental traits with the ideal environment for athletic success (3).

Heritability of sub-traits

The heritability of a trait is generally considered an estimation of the importance of genetic factors to that trait. For example, the heritability of athletic status (regardless of sport) is estimated to be 66% (4). Height, which is critical for success in some sports, is highly heritable, with about 80% of the variation due to genetic factors (5). Body type (having mesomorphic or ectomorphic somatotype) is also highly heritable (6). These somatotypes are classically associated with power or endurance athlete status, respectively (7).

Costa et al. (8) recently reviewed the existing family and twin studies related to specific endurance and muscular strength phenotypes. Aerobic endurance, as reflected by VO_{2max} has a heritability of about 50% (9). Heritability estimates for muscular strength, and power range from 30 to 83%, depending on the specific muscle and type of contraction (8).

Key Performance Genes

Though many specific genes and sequence variants (polymorphisms) within genes have been associated with performance, many of the findings to date have not been adequately replicated. Two notable exceptions are the angiotensin-1 converting enzyme insertion/deletion (*ACE I/D*) polymorphism, and the α -actinin-3 (*ACTN3*) R577X polymorphism, both of which have been examined in several populations using a variety of experimental approaches.

ACE I/D

Fifteen years ago, the *ACE I/D* polymorphism was the first genetic factor to be associated with human performance (10). The *ACE* gene codes for angiotensin-1 converting enzyme, part of the renin-angiotensin system responsible for controlling blood pressure by regulating body fluid levels. The *ACE I* allele represents a 287 bp insertion and is associated with lower serum (11) and tissue (12) *ACE* activity while the D (deleted) allele is associated with higher serum and tissue *ACE* activity (13). The *ACE I/I* genotype is consistently associated with endurance performance and higher exercise efficiency while the D/D genotype is associated with strength and power performance, though some conflicting reports do exist (13). Notably, there is no association between I/D genotype and elite athlete status in Kenyans (14), highlighting the potential confounding factors of ethnicity and/or geography. An extensive review of the existing literature on *ACE* genotype and athletic performance through 2011 is available elsewhere (13). Additionally, a systematic review and meta-analysis of 25 studies examining the association of *ACE* genotype with sport performance was recently performed by Ma et al. (15). Overall, the *ACE I/I* genotype was specifically associated with performance in endurance, but not power, athletes, supporting the general consistency in the literature for an association of *ACE I/D* genotype with endurance performance.

ACTN3 R577X

The *ACTN3* gene codes for the protein α -actinin-3, a structural sarcomeric protein found exclusively in the fast type II muscle fibers used during explosive activities. A polymorphism leads to a premature stop codon (X) rather than an arginine (R) at position 577. The R allele is generally considered to be advantageous in power-oriented events, as the RR genotype is overrepresented in elite power athletes (16) while the XX genotype is associated with lower sprinting ability and muscle strength (17). The *ACTN3* R577X variant was recently studied across three groups of elite European athletes (633 athletes and 808 controls). In line with previous literature, power athletes were approximately 50% less likely to have the XX genotype and endurance athletes were approximately 1.88 times more likely to have the XX genotype vs. the RR genotype. Interestingly, for endurance athletes, the odds ratio for having the XX genotype was about 3.7 times larger for world-class compared to

lower competition level athletes, suggesting the *ACTN3* genotype may be even more important at the highest levels of performance (18).

A recently published meta-analysis of 23 studies examining the association of *ACTN3* with sport performance (15) demonstrated increased probability of performance in power events in R carriers, supporting the general consistency in the literature of the association between the *ACTN3* genotype and power-oriented athletic performance. The association of the *ACTN3* R577X variation with performance is arguably the strongest such association to date. Genotype frequencies have not only been repeatedly linked to athlete status and performance phenotypes, but experimental animal models also support the detrimental effect of α -actinin-3 deficiency on muscle performance. It is important to note that the most consistent associations between the *ACTN3* genotype and performance have been observed in athletes; these associations have been recently reviewed by Eynon et al. (19). A 2011 meta-analysis also supported higher prevalence of the RR genotype in sprint and power athletes but found no association of *ACTN3* with physical capabilities in the general population (20), thus the importance of *ACTN3* on muscle function in the general population remains somewhat unclear.

Injury Risk

Resistance to and/or the ability to recover from injury is another critical factor for optimal performance. Two main injury types have been studied with regard to genetic risk: concussion and tendinopathies. These areas of research are particularly important to the skill development of the pediatric athlete, as injuries can dramatically decrease time spent in training. Additionally, some injuries can result in recurrent issues throughout life. For example, athletes who sustained concussions decades earlier exhibited more brain anomalies and greater cognitive decline with aging compared to athletes that had never been concussed (21). A better understanding of the genetic components to injury risk and recovery could improve our ability to protect at-risk young athletes from serious injury and to optimally treat the injuries that do occur.

Concussion

The gene most frequently studied with regard to concussion/mild traumatic brain injury has been *APOE*. *APOE* has three isoforms (ϵ 2, ϵ 3, and ϵ 4 alleles) and its ϵ 4 allele has been associated strongly with Alzheimer's disease over the past decade (22). Based on this association, several groups have begun to evaluate the association of the ϵ 4 allele with risk for concussion and outcomes from traumatic brain injury, though the research to date is unclear. For example, individuals with the ϵ 4 allele suffered worse outcomes from head injury (23) and boxers possessing an ϵ 4 allele had higher chronic brain injury scores (24), consistent with the idea of ϵ 4 as a risk allele. However, a prospective study of collegiate athletes did not find an increased risk of concussion in athletes carrying the ϵ 4 allele (25) and the *APOE*- ϵ 4 genotype was not associated with poorer outcomes following mild traumatic brain injury in children (26). A separate *APOE* variant (G-219T) has been retrospectively associated with concussion risk in athletes, with 3-fold higher risk in athletes with the TT genotype compared to the GG genotype (27). The same study also identified a

weak association between the τ^{Ser53Pro} polymorphism in *MAPT*, the tau-protein encoding gene, and concussion risk.

Tendinopathy

With regard to tendinopathies, collagen is the primary structural component of tendons and ligaments. Unsurprisingly, variants in two collagen-encoding genes (*COL1A1* and *COL5A1*), a gene involved in connective tissue wound repair (*MMP3*), and the gene encoding *TNC*, an extracellular matrix protein, have all been linked to increased risk for tendinopathy (28,29). The presence of multiple risk alleles appears to further increase injury risk (30). As with most areas of genetics and performance, these studies are among the first to provide evidence for association and require considerable replication and validation.

Relevance for Young Athletes

Few studies have examined the association between genetic variation and athletic performance phenotypes in child or adolescent athletes. This is unsurprising given the potential ethical considerations of genetic testing in children. The *ACE II* polymorphism was reported to be associated with significantly greater handgrip strength and vertical jump performance in female, but not male Greek adolescents (31), which contrasts the typical association of the D allele with better strength and power in adults. Recently, the *ACE D* allele has been associated with greater handgrip strength in adolescent girls (32) and standing long jump performance in middle-school age children (33).

The association of the *ACTN3* genotype with performance has also been studied in children. Boys with *ACTN3* RR genotype tended to swim faster (25m and 100m) (34) regardless of training status. The R allele was also associated with better 40m sprint performance in adolescent Greek boys (35). Late adolescent girls with the RR genotype performed better on sit up tests than girls with the RX genotype (32). However, the *ACTN3* genotype was not associated with several other power or endurance phenotypes in adolescents of either sex (35). Additional correlations between *PPARA*, *PPARD*, and *PPARGCIA* genotypes with standard fitness tests in children were also reported (32,33). Overall, many of these studies associating genetic variation with performance in children have been underpowered and have failed to correct for multiple comparisons, so it is premature to draw firm conclusions. Further, the drive behind the prediction of athletic performance with genetics is primarily aimed at the early identification of individuals who will become exceptional athletes as adults.

Genetic Testing

Talent selection, the identification of promising athletes at a young age allows for an earlier adoption of specialized/dedicated training. Historically, talent identification has been based on physical and psychological characteristics and sport-specific performance. Genetic testing may provide an additional way to predict adult performance traits prior to their full development in untrained children by profiling combinations of gene variants associated with a particular trait. As DNA sequence is constant throughout life, genetic testing can be performed as soon as a DNA sample is available (in infancy or even prior to birth).

Despite the lack of performance predictability offered by single genetic variants, several companies are marketing genetic tests claiming to do just that. Tests are available for frequently studied genes (e.g., *ACTN3* and *ACE*) as well as several genes with relatively little scientific evidence (36). In fact, a genetic test for *ACTN3* was developed in 2004, only one year after Yang et al. (16) first described its potential connection to sport performance. Now this test is being marketed directly to coaches and parents with no prescription required (37). Based on this single test, this company will interpret an individual's "genetic advantage" as "predisposed to endurance events," "predisposed to sprint/power events," or "equally suited for both endurance and sprint/power events." This is by no means the only available direct-to-consumer genetic test, but is a representative example of the existing commercial options.

Beyond the oft-insufficient rationale for testing these variants, most coaches, parents, and athletes lack the scientific background required to understand the limitations of these tests or the implications of the results. However, some professional sports teams are already using the results of these tests to partially direct training prescriptions (38,39).

It remains to be seen whether the complex contribution of genetic factors to athletic performance can be used to improve talent selection. It is important to remember that genetic association studies reveal factors that are associated with athletic performance traits at a population level and the relative importance of any given variant for an individual is undoubtedly more variable, thus genetic screening cannot be used to conclusively predict or rule out athletic success (40). There is neither currently nor is there likely to be a gene variant that is either required or sufficient for superior athletic performance.

The potential for genetic testing to predict injury susceptibility, such as *APOE* genotype with response to concussion, may provide a unique and important avenue to improve safety for athletes. Though consensus remains elusive, the existing evidence points to the idea that genetic factors will be identifiable as important for injury susceptibility and could potentially be used to the advantage of young athletes as they consider sport participation. But, the ethical challenges related to genetic testing in relation to sport performance, especially in children, are especially difficult, as reviewed recently by Wackerhage et al. (41), and need to be considered carefully.

Conclusion

Current evidence suggests that a favorable genetic profile, when combined with the appropriate training, is advantageous, if not critical for the achievement of elite athletic status. However, though a few genes have now been repeatedly associated with elite athletic performance, these associations are not strong enough to be predictive and the use of genetic testing of these variants in talent selection is premature.

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Key Points

- Athlete status as well as many cardiovascular endurance and muscular phenotypes are highly heritable, supporting a role for genetic factors in the achievement of athletic success.
- The *ACE I/I* genotype is consistently associated with endurance performance.
- The *ACTN3 R/R* genotype is consistently associated with power-oriented performance.
- Genetic variants may alter injury risk or and/or post-injury outcomes, though more research is needed in this area.
- No genetic variant has reached the level of predictability for athletic success.