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GENETICS AND SPORT PERFORMANCE: ARE WE READY FOR GENOTYPE-BASED TRAINING?

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ABSTRACT

Background: Sports genomics explores the genetic basis of athletic ability and trainability, gaining growing scientific and public interest. This has led to a surge in direct-to-consumer (DTC) genetic tests claiming to offer personalized training programs based on individual genotypes. However, a gap remains between these marketing claims and solid scientific validation.

Purpose of Research: This systematic review evaluates the strength of association between specific genetic polymorphisms and athletic performance, and examines the scientific support for genotype-based training.

Materials and Methods: Relevant literature was sourced from the PubMed database using keywords such as "genetics", "athletic performance", "genotype", and "personalized training".

Results: Several studies reported associations between genetic variants and performance traits—most notably, ACTN3 with power and ACE with endurance. However, the predictive value for individuals remains limited. There is also a lack of high-quality randomized controlled trials (RCTs) testing genotype-based training programs. Existing trials often yield conflicting or inconclusive results.

Conclusions: Current scientific evidence does not support the widespread adoption of genotype-based training. Although certain genes influence physical potential, athletic performance is a complex, polygenic trait shaped significantly by environmental and lifestyle factors. DTC genetic tests currently lack the robust validation required to guide individualized training protocols.

Introduction

The pursuit of elite athletic performance has historically centered on optimizing environmental factors, such as rigorous training protocols, tailored nutrition, and psychological conditioning (1). These elements are undeniably the cornerstones of athletic development, forming the basis of coaching and sports science. However, it has long been observed that individuals exhibit significant variability in their baseline abilities and their response to identical training stimuli, suggesting an underlying biological component to athletic potential (2). This has led to a paradigm shift over the past two decades, moving beyond purely environmental explanations to explore the genetic architecture of sport-related traits.

The field of sports genomics emerged from this inquiry, founded on the principle that traits critical to performance, such as maximal oxygen uptake (VO2 max), muscle strength, and power, are significantly heritable (3). With advancements in molecular biology, researchers have moved from estimating broad heritability to identifying specific genetic variants, or polymorphisms, that may contribute to these traits. Initial research focused heavily on a few genes, most notably *ACTN3*, often mentioned as the sprinter gene, and *ACE*, which has been associated with endurance capacity (4). The RR genotype of *ACTN3* is linked to the presence of the α-actinin-3 protein, beneficial for forceful muscle contractions, while the I allele of the *ACE* gene is associated with greater efficiency in endurance activities.

This line of scientific inquiry has been rapidly commercialized, leading to the proliferation of a global direct-to-consumer (DTC) genetic testing market. These companies often make compelling claims, offering to analyze an athlete's DNA to provide bespoke training and nutritional advice aimed at maximizing their genetic potential (5). However, a significant and concerning gap has emerged between the deterministic marketing of these products and the current state of scientific evidence, which often highlights the complexity and polygenic nature of athletic performance (6). This disparity creates confusion for athletes, coaches, and clinicians, and it underscores the need for a clear, evidence-based synthesis of the available data.

This systematic review, therefore, aims to bridge this gap by comprehensively examining the current scientific literature. Specifically, it will:

1. Evaluate the strength of the association between commonly studied genetic polymorphisms and objective measures of athletic performance or elite athlete status.

2. Critically assess the quality and outcomes of intervention studies that have tested the efficacy of genotype-guided training protocols.

3. Synthesize the findings to provide a clear conclusion on whether the scientific community is ready for the widespread application of genotype-based training.

The Evidence for Gene-Performance Associations

ACTN3 **and its Association with Sprint and Power Performance.**

The R577X polymorphism within the *ACTN3* gene stands as a premier example of a genetic variant with a demonstrable influence on muscle function and athletic performance (7). Often referred to as the gene determining the speed, its biological role is tied to the expression of the protein α-actinin-3. This protein is a critical structural component of the Z-disc in skeletal muscle sarcomere, found exclusively in the fast-twitch (Type II) fibers that are essential for generating explosive, high-velocity contractions (8). The common R allele allows for the production of functional α-actinin-3, while the X allele introduces a premature stop codon, leading to a complete absence of the protein in individuals with the XX genotype. This deficiency has profound mechanistic implications, altering the muscle's functional capacity by affecting its stress and calcium sensitivity, ultimately influencing the properties of fast-twitch fibers (8).

The performance consequences of this genetic variation are significant. Individuals with at least one copy of the functional R allele (i.e., the RR and RX genotypes) produce α-actinin-3, and studies consistently link these genotypes to superior performance in power and sprint activities (7). Research focusing specifically on the effect of heterozygosity has shown that individuals with the RX genotype generally exhibit muscle performance profiles that are more similar to the RR genotype than to the α-actinin-3 deficient XX genotype, suggesting that a single functional copy of the gene is largely sufficient for the power/sprint phenotype (9). Beyond raw performance, the *ACTN3* polymorphism also appears to impact the body's response to physical stress. Emerging evidence suggests a link between the R577X variant and susceptibility to muscle damage following exercise, indicating that an individual's genotype may influence their recovery and adaptation processes after strenuous strength or aerobic training sessions (10). Despite its clear biological function and association with performance, it is crucial to recognize *ACTN3* not as a deterministic gene, but as a significant genetic influence within a complex network of factors that shape an athlete's ultimate potential (7).

ACE **and its Association with Endurance**

Alongside *ACTN3*, the angiotensin-converting enzyme (*ACE*) gene's insertion/deletion polymorphism has been extensively investigated for its association with endurance performance. This genetic variation is significant because it is understood to modulate the metabolic response of skeletal muscle during prolonged physical activity, with the I allele generally being linked to lower ACE activity and greater physiological efficiency (11). Studies on elite endurance athletes have provided compelling evidence for this link. For instance, among participants of the grueling South African Ironman triathlon, the presence of the I allele was not only associated with a greater likelihood of completing the race but also with faster finishing times among the top performers (12). This trend has been observed in other endurance disciplines as well, with separate research showing a significantly higher frequency of the *ACE* I allele in elite endurance swimmers compared to non-athlete controls (13). More recent research continues to reinforce this association across different populations; a case-control study of Korean elite endurance athletes also identified a significant link between complex polymorphisms involving the *ACE* gene and elite status, underscoring its role as a key marker in the genetic profile of top-tier endurance athletes (14).

Other Candidate Genes and the Expanding Landscape

While *ACTN3* and *ACE* have dominated the sports genomics narrative, a narrow focus on them provides an incomplete picture of the genetic landscape influencing an athletic career. A broader investigation reveals that the genetic basis for sport-related traits extends to a wide array of physiological systems, including tissue integrity and metabolic function. For instance, variants within the *COL5A1* gene, which codes for a crucial component of type V collagen, are essential for the structural integrity and tensile strength of connective tissues. A comprehensive meta-analysis has confirmed that specific polymorphisms within *COL5A1* are significantly associated with an increased risk of tendon and ligament injuries among Caucasian populations, making this gene a key area of study for understanding and potentially mitigating injury risk in athletes (15).

Beyond injury predisposition, genes crucial for metabolic efficiency are also paramount. The *PPARGC1A* gene and its Gly428Ser polymorphism have been identified as significant contributors to athletic potential. A meta-analysis synthesizing data on this variant revealed a strong association with sports performance and overall athletic ability, likely due to its role in regulating mitochondrial biogenesis which is a process fundamental for cellular energy production and a cornerstone of aerobic adaptation and endurance capacity (16). Furthermore, the genetic influence on injury can arise from less obvious biological pathways, such as vascular health. The *VEGFA* gene, which promotes the formation of new blood vessels, has been linked to injury susceptibility. A cross-sectional study demonstrated that certain promoter polymorphisms in *VEGFA* are associated with an elevated risk of anterior cruciate ligament ruptures in athletes, suggesting that variations in vascular support and tissue repair mechanisms also play a critical genetic role (17). The collective evidence from these diverse candidate genes powerfully illustrates that the genetic architecture of an athlete is not a simple blueprint but rather a complex mosaic of variants influencing musculoskeletal resilience, metabolic efficiency, and vascular health.

The Shift to a Polygenic View and the Limits of Single-Gene Analysis

The candidate gene approach, while historically important, is fundamentally insufficient for explaining the complex nature of athletic success. Modern research has firmly established that elite athletic status is a classic polygenic trait, meaning it is influenced by the aggregate effect of numerous genetic variants rather than a single gene. This concept is clearly demonstrated in studies of elite strength athletes, where performance is not determined by one "power gene" but by a favorable polygenic profile. By calculating a total genetic score based on multiple relevant DNA polymorphisms, researchers have shown that a higher accumulation of advantageous variants is characteristic of elite strength athletes, confirming that it is the combined, cumulative impact of many genes that contributes to top-tier athletic performance (18).

This shift towards a polygenic model is propelled by the use of powerful, unbiased methodologies like Genome-Wide Association Studies (GWAS). These studies analyze the entire genome to uncover novel genetic associations without prior hypotheses. For example, a metabolic GWAS conducted on elite athletes moved beyond simple performance metrics to investigate the genetic influence on underlying biological pathways. This research successfully identified novel genetic variants that affect the levels of specific metabolites, such as those involved in lipid and amino acid metabolism, which are in turn associated with athletic performance (19). This discovery highlights the intricate reality of sports genomics: genes often exert their influence indirectly by modulating complex metabolic networks. The evidence from both polygenic profiling and metabolic GWAS provides a clear conclusion that the athletic ability is a deeply complex, polygenic trait whose genetic architecture cannot be captured by analyzing only a handful of variants. This modern scientific understanding stands in direct opposition to the simplistic models used by many direct-to-consumer tests.

Critically Assessing the Evidence for Genotype-Based Training

While the association between certain genes and athletic phenotypes is well-documented, the crucial question remains whether this knowledge can be practically applied to create superior, genotype-guided training programs. When systematically reviewed, the scientific literature reveals a significant and critical gap between the concept of personalized training and the available intervention-based evidence (20). The field is characterized by a profound scarcity of high-quality, randomized controlled trials designed to prospectively test whether matching a training protocol to an individual's genotype yields better results than a standard or mismatched protocol. This lack of robust interventional data is the primary reason why current recommendations from expert bodies advise against the use of direct-to-consumer genetic tests for talent identification or training prescription (21). Most existing research does not test genotype-guided interventions but rather observes how different genotypes respond to the same standardized training. For example, one intervention study demonstrated that the response of vascular reactivity to a standardized exercise program was modulated by a polymorphism in the bradykinin B_2 receptor gene, showing that genetics can indeed influence physiological adaptations to training (23). However, such studies, while valuable, only establish a gene-training interaction, they do not provide evidence on how to modify the training protocol for a specific genotype to achieve an enhanced outcome.

The future of this field is likely to move away from simplistic single-gene models and toward more complex, multi-faceted approaches. Acknowledging the polygenic nature of training adaptation, recent research has focused on developing sophisticated models that integrate multiple genetic and phenotypic factors to predict training response. One such study created a combined genotype-phenotype model that used a panel of DNA variants alongside baseline physical characteristics to predict an individual's improvement in leg press

performance following a resistance training program (20). While this represents a significant step forward in understanding the complex interplay of factors determining trainability, it remains a predictive tool, not a prescriptive one. It helps forecast who might respond well but does not yet validate a specific training program for a specific genetic profile. Therefore, based on the current body of evidence, the conclusion is clear that the science to support the widespread implementation of genotype-based training does not yet exist. The foundation of gene-training interactions is being built, but the necessary interventional trials to validate specific genotype-guided recommendations are conspicuously absent (21, 22).

Conclusions

This systematic review confirms that while certain genetic variants, most notably in the *ACTN3* and *ACE* genes, are statistically associated with power and endurance phenotypes at a population level, their predictive power for an individual athlete is minimal. The evidence clearly demonstrates that elite athletic ability is not determined by a handful of specific genes, but is instead a deeply complex, polygenic trait. Performance arises from the small, cumulative effects of hundreds, if not thousands, of genetic variants interacting with each other and with a host of non-genetic factors.

Therefore, to answer the central question posed by this review: are we ready for genotype-based training? The answer, based on the current body of scientific evidence, is a definitive no. The evidence base to support its practical application in the field is profoundly insufficient. A glaring scarcity of high-quality, randomized controlled trials demonstrating any tangible benefit of matching training to genotype means that recommendations offered by direct-to-consumer genetic tests are speculative at best, and risk oversimplifying the intricate interplay between an individual's unique biology, their training history, nutrition, and psychological fortitude.

The future of sports genomics holds promise, but it requires a significant shift in research priorities. Future studies must move beyond simple gene-association analyses and focus on conducting large-scale, well-designed intervention trials that rigorously test the efficacy of genotype-guided protocols. Until such evidence exists, athletes, coaches, and practitioners should continue to rely on the established, evidence-based principles of athletic development: consistent effort, proper recovery, sound nutrition, and programming individualized based on an athlete's observed performance and feedback, rather than on recommendations derived from the premature and commercially-driven application of genomics.

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