Title:

Summary Findings on Genetics and Sports

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Abstract

Exercise training results in a plethora of morphological, metabolic and functional adaptations in skeletal muscle. Despite the clear benefits of exercise training to the function of many physiological systems, there is significant individual variability in responses to exercise training. There are many factors that influence sports performance and genetics is one of them. Without the appropriate genetic make-up, the chance of success as an elite athlete is reduced. With the advance in technology, several different genetic variants (i.e., polymorphisms) have been linked with sports performance in the past few years. It has become clear that sports performance is a complex trait, or in other words is influenced by many genes. However each of those genes have a small contribution to the phenotype This chapter summarizes the knowledge to date in the field of genetics and sports performance and highlights future directions for the field.

Key words: genes, sports performance, GWAS, candidate genes

1. Introduction

In the past decades the genetic basis for athletic performance and response to exercise training (trainability) has become a topic of great interest. Twin and familial studies have shown that part of the inter-individual variability reported in sports science studies can be explained by the genetic makeup of individuals (16). Although humans' DNA sequences are similar at 99.9%, genetic mutations are found across the genome at a rate of ~ 1 change per 1000 base pairs. Some of these mutations consist in the replacement of a single nucleotide by another and are referred as single nucleotide polymorphisms (SNPs). Those SNPs can be rare

(occur at a frequency < 1%) or common (occur at a frequency > 1%) within a given population. Each human carries 3-4 million common variants and 200,000-500,000 rare variants, and some of these variants are involved in athletic performance and trainability. To discover those variants, initially candidate gene approaches and later on Genome-wide association studies (GWAS) were conducted (Figure 1). To date, more than 200 genetic variants have been associated with athletic performance or trainability in at least one study (1, 10, 14, 22, 52, 53, 65). These findings suggest that athletic performance and trainability are not determined by a single gene but by a plethora of genes and are therefore considered complex traits. In this chapter, we will summarize the findings on genetics and sports and we will discuss some of the current research efforts that are undergoing to further characterize 'exercise genes'.

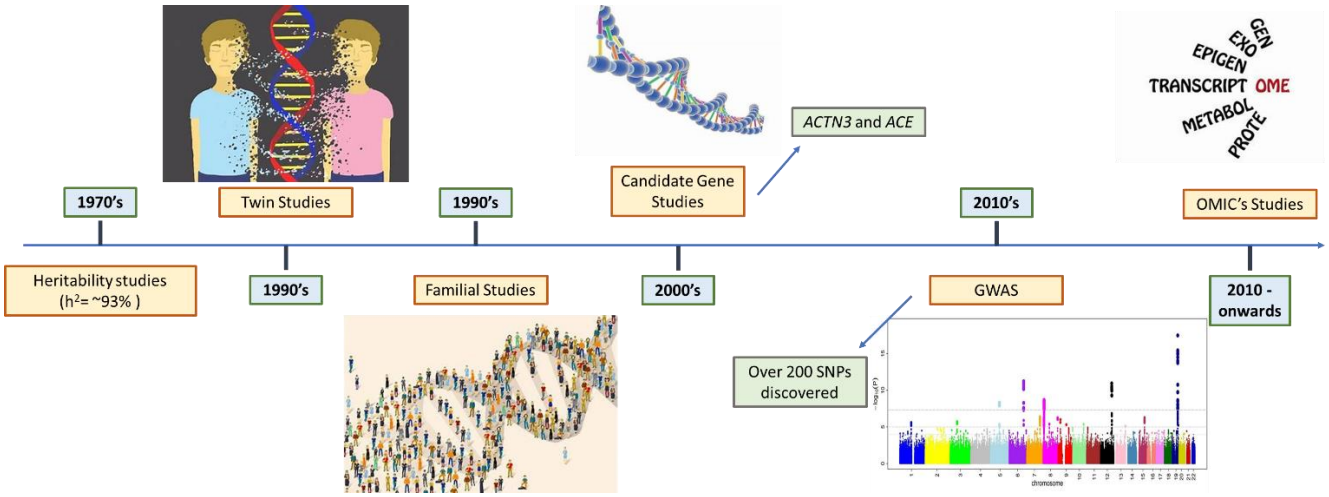

Figure 1: Timeline of genetic studies in sports science

2. Exercise Performance and Heritability

It is common for more than one family member to be an athlete. There is a long list of successful sibling athletes (i.e. Williams sisters in tennis), and parent and child athletes (i.e. John Kelly and John Kelly Jr. in rowing). Examples like these highlight not only the significance of family support in producing a successful athlete, but also the potential role of genetic predisposition to exceptional athletic performance. In science, the genetic predisposition for a given trait is measured by a quantity called 'heritability'. Heritability is defined as the proportion of variance in a trait that is explained by heritable factors, for a given population at a given moment in time (7). Heritability in exercise performance was first introduced by twin and family studies in the 1970s-1990s. A pioneering study on 25 pairs of twins found that about 93% of the variation in VO_{2max} is explained by genetic factors (26). However, this study assumed similar environmental interaction between twin pairs and the absence of gene-environment correlation, which is not necessarily true and may overestimate heritability (19). High heritability estimates were also found for skeletal muscle fibre composition (h^2 = 96.5%) (26), maximal power (h^2 = 97%) and maximal isometric force (h^2 = 83%) (23). Subsequently to these pioneering studies, other twin and family studies also reported high heritability estimates for VO_{2max} (77% (17), 69-87% (31) and 71% (38)). A meta-analysis of eight twin studies found a weighted VO_{2max} heritability estimate of 72% (50). In addition to those, several other studies in different areas have attempted to estimate heritability in different cohorts and phenotypic traits (28, 29, 34, 35, 57, 58). Although heritability studies did not require genetic testing to create estimations, they played an important role on the fully comprehension of the heritability concept, often misunderstood (19). For example, when said that VO_{2max} h^2=93%, is almost always misinterpreted to mean that 93% of this phenotype is genetically determined and only 7% would be affected to environment stimuli. Heritability only has a meaning at the population level and is irrelevant at an individual level. In addition,

heritability varies depending on the studied population (e.g. young, old, healthy, diseased) and time as the environment can change with time. As previously written:

"[Heritability] describes the extent to which heredity affects the variation of a given attribute in a given population exposed to common environmental influences at a given time. A high heritable attribute does not mean that a phenotype is predetermined and the environment has no effect. It only indicates that the observed individual differences in the given attribute are due to genetic differences and are highly predictable" (19)

Following heritability estimates for aerobic and muscular fitness at a single timepoint, the heritability of *responses* to exercise training (trainability) was also calculated in the large-scale HEalth, RIsk factors, exercise Training And GEnetics (HERITAGE) Family study in the 1990s. After adjusting for confounders such as age, sex, baseline VO_{2max}, body mass and composition, the HERITAGE study reported that ~47-50% of the variance in VO_{2max} improvements following exercise training was due to genetic factors (3). The variance in individual training response between families was 2.5 times higher than within families. As a result of family and twin studies reporting consistently high heritability estimates, a hunt for the genes responsible for both athletic performance and trainability began.

3. Linkage analyses and the candidate gene approach

The pivotal HERITAGE study (4) and two other twin and family studies (36, 56) performed linkage analysis to detect the chromosomal location of genes associated with athletic status, physical activity level and trainability. They identified markers on several chromosomes, which

were associated with their traits of interest, but few of them were in common. The completion of the human genome project in 2001 (59) allowed for the development of genetic studies based on genes with a specific function. This method called the 'candidate gene approach' was a hypothesis-driven approach whereby the frequency of mutations in genes with a potentially relevant function for exercise was compared between athletes and controls, or associated with aerobic and muscular fitness measures (20). A recent review reported that ~200 SNPs have been associated with performance traits in at least one study, and around 25 SNPs with athletic status (16, 61, 65). These SNPs were found to have an extremely small effect size, which means that their individual contribution to the variability in performance traits and athletic status was tiny, and therefore hard to detect. In addition, only two SNPs showed consistent replication across different studies and populations.

One of them is located in the *ACTN3* gene. The alpha-actinin-3 protein, encodes the *ACTN3* gene, and is almost exclusively expressed in the sarcomeres of fast glycolytic type II fibres that generate powerful, explosive contractions (97). The unique expression pattern and sequence conservation of alpha-actinin-3 over 300 million years in humans, suggest that it has an important function in fast, glycolitic (type IIX) muscle fibres (33). A common SNP in this gene causes the substitution of an R (arginine) for a stop codon (X) at the 577 amino acid, resulting in complete deficiency of the alpha-actinin-3 protein (*ACTN3* XX variant) (97). The *ACTN3* R577X variant has been extensively studied in sports performance. The earliest findings reported that fewer Australian sprint elite athletes than healthy controls carried the XX genotype (66). Many replication studies in different cohorts of varying ethnicities found a systematically lower frequency of the XX genotype in strength and power athletes compared with controls and endurance athletes (13, 15, 21, 40, 42, 49, 67). Overall, nearly all studies on *ACTN3* and sports performance reported the same findings: the RR genotype is associated with

strength and muscle power, while the XX genotype tend to be associated with endurance performance, but this association is less pronounced (12, 15, 18, 24, 25, 30, 41, 43, 54, 55).

Another gene that has showed consistent replication in exercise science is the *ACE* gene. The Angiotensin-Converting Enzyme (ACE) converts the angiotensin I hormone to another form named angiotensin II (46). Angiotensin II helps regulate blood pressure and may also influence skeletal muscle function, although this role is not completely understood (9). A polymorphism in the *ACE* gene that consists in an insertion (I) or a deletion (D) of a piece of DNA (with a length of 287 base-pairs of nucleotides), alters the levels of the ACE enzyme in blood. Individuals can have either zero (DD genotype), one (ID genotype) or two (II genotype) insertions at the *ACE* I/D polymorphism. Of the three genotypes, DD is associated with the highest levels of angiotensin-converting enzyme in blood (64). DD carriers have a higher proportion of fast-twitch muscle fibres and greater speed (44, 52). However, findings on *ACE* are more conflicting, and less convincing than those on *ACTN3*. The initial findings that II carriers are better at endurance while DD carriers are better at power/strength (37, 46) was not replicated in some studies (8, 51), perhaps due to different cohorts or small sample sizes.

In addition to *ACTN3* and *ACE*, many other genes with diverse functions have been associated with exercise-related traits without showing consistent replication. Some are involved in skeletal muscle function, while others play roles in the production of cellular energy or communication between nerve cells. From the candidate-gene approach, the large-scale screening of millions of SNPs and their association with exercise-related traits in Genome-Wide Association Studies has greatly advanced the field.

4. GWAS

With advances in microarray-based high-throughput technologies, screening hundreds of thousands, and even millions of SNPs simultaneously has been made possible. The GWAS approach is an unbiased hypothesis-free design that has led to substantial progress in the field of diseased-genetics (32) and more recently in the field of sports and performance. In fact, this method has identified a plethora of genes, whose variants can be related to physical performance, achievement and sports results. Unfortunately, this method also revealed that genes influencing exercise performance and their relationships are more complex than previously though. The HERITAGE study was the first GWAS to identify several SNPs related to VO2max trainability in an unbiased, hypothesis-free manner (5). However, replications of those SNPs were unsuccessful (19). This lack of replication may be explained by a lack of statistical power in replication studies, as SNPs that influence exercise-related traits have typically very small effect sizes. In other words, those SNPs have such a small effect on the phenotype of interest that it is challenging to detect their effect, thus leading to negative results. A recent GWAS was conducted on a total of 1,520 elite athletes and 2,760 controls spanning eight different cohorts of athletes from Australia, Ethiopia, Japan, Kenya, Poland, Russia and Spain (47). Forty-five promising SNPs were found during the discovery phase but failed pass the replication phase. The study was likely underpowered to identify alleles with small effect sizes, perhaps due to the fact that the technology used was an earlier generation microarray covering only 195,000 gene markers (48). Another GWAS of 492 strength/power and 227 endurance athletes found that the rare T allele of rs939787 in the dystrophin gene (*DMD*) was overrepresented among strength/power athletes compared with endurance athletes (25% vs. 8.8%) (39). Even more recently, 16 novel genetic loci were associated with hand grip strength (a simple measure of functional strength) in a large-scale GWAS of 195,180 individuals.

However, those interesting findings await replication (63). Although candidate-gene and GWAS studies have increased our understanding of the genetic contribution to athletic performance, especially with regards to effect sizes, those initial findings need to be replicated. In addition, the molecular mechanisms by which those SNPs act need to be uncovered to have a clear picture of how the genetic makeup shapes the athletic potential and exercise adaptation.

5. Conclusion and recommendations for future research

To date neither candidate genes nor genome-wide associations have validated any of the target genes discovered by the pioneering HERITAGE study (5), and the largest GWAS combining more than 1,500 athletes found no evidence of a common DNA variant profile specific to World-class endurance athletes (47). The limited progress in genetics and sports performance achieved today is due to small and mostly heterogeneous cohorts, resulting in doubtful and conflicting findings (19, 62). There is a necessity for larger collective work, with well-defined phenotypes of interest, tightly controlled interventions, and subsequent replications to produce robust results. Sports scientists have answered this call by creating the "Athlome Project Consortium" (www.athlomeconsortium.org). This multi-centred international collaborative action intends to create a large databank, with enough expertise and state-of-art "omics" technologies from around the world. This project aims to expand knowledge on genetic variants involved in sports performance, trainability and injury predisposition (more about this project can be found in review (62)). Bouchard also argued that there is a need for a paradigm shift in the field (2). Research should be conducted using an unbiased approach, using the full power of genomics, epigenomics and transcriptomics together with large-scale cohorts and validation studies. Fortunately, the Athlome Consortium meets those suggested criteria, and the project

published a GWAS on 8 different cohorts of athletes (48) and announced the sequencing of 1,000 of the World's greatest athletes as part of the 1,000 Athlomes project (45). The field has progressed from heritability models to comprehensive sequencing and genetic screening, but to fully comprehend the mechanism of action of exercise-related variants, it is essential to consider interactions between those genetic variants and the environment. Perhaps the epigenetic response to exercise training will help scientists understand changes in gene function that cannot be explained by changes in DNA sequence (60). Epigenetics is an attractive hypothesis to explain the paradoxical findings of identical twins that differ in heritable traits (6, 27). The field of sports and epigenetics is still in its infancy, and the mechanisms that modulate gene expression are not well understood (11). Great challenges lay ahead in the field of sports and genomics/epigenomics, but it is an exciting future to dissect the role of epigenetic and genetic modifications on sports performance and trainability.

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