GENES AND ELITE ATHLETIC STATUS

MOVING FORWARD

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Every 4 years we enjoy the extraordinary abilities of Olympic athletes, wondering how many gold medals Michael Phelps will win or how fast Usain Bolt will run the 100 metres. Talking about running, as the most natural sport, with no additional equipment, have you ever wondered why there are no Europeans, Asians or even east Africans ranked among the world's best 100 metre sprinters? Although the most frequent explanation for this phenomenon has been environment and nurture, today science says otherwise.

Elite sport performance represents a complex phenotype, composed of various intricately intertwined biological traits, some of which are manifested at the biochemical or physiological level (state of the musculoskeletal, cardiovascular, central nervous, pulmonary or even immunological systems), while others are expressed as psychological traits (dedication, motivation, perseverance, diligence etc). Each of these traits is shaped by both environmental and genetic factors, as well as by the interaction of these factors. The relative magnitude of the effect of each of these factors on the expression of specific traits related to sport performance became a subject of debate soon after the birth of genetics as a field of scientific study, reiterated in the 'born vs bred' or 'nature vs nurture' discussion and summarised in the question: 'are champions born or made'?

Also, it is well known that to date 'The human gene map for performance and health-related fitness phenotypes' is made up of more than 200 single nucleotide polymorphisms (SNPs) associated with some performance and fitness-related traits[1,2].

Additionally, recent years have witnessed the rise of an emerging market of direct-to-consumer (DTC) tests that claim to be able to identify children's athletic talents, although, based on the general consensus, current exercise genetics researchers claim that genetics have an unspecified role in talent identification or in the individualised prescription of training to maximise performance[3].

Even today, amid the recognition of the genetic component of elite athletic status and scientific spotlight which therefore shines on the topic, the complexity of genetic pathways underlying sport performance makes the endeavour to identify 'sport genes' practically impossible and therefore futile.

However, a considerable number of studies have emphasised associations between specific genetic polymorphisms and elite athletic performance[1,2,4,5].

GENE VARIANTS IN ENDURANCE ATHLETES

ACE I allele

ACE is an important component of the renin-angiotensin-aldosterone system. Its main role is to generate angiotensin II, a vasoconstrictor hormone, and also to degrade the vasodilator kinins[6]. The angiotensin I-converting enzyme (ACE) gene

Table 1

Gene	*Location*	*Polymorphism*	*Endurance-related marker*
ACE	*17q23.3*	*Alu I/D (rs4646994)*	*insertion*
ACTN3	*11q13.1*	*R577X (rs1815739 C/T)*	*577X*
ADRA2A	*10q24–q26*	*6.7/6.3 kb*	*6.7kb*
ADRB2	*5q31–q32*	*Gly16Arg (rs1042713 G/A)*	*16 Arg*
CKM	*19q13.32*	*rs8111989 A/G (NcoI)*	*rs8111989 A*
BDKRB2	*14q32.1–q32.2*	*+9/–9 (exon 1)*	*-9*
HIF1A	*14q23.2*	*Pro582Ser (rs11549465 C/T)*	*Pro 582*

Table 1: Genetic markers for endurance athlete status. ACE=angiotensin-converting enzyme, ACTN3=alpha actinin3, ADRA2A=alpha 2a adrenoreceptor, ADRB2=beta 2 adrenoreceptor, CKM=creatine kinase, BDKRB2=bradykinin receptor B2, HIF1A=hypoxia inducible factor 1 alpha subunit.

is the most popular and frequently studied gene and therefore of particular interest as a candidate gene for elite performance phenotypes[7].

Additionally, the ACE gene I/D polymorphism, especially the presence (insertion, I allele) of a 287 bp fragment is associated with lower ACE activity both in tissues and in circulation. This is even more important when considering the fact, confirmed by many studies, that ACE insertion polymorphism is associated with better endurance performance in elite athletes[8,9].

An excess of the 'I' allele has been identified in studies on different types of elite endurance athletes. Myerson et al identified an excess of the I allele in 25 elite mountaineers and 34 elite British distance runners (>5000 m)[10]. Other studies confirmed these results, suggesting similar I allele distribution in elite Australian, Croatian and Russian rowers[11-13]. Further, similar studies have confirmed the overrepresentation of ACE I allele among the100 fastest Ironman triathletes, elite Spanish runners and Italian Olympic endurance athletes[14-16].

However, it should be noted that some studies show no association between the ACE I/D polymorphism and elite athletic status. In fact, Tobina and colleagues showed that average running speed was significantly higher in Japanese elite endurance runners with the combined DD/ID genotypes than in runners with the II genotype[17].

ADRA2A (Alpha 2a adrenoreceptor) and ADRB2 (Beta 2 adrenoreceptor)

The adrenergic receptors are a prototypic family of guanine nucleotide-binding regulatory protein-coupled receptors. Their main role is to mediate the physiological effects of the hormone adrenaline and the neurotransmitter noradrenaline. Additionally, it is well known that adrenergic receptors can influence the regulation of adipose tissue lipolysis – one of the most important steps in meeting energy demands during endurance training[18].

Blood pressure and heart rate, as the main cardiovascular responses to systemic sympathetic activity, are predominantly regulated by the α-2A-adrenergic receptor (ADRA2A).

The restriction enzyme Dra I identifies a restriction fragment length polymorphism in the 3'-untranslated region (3'-UTR) (6.7/6.3 kb polymorphism) of the ADRA2A gene located on chromosome 10 (10q24–q26)[2,18].

In a comparison of elite endurance athletes and sedentary controls, Wolfarth and colleagues observed significantly higher frequency of the 6.7-kb allele in athletes, suggesting that this genetic variation in the ADRA2A gene may play a role in sustaining the endurance training necessary for enhanced maximal aerobic power[4].

Additionally, some studies show that during prolonged physical activity, hormone sensitive lipases bind to the beta 2 adrenoreceptor (ADRB2, stimulatory) and alpha 2 adrenoreceptor (ADR2A, inhibitory), inducing lipolysis. These two adrenoreceptor genes (ADRB2 and ADR2A) are located on chromosomes 10 (q24-q26) and 5 (q31-q32), respectively[5,18].

The beta 2 adrenergic receptor is a member of the G protein-coupled receptor superfamily. It is expressed in many cell types and plays an important role in the regulation of the cardiac, pulmonary, vascular and central nervous systems. Numerous studies have associated the Gly16Arg SNP (rs1042713 G/A) of the ADRB2 gene with several phenotypes. Wolfarth et al described the overrepresentation of the 16 Arg allele in elite endurance athletes compared to sedentary controls[4].

GENE VARIANTS IN STRENGTH/POWER ATHLETES

ACE D allele

Previous studies have shown that individual renin-angiotensin system activity depends on the I/D polymorphism of the ACE gene, with the D allele being significantly associated not only with superior sprint and other anaerobic

performance in elite athletes, but also with increased muscle volume and an increased percentage of fast-twitch muscle fibres. This may be controlled by increased degradation of growth-inhibitory bradykinin and increased ACE-mediated activation of the growth factor angiotensin II[2,7,8].

Studies have shown the D allele and/or DD genotype overrepresentation in British, Russian and European short-distance swimmers, sprinters and short- and middle-distance swimmers[19].

However, it should also be noted that some studies showed no association between ACE I/D polymorphism and elite athletic status. For example, Wang and colleagues compared east Asian short-distance swimmers with a control group and reported that the swimmers had a prevalence of I allele compared to controls. Additionally, there are studies that showed no association between the ACE I/D polymorphism and power athlete status[20].

> ***further research is required before direct-to-consumer genetic tests can be considered viable***

ACTN3 Arg 577 Allele

Another gene widely studied for its relation to elite performance is ACTN3, which encodes skeletal muscle protein α-actinin-3 – the family of actin-binding proteins that is expressed exclusively in type 2 muscle fibres. According to previous studies this gene is almost exclusively expressed in fast twitch muscle fibres responsible for rapid and strong muscle contractions, mainly in sprint and power activities[1,2]. A very common genetic variation in the ACTN3 gene leads to arginine (R) replacement with a stop codon (X) at amino acid 577 (R577 X, rs 1815739). Although it is well known that the ACTN3 variation, which leads to α-actinin-3 protein deficiency, does not lead to muscular functional impairment, there are several studies confirming a positive association between high-power muscle contractions and the presence of the R allele[21]. One of the most important studies in this field was conducted by Ma et al, who reported that the frequency of the ACTN3 XX genotype was reduced in elite power athletes compared to a sedentary control group. Additionally, they also showed that none of the Olympians or elite female power athletes included in the study had an XX genotype[8].

Later case-control studies confirmed these results. The ACTN3 XX genotype was reduced in elite Finnish sprint athletes, elite Greek track-and-field athletes and top-level professional soccer players, participating in the Spanish league[22-24].

Additionally, it is documented that the presence of an X allele may lead to better endurance performance. Some studies have shown that the proportion of the XX genotype and/or X allele was higher in endurance-oriented athletes compared with sedentary individuals. However, the majority of authors reported no association between the ACTN3 R577X polymorphism and endurance athlete status[1,8].

What is the current scientific evidence for genetic testing for talent identification for sport?

Nowadays, although a scientific understanding of the link between the polymorphisms described here and sport performance is still being sought, companies have been trying to take advantage of the association for years. Direct-to-consumer genetic tests are marketed to parents, young athletes and coaches as a powerful instrument for guiding decisions on the most suited sporting discipline for a child. However, it is clear that the current understanding of the link between genetics and athletic performance is not sufficient to advocate the use of such tests for talent identification. A recent consensus statement cited a lack of evidence on the efficacy of direct-to-consumer genetic testing, as well as raising concerns on the absence of related guidelines and legislation, clear information on which gene variants are tested, appropriate genetic counselling and quality control[3]. In the future we may have to pose the question: is pushing a child toward a sport he is likely to be good at much different than hiring a violin teacher for a musical child? But for now, further research is required before direct-to-consumer genetic tests can be considered viable.

Currently, it is a well-recognised fact that inter-individual variability of physical performance traits has a significant genetic basis. Therefore, the scientific question is not what the potential role of genetic components is, but rather, exactly which genes and DNA polymorphisms are involved and by which mechanisms and pathways do they exert their effect?

Therefore, one of the first priorities for future research should be to gain knowledge about the application of sport genetics and whether this could lead to the development of genetic performance tests with the ability to provide better opportunities, not only by determining genetic suitability for

specific team positions and roles, but also by gaining insights into athletes' development in various sports or physical activities.

Studies should target whole-genome sequencing, epigenetic, transcriptomic, proteomic and metabolomics profiling using meta-analyses, in order to extend the present knowledge and implement it in practice.

Last but not least, putting the available genetic information into the right context, as well as including the limitations of its usefulness, is absolutely necessary.

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