Genetic test for the personalization of sport training

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Abstract. Genetic variants may contribute to confer elite athlete status. However, this does not mean that a person with favourable genetic traits would become a champion because multiple genetic interactions and epigenetic contributions coupled with confounding environmental factors shape the overall phenotype. This opens up a new area in sports genetics with respect to commercial genetic testing. The analysis of genetic polymorphisms linked to sport performance would provide insights into the potential of becoming an elite endurance or power performer. This mini-review aims to highlight genetic interactions that are associated with performance phenotypes and their potentials to be used as markers for talent identification and train-ability. (www.actabiomedica.it)

Key words: sports phenotype, endurance, power, genetic variants, polymorphisms

Introduction

To be a sportsman is a highly demanding job that not only requires determination, dedication, nutrition, supportive environment and intensive training but the ‘intrinsic ability’ coined by genetic traits. The finding that sport performance has a genetic background became a promising area of research in sports genetics since late 1990s when the first discoveries highlighting hereditary involvement in achieving elite sports status were published (1,2,3). Since then, several studies have been conducted to elucidate the gene-gene and gene-environment interactions that contribute to sport-related phenotypes contributing to elite performance status (4-8). In fact, sports performance is a complex multifactorial phenomenon governed by several intrinsic factors such as genetic polymorphism, psychomotor skills, physical fitness that are greatly influenced by extrinsic factors such as diet, training and health status (9-11).

Sport performance is difficult to define precisely. In fact, it greatly depends on aim and objectives of the sports. For instance an endurance performer such as weightlifter has different parameters of assessing performance than a sprint or power performer such as a runner. This implicates that each sport discipline has unique physiological, psychological, biochemical and anthropometric demands that result in shaping an overall performance phenotype encoded by heritable genetic traits (12,13,14). For instance, endurance performance is largely dependent on maximal oxygen uptake (VO2 max), VO2 at lactate threshold and efficiency of movements (15). It is necessary the coordinated action of cardiovascular system and muscular metabolism involving transportation of oxygen to and utilization of oxygen by the muscles (16). Besides that
enhanced aerobic endurance involves elevated mitochondrial gene expression and corresponding enzyme activity during aerobic respiration (17).

On the other hand power performance is dependent upon muscle structure, strength and the ability to generate force without being injured (18). Maximal power is a function of force and velocity of muscle contraction which in turn depends on the cross-sectional area and volume density of myofibrils of muscle fibre (19). Muscle power is the driving force behind sprinting, jumping and weightlifting (20).

Performance-enhancing gene polymorphisms

During the last two decades, several studies have provided compelling evidences that both endurance and power performances are influenced by genetic factors that collectively are called performance-enhancing gene polymorphisms (PEPs) (21). Surprisingly, PEPs are common in general population and more than 200 PEPs have been reported so far (21,22). However, only 20 out of 200 were specifically found in athletes and only 10 could be replicated in association studies (22). Since then approaches such as twin studies, familial aggregation studies, genome wide linkage and association analyses have revealed structural variants in genes having great influence on sport performance indicators such as aerobic endurance, muscular strength and power.

To understand the link between performance and PEPs we will consider the classic example of two of the most well-documented and adequately replicated PEPs, ACE I/D and ACTN3 R577X that are consistently linked with endurance and power performance phenotypes (23).

Angiotensin-conversion enzyme (ACE)

The pioneering study that revolutionized sports genetics is the finding of a polymorphism in ACE gene encoding angiotensin-conversion enzyme (ACE) in 1998 (23). ACE is an important enzyme of renin-angiotensin system which regulates blood pressure by controlling body fluids (24). Besides this, ACE is involved in bradykinin degradation, respiratory drive, regulation of inflammatory reactions to lung injury, erythropoiesis, tissue oxygenation, and the regulation of skeletal muscle efficiency (25).

ACE may exist in two polymorphic forms, I or D, depending on an intronic indel of 287 bps (26). ACE I has an intronic insertion of 287 bps which results in decreased serum and tissue ACE activity (27,28). ACE I/I genotype has been consistently linked to improved endurance performance and high exercise efficiency (28,29). On the other hand, the deleted form of the variant (D allele) is associated with higher circulating and tissue ACE activity (29) and enhanced power and strength performance in sprinting (30). In addition to this significantly higher frequency of ACE I allele was reported in elite Australian rowers as compared to normal control (31) while the I/I genotype was more frequently observed than the D/D genotype in elite British mountaineers. Besides this, all the top performers had and ACE I/I homozygous genotype (32). Similar results have been reported by Woods & Montgomery (33) and Thomson et al (34). The role of the ACE gene in endurance performance has been recently extensively reviewed (35,36). These systematic reviews revealed that with few exception, I allele is typically associated with endurance performance in elite distance runners, mountaineers, swimmers and rowers while the D allele is associated with elite power-oriented performance and training-related gain of strength (35, 36). Besides that, I allele is involved in the alteration of metabolic response by maximizing oxidation fuel for metabolism whereas the D allele in gaining strength and VO2 max in response to training (36).

It is worth mentioning that although several studies have reported positive involvement of ACE I/D polymorphism in enhancing endurance and power performance some other studies have failed to report such association which could be due to inclusion of mixed sporting disciplines that results in phenotypic heterogeneity, sample size issues, and other confounding factors such as ethnicity and geography. For instance, none of the ACE I/D alleles were linked with the athletic performance in Kenyans depicting the involvement of ethnic and geographic factors (37). This suggests that, although the genotype is associated with elite performance phenotype, the effect of environment and other confounding factors determine the ultimate performance phenotype (38).
Another classical example of PEPs is ACTN3 gene that encodes a structural sarcomeric protein α-actin-3 found exclusively in fast type II muscle fibres used during explosive activities (28).

Association of ACTN3 genotype with human elite athletic performance was first reported by Yang et al in 2003 (39). This was the first PEPs reported for genes regulating skeleto-muscle formation and function (38,39). They reported a significantly higher frequency of the functional 577R genotype in both male and female elite sprinters. Subsequent studies highlighted the association of RR genotype with elite power performance (40) and XX genotype with lower sprinting ability and muscle strength (41). Furthermore the power athletes were 50% less likely while endurance athletes were 1.88 % more likely to have XX genotype as opposed to RR genotype. Moreover the world class endurance performers had 3.7% more chances of having an XX genotype as compared to lower level athletes implicating the importance of ACTN3 at highest performance levels (42). ACTN3 has been consistently associated with high performance in sprint and power athletes as compared to normal control population where it has no association with physical capabilities (43). Although the role of ACTN3 in general population is speculative the frequency of homozygous XX allele differs between human population of different ethnic origins e.g. 16% of Africans and approximately 51% of some Eurasian populations have XX genotype suggesting ethnic factors in the inheritance pattern (44).

Genetic variants linked with injury risk

In addition to above mentioned performance indicators the underlying risks for getting injury during sports and training is another important aspect to consider during talent identification. Like other performance associated polymorphisms resistance to injuries and capability to recover is also conferred by genetic variants (45). Athletes generally suffer from concussion (mild traumatic brain injury) and tendinopathies.

Genes linked with concussion

Apolipoprotein E (APOE)

Several research groups are trying to find a link between the apolipoprotein E (APOE) e4 allele and concussion. APOE e4 has a strong association with Alzheimer’s diseases (AD) (46), confers risk of severe brain injury (47) and particularly boxers having this allele are more likely to develop chronic injury (48) hence it is speculated to be a ‘risk allele’. However in contrast to these reports, e4 allele was not observed to be associated with increased risk of concussion and poor outcomes after mild brain injury in college athletes and children, respectively (49,50). While other studies have reported effect of ethnicity, age and sex on expression of APOE e4 allele on development of poorer outcomes after traumatic brain injury (51,52). Besides this, three variants in the promoter region of APOE -219G>T , -419A>T , -427T>C have been studied in the context of head injury (51). -219G>T has been found to increase the risk of concussion and AD in athletes with TT genotype as compared to GG genotype (51). Besides that, -219T augments the expression of e4 while -419T reduces the expression and presence and absence of these two variants have been linked with association of e4 with concussion (52,53).

Microtubule associated protein tau

The microtubule-associate protein tau is another important protein encoded by the MAPT gene that has been extensively associated with many neurodegenerative disorders (54). Higher levels of tau protein have been reported in amateur boxers following head bows (55) and concussed hockey player in a study conducted among Swedish professional hockey players (n=47) with these levels declining after appropriate rest and rehabilitation (56). However there are scarce reports of tau protein association with concussion and only Terrell et al (2008) reported a weak association between tau Ser53Pro and increased concussion risk (51).

Genes linked with tendinopathies

Another important risk factor associated with performance is risk of having muscle injuries or ten-
dinopathies which have been linked with genetic variants in collagen-encoding genes such as \textit{COL1A1} and \textit{COL5A1}, connective tissue wound repair gene \textit{MMP3} and the \textit{TNC} gene encoding tenasin C. Exonic SNPs in \textit{TNC} have been linked to risk for failure in healing and recovery (57,58). Presence of multiple risk alleles in an individual potentially increase the risk of injury and delayed recovery (59).

**Effect of single vs multiple genetic polymorphisms on sport phenotype**

Sport performance is based on complex interactions of interconnected genes and their variants which are responsible for regulating the key performance indicators and shaping the overall sports phenotype. In this context, the polygenic model of inheritance becomes more suitable for the explanation of sports performance (60). For example, the presence of more alleles associated with aerobic metabolism would result in better response to aerobic training (61) while having more alleles associated with endurance will increase likelihood of becoming a successful endurance performer (62). Besides that, some of the polymorphisms may fail to create an impact on performance alone but the presence of other polymorphisms may result in enhancing their impact on phenotype via genetic interactions. This means that a combination of polymorphisms might have a significant effect on overall sports phenotype than single polymorphisms and they need to be taken into account to predict sports performance and training regime (62, 63). William and Folland (63) proposed the total score genotyping (TGS) for helping the assessment of the balance between selected PEPs and has proven to be a very sensitive and reliable tool in differentiating the endurance and power athletes (64,65) as well as in distinguishing the elite athletes from general population on the basis of their genetic profile (66). However the sensitivity and sensibility of the TGS is dependent upon type and number of PEPs included in the calculations necessitating careful selection of only consistent polymorphisms associated with a particular sports type for TGS calculation (67). The application of TGS however is limited by the fact that it gives same weight to all polymorphisms used (68).

**Rare genetic variants**

Unravelling the physiological mechanism by which genetic variants effect performance becomes essential in linking these variants to sports phenotype (69). In addition to this, rare genetic variants might result in sports excellence (70). For example, truncating mutations in myostatin gene (\textit{MSTN}) result in enhancing sprinting (71). Similarly, a rare erythropoietin receptor gene (\textit{EPOR}) variant has a significant effect on haematocrit and VO$_2$ max and an Olympic gold medallist in country skiing was found to be carrier of this variant (72). Identifying more rare genetic variants may help in prediction of multitalented and gifted athletes with exceptional performances. Nevertheless, this area is still poorly understood (72).

Our current knowledge related to PEPs is still scarce and more research in this area is required to fully understand the genetic interactions resulting in high level sports performance. Identification of new polymorphisms with significant consistent association with sports phenotype and replication of the association of existing PEPs across various ethnic groups and different environmental conditions would help to predict the sport performance of potential athletes thus helping in talent identification.

**Genetic variants for talent identification**

The overall peak performance of an individual depends upon the intrinsic ability to perform well and the trainability. However numerous articles published in the past two decades highlight the association of fitness and sport performance with autosomal, X-linked and mitochondrial genes and their polymorphic variants (73,74). Hence, attaining elite athlete status cannot be solely attributed to practice and hard work but also to the right genetic background (75). Genetic variations have been reported to influence every single aspect of elite performance such as trainability (76), post exercise recovery (77-80), risk of injury (81), skill acquisition (82), post exercise fatigue (83), psychological traits (84) and athletic development (85). Thus proving their potential in identification of elite athletes status.
**Genetic variants related to endurance performance**

Recent advances in sports genetic have led to the identifications of genetic variants with potential influence on key performance indicators in both endurance and power sports (Table 1). The major genetic variants linked with endurance athlete status are those which influence aerobic endurance capacity, muscular strength, and other factors.

### Table 1. Genetic polymorphisms associated with sport performance

| Gene     | Full name                                      | Associated phenotypes                                                                 | Polymorphism ID                           | References                           |
|----------|-----------------------------------------------|--------------------------------------------------------------------------------------|------------------------------------------|--------------------------------------|
| **ACE**  | Angiotensin I converting enzyme                | I allele, endurance performance; D allele, power performance                          | rs4646994 (Alu I/D)                     | 28,29,31,146                        |
| **ACTN3**| α-actinin-3                                    | 577Ter (T) allele, endurance performance; Arg577 (C) allele, power performance       | rs1815739 C>T                           | 28,39,91,147                        |
| **ADRB2**| β-2-adrenoreceptor                            | 16Arg (A) and Gln27 (C) alleles, endurance performance                               | rs1042713 G>A; rs1042714 C>G           | 92,93,94,146                        |
| **BDKRB2**| Bradykinin receptor B2                        | T allele, endurance performance                                                      | rs1799722 C>T                           | 93,146                               |
| **COL5A1**| Collagen, type V, α1                           | CC genotype, protection from exercise-associated muscle cramps during an ultra-marathon; T allele, endurance performance | rs12722 C>T                           | 95,96,146,148                     |
| **CRP**  | C-reactive protein, pentraxin-related          | A allele, endurance performance                                                      | rs1205 A>G                             | 97,98,146                           |
| **GABPB1**| GA binding protein transcription factor, β subunit 1 (nuclear respiratory factor 2) | G allele, endurance performance                                                      | rs7181866 A>G                           | 99,146                              |
| **PPARA**| Peroxisome proliferator-activated receptor α   | G allele, endurance performance; C allele, power performance                         | rs4253778 G>C                           | 100,101,146                        |
| **PPARGC1A**| Peroxisome proliferator-activated receptor γ coactivator 1 α | G allele, endurance performance                                                     | rs8192678 G>A                          | 102,103,146                        |
| **VEGFA**| Vascular endothelial growth factor A           | C allele, endurance performance                                                      | rs2010963 G>C                           | 104,105,146                        |
| **ADRA2A**| α-2A-adrenergic receptor                      | Central role in the regulation of systemic sympathetic activity and hence cardiovascular responses such as heart rate and blood pressure | *Dra* I identifies a restriction fragment length polymorphism in the 3’-untranslated region (6.7-/6.3-kb polymorphism) | 92 |
| **AMPD1**| Adenosine monophosphate deaminase 1           | GG homozygotes, elite power athlete status, quicker acceleration and sprint times    | rs17602729 G>A                          | 77,149                              |
| **EPAS1**| Endothelial PAS domain protein 1              | AA genotype in rs1867785, underrepresented in sprint/power athletes; TT genotype in rs11689011, underrepresented in sprint/power athletes | rs1867785; rs11689011                   | 124     |
| Gene     | Full name | Associated phenotypes                                                                 | Polymorphism ID | References       |
|----------|-----------|----------------------------------------------------------------------------------------|-----------------|------------------|
| **NFATC4** | Nuclear factor of activated T cell calcineurin-dependent 4 | G allele, elite endurance athlete status                                                  | rs2229309 G>C   | 125              |
| **NOS3**  | Nitric oxide synthase 3                                   | GG genotype, slower than the other genotypes                                              | rs179983 T>A>G   | 92,126           |
| **AGT**   | Angiotensinogen                                          | 235Thr (C) allele, power performance                                                     | rs699 T>C        | 106,107,146      |
| **IL6**   | Interleukin-6                                           | G allele, power performance                                                              | rs1800795 C>G    | 108,109,146      |
| **TRHR**  | Thyrotropin- releasing hormone receptor                   | C allele, muscle mass                                                                    | rs1689246 A>C    | 110,146          |
| **VDR**   | Vitamin D receptor                                       | A allele, power performance                                                              | rs1544410 A>G    | 111,112,146      |
| **PPARGC1B** | Peroxisome proliferator-activated receptor γ coactivator 1 α | C allele, power athlete status                                                           | rs1006042 T>A,C  | 114              |
| **PPARG** | Peroxisome proliferator-activated receptor γ             | G allele, short-term and very intense exertion with anaerobic energy production           | rs1801282 C>G    | 115              |
| **HIF1A** | Hypoxia-inducible factor 1α                              | T allele, higher frequency in weightlifters and power-orientated athletes                | rs1154965 C>T    | 115,117,118      |
| **PTPRK** | Protein tyrosine phosphatase receptor type K              | C allele, sprint test performance                                                        | rs55743914 C>T   | 120              |
| **TERT**  | Telomerase reverse transcriptase                          | G allele, sprinters                                                                       | rs33954691 G>A   | 120              |
| **RDH13** | Retinol dehydrogenase 13                                 | G allele, increased proportion of fast-twitch muscle fibres                              | rs4806637 A>G    | 120              |
| **CBLN2** | Cerebellin 2 precursor                                   | G allele, sprinters                                                                       | rs8093502 C>T    | 120              |
| **CPNE5** | Copine V                                                | G allele, sprinters                                                                       | rs3213537 C>T    | 120              |
| **CNTN4** | contactin 4                                             | A allele, overrepresented in football players                                            | rs62247016 A>T   | 120              |
| **LINC00305, LINC01924** | Long intergenic non-protein coding RNA 305, 1924 | Functional role in development of atherosclerosis by inducing production of inflammatory cytokines in monocytes, by regulating apoptosis via miR-153 | rs2850711 A>T | 150              |
| **AGTR1** | Angiotensin II receptor type 1                           | C allele, essential hypertension. A allele, downregulated by the miR-155                | rs5186 A>C        | 151              |
| **MIR499A** | MicroRNA 499a                                           | GG genotype, myocardial infarction and ischemic stroke. The rs3746444 polymorphism disturbs regulation of blood pressure and anti-apoptotic effect in cardiomyocytes | rs3746444 A>G    | 152              |

(continued on next page)
### Table 1 (continued). Genetic polymorphisms associated with sport performance

| Gene       | Full name                        | Associated phenotypes                                                | Polymorphism ID       | References |
|------------|----------------------------------|----------------------------------------------------------------------|-----------------------|------------|
| **MIR4513** | MicroRNA 4513                    | Blood pressure, total lipids, total cholesterol, low-density lipoprotein cholesterol, blood glucose. TT genotype, coronary artery disease. T allele, decrease in Mir-4513 | rs2168518 C>T        | 152        |
| **MIR149**  | MicroRNA 149                     | Coronary artery disease                                              | rs2292832 T>C        | 152        |
| **MIR27A**  | MicroRNA 27a                     | C allele, increases in the expression of the miR with negative effect on adipogenesis. CC genotype, protective role against T2DM. G allele, increased risk of early cardiovascular autonomic neuropathy | rs895819 T>A,C,G     | 152        |
| **CREB1**   | CAMP responsive element binding protein 1 | A allele, smaller reduction in heart rate during a submaximal exercise test following training; greater exercise-induced temperature increase | rs2253206 A>G,T      | 148        |
| **CPT2**    | Carnitine palmitoyltransferase 2 | Minor alleles, CPT2 deficiency                                        | rs1799821 G>A; rs1799822 A>G | 149        |
| **PYGM**    | Muscle associated glycogen phosphorylase | Truncating variant, exercise intolerance, cramps and contractures during exercise and stressful situations | rs116987552 G>A      | 149        |
| **CNTF**    | Ciliary neurotrophic factor      | GG genotype, athlete phenotype                                        | rs1800169 G>A        | 147        |
| **ACVR1B**  | Activin A receptor type 1B       | Dynamic knee flexion and extension, isometric strength               | rs11612312 T>C; rs2854464 A>C,G | 153        |
| **NGF**     | Nerve growth factor              | CC genotype, more anxious females; TT genotype, more anxious males, less anxious females | rs6330 C>T           | 154        |
| **BDNF**    | Brain–derived neurotrophic factor | CC genotype, quicker sprinters than A allele carriers               | rs6265 G>A           | 154        |
| **NGFR**    | Nerve growth factor receptor     | Vagal autonomic dysregulation                                         | rs2072446 C>T        | 154        |
| **MSTN**    | Myostatin                        | Peak power during muscle contractions                               | rs1805086 A>G        | 154,155    |
| **SCN9A**   | Sodium voltage-gated channel alpha subunit 9 | AA genotype, increased perception of pain                           | rs1805086 A>G        | 154        |
| **COMT**    | Catechol-O-methyltransferase     | A allele, higher dopamine levels; lower pain threshold; enhanced vulnerability to stress. G allele, lower dopamine levels; higher pain threshold; better stress resiliency | rs4680 G>A           | 154        |
biomechanical efficiency, mental endurance and physical characters such as weight and height (86,87). Not only these genetic variants are heritable but differ between ethnicities and their effect are modified by environmental factors such as training and nutrition (88).

A recent review by Ahmetov et al has highlighted 93 endurance associated DNA variants (89) while a systematic research by William et al has identified 97 DNA variants associated with VO₂ max/peak trainability (90). The key genetic variants involved in endurance performance and trainability are located in the following genes: ACE, ACTN3, ADRB2, BDKRB2, COL5A1, CRP, GABPB1, PPARA, VEGFA, ADRA2A, AMPD1, EP4S1, NFATC4, NOS3, TFAM. The functions and associated phenotypes of these genes are listed in Table 1.

Genetic variants related to power performance

On the other hand the current literature review revealed 69 genetic markers associated with power athlete status. Most genetic markers associated with power athlete status are linked with skeletal muscle structure and function, blood pressure control, modulation of oxygen uptake, inflammatory and repair reactions during and after exercise, regulators of energy metabolism and cellular homeostasis, factors that control gene expression and cellular signalling pathways (Table 1). The most important of these are AGT, ACE, ACTN3, HIF1A, PPARA, PPARGC1A, PPARGC1B, PPARG, PTPRK, SEMA4A, TERT, RDH13, CBLN2, MORC4, CPNE5, CNTN4, TRHR, VDR, IL6.

In addition to the genes listed in Table 1 there are some SNPs near MORC4 that were reported to be linked with enhancing the expression of RNF128 in nerves while the C allele increases the expression of CLDN2 in thyroid tissue. These are important with respect to gene expression in skeletal muscles, nerves, blood and thyroid tissue and in skeletal muscle fibre composition and fast twitch muscle fibres (122,123). Another SNP rs12688220 near MORC4, was found to be associated with sprint performance, elite sprint athlete status, and increased proportion of fast twitch muscle fibres. However the mechanism through which this locus affect the sprint phenotype is poorly understood (120).

Performance prediction and talent identification based on genetic profiling

Although the association of most genetic variants with sports performance has weak scientific background, their presence in an individual either alone or in combination predisposes towards an increased chance of success in power or endurance performance (127). Nevertheless, it should be highlighted here that each individual polymorphism has only limited contribution to an elite athlete status and if considered alone may result in inadequate predicting of potential elite athlete phenotype (11, 127). Consequently genetic tests based on one or few genetic markers lack scientific backing for prescription of personalised exercise and sports training. Therefore considering a polygenic profile of various polymorphic variants encoding diversified products involved in wide variety of cellular processes and pathways becomes crucial for accurate talent identification (128). Besides that, the identification of large numbers of SNPs affecting a given trait and then combining them into a TGS model for that trait, would probably improve the predictive precision of genetic evidence (11).

Another important consideration in selecting the genetic markers for performance prediction is that rare genetic variants have a more powerful impact on sports phenotype as compared to common variants. One of the rare variants that conferred the winning performance to Finnish cross country skiing Champion Eero Mantyranta is the EPOR that resulted in an increased red blood cell production corresponding to elevated oxygen carrying capacity and aerobic endurance (72, 129). Another rare variant in lamin/AC (LMNA) gene was reported in one of the best Canadian sprint hurdler Priscilla Lopes-Schilep (130).

Although using rare genetic variants as markers for elite performance predictions sounds interesting and promising their low frequency make them hard to identify (11). Moreover to associate these variants to sports phenotypes would require studies with very large samples of unrelated individuals (11, 72). And finally there are ethical concerns as some of these variants might also predispose to disease states (129).
Commercial genetic testing

A study conducted by William et al in 2016 reports on the commercial direct to consumer (DTC) genetic testing. They surveyed 39 commercial testing companies and collected information regarding genetic variants tested by them. Their results indicated that only 18 companies had provided details of genetic variants they test. *ACTN3* was found to be the most frequently analysed variant with 88.8% of the 18 companies using it for commercial testing followed by *ACE* (61.1%), *PPARGC1A* (50%), *ADRB2* (44.4%), *COL5A1*, *VDR* (38.9%), *COL1A1*, *VEGF* (33.3%), *AGT*, *AMPD1*, *NOS3* (27.7%), *MMP3*, *PPARD*, *TRHR*, *CRP* (22.2%). Total number of genetic variants tested by these companies was 54 and only a few companies (7) provided a polygenic profile ranging between 14-27 genetic variants. 11 companies with exception of 2 companies which were providing test for single gene variant rest were conducting tests for 2-9 genetic variants (127).

Genetic performance tests pros and cons

Genetic plays a critical role in development of sports phenotype and exercise response. However to get positive benefits, training regimes and healthy lifestyle habits are of utmost importance. In other words, genetic coupled with a fitness and training regime can lead to development of an elite performance phenotype. Consequently, one of the most interesting application of sports genetic is development of tests for predicting performance and devise training regime. Furthermore, the potential for genetic testing to predict injury predisposition, may help in ensuring health and safety of athletes during sports training.

An excellent example of this is one of the Australian Rugby team which claimed that it has utilized genetic testing to develop training programs for its team members to gain a competitive edge over other teams. The team got tested 18 of its 24 players for 11 exercise-related genes (140). Subsequently their training programs were redesigned according to their genetic profile. In addition to this some professional sports teams are using the genetic test results for direct training recommendations (127).

However it is important to consider that studies identifying these gene linkages with sports performance have been conducted at population level and therefore they indicated the effect of these genetic variants on a study population while the effect of a particular genetic variant may differ considerably when seen in perspective of a single individual. Moreover, neither currently nor in future there is a chance of having a single gene variant that can conclusively provide sufficient information for an overall sports performance. Therefore genetic profiling to identify many genetic variants can help predict a world class talent and that can be useful if proper diet, nutrition and training regimes and positive environment are provided to develop the desired phenotype. It is worth mentioning here that, although the interest in commercial genetic testing is increasing, there is scarcity of evidence supporting notion of exercise prescription and talent identification. Consequently, it is far too realistic to claim the prediction of next generation of sports champions (60-64). Similarly, recommendation of target specific training protocols for power and endurance performance based on genotype or polygenic profile have insufficient evidence to guarantee their authenticity at the present (141). However some of the commercial genetic testing companies prescribe training regimes based on algorithmic approaches described in peer-reviewed research (142). Even though these tests might provide an insight into individual responses to training and exercise based on the genetic profiles these lack scientific backing unless improved methodologies with much larger sample sizes are used (141, 142).

There should be a standardized procedure of categorizing individuals as endurance or power in order to remove potential bias in replicating the studies (143).

Ethical concerns related to genetic testing for sports

Genetic testing in sports can raise several ethical concerns related to basic human rights of safety, privacy and secrecy of information. Besides that, the consequence of genetic tests specifically in children that aspire to become athletes can have several negative impacts such as depression and psychological problems in case the sports related genotype is not identi-
fied. Furthermore, most coaches, parents and athletes themselves do not have enough scientific background to understand the limitations and implications of results and this raises the question that who should actually be allowed to ask for a test? (127)

In addition to that, genetic testing of athletes has a potential to be misused by commercial sports companies with preferences being given to some athletes over others thus violating basic human rights. Therefore, the research in human sports and exercise genetics is also subjected to rigorous ethical screening by the ethical review committees as per the Helsinki declaration (World Medical Association, 2008). This ethical review process minimizes the ethical problems arising from genetic research and their future applications (127,143-145).

Conclusion

Traditionally, sports talent identification is based on physical and physiological characteristics and performance in a specific sports discipline. However, inclusion of genetic tests in talent hunt would revolutionize the field of sport. Genetic tests to elucidate the inherent capabilities of youth with respect to sport performance will not only help them in selecting the right sports career but also the exercise and training regime that would complement their genetic background. Early detection of potential traits of practical utility will help in devising training plans during growth and development, thus enhancing the capabilities and skills for attainment of peak performance. Current evidence suggests that a favourable genetic profile, when combined with the appropriate training, is advantageous, if not critical for the achievement of elite athletic status. However, though 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. Nevertheless, further molecular level research is required to strengthen our understanding of sports genetics, however this is possible only through a shift in the approach of policy makers followed by substantial funding that would lead to achieving excellence in sports.

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References

1. Lippi G, Longo UG, Maffulli N. Genetics and sports. Br Med Bull 2010; 93: 27–47.
2. Kiss MAPDM, Böhme MTS, Mansoldo AC, Degaki E, Regazzini M. Performance and sports talent. Rev Paul Educ Fis 2004; 19: 89–100.
3. Gibson WT. Key concepts in human genetics: understanding the complex phenotype. Med Sport Sci 2009; 54: 1-10.
4. Tucker R, Collins M. What makes champions? A review of the relative contribution of genes and training to sporting success. Br J Sports Med 2012; 46: 555-61.
5. Eynon N, Ruiz JR, Oliveira J, Duarte JA, Birk R, Lucia A. Genes and elite athletes: a roadmap for future research. J Physiol 2011; 589: 3063-70.
6. Puthucheary Z, Skipworth JR, Rawal J, Loosemore M, Van Someren K, Montgomery HE. Genetic influences in sport and physical performance. Sports Med 2011; 41: 845–59.
7. Tanaka M, Wang G, Pitsiladis YP. Advancing sports and exercise genomics: moving from hypothesis-driven single study approaches to large multi-omics collaborative science. Physiol Genomics 2016; 48: 173–4.
8. Tanana M, Tanisawa K, Wang G, et al. The 1000 Athlomes project for 2020 summer Olympics in Tokyo. 35th FIMS world Congress of sports medicine. Rio de Janeiro, 2018.
9. Bray MS, Hagberg JM, Pérusse L, et al. The human gene map for performance and health-related fitness phenotypes: the 2006–2007 update. Med Sci Sports Exerc 2009; 41: 35–73.
10. Bouchard C. Genomic predictors of trainability. Experimental Physiology. 2012; 97: 347–52.
11. Guilherme JPLF, Tritto ACC, North KN, Lancha Junior AH, Artioli GG. Genetics and sport performance: current challenges and directions to the future. Rev Bras Educ Fis Esporte 2014; 28: 177-93.
12. Guth LM, Roth SM. Genetic influence on athletic performance. Curr Opin Pediatr 2013; 25: 653-8.
13. MacArthur DG, North KN. Genes and human elite athletic performance. Hum Genet 2005; 116: 331–9.
14. Moran CN, Vassilopoulos C, Tsioikanos A, et al. The associations of ACE polymorphisms with physical, physiological and skill parameters in adolescents. Eur J Hum Genet 2006; 14: 332–9.
15. Bouchard C, Sarzynski MA, Rice TK, et al. Genomic predictors of the maximal O(2) uptake response to standardized exercise training programs. J Appl Physiol 2011; 110: 1160-70.
16. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and
Cardiovascular events in healthy men and women: a meta-analysis. JAMA 2009; 301: 2024–35.

17. Kanzleiter T, Rath M, Penkov D, et al. Pknox1/Prep1 regulates mitochondrial oxidative phosphorylation components in skeletal muscle. Mol Cell Biol 2014; 34: 290–8.

18. Bouchard C, Rankinen T, Timmons JA. Genomics and genetics in the biology of adaptation to exercise. Compr Physiol 2011; 1: 1603–48.

19. Hughes DC, Day SH, Ahmetov II, Williams AG. Genetics of muscle strength and power: polygenic profile similarity limits skeletal muscle performance. J Sports Sci 2011; 29: 1425–34.

20. Hagberg JM, Rankinen T, Loos RJ, et al. Advances in exercise, fitness, and performance genomics in 2010. Med Sci Sports Exerc 2011; 43: 743–52.

21. Roth SM, Rankinen T, Hagberg JM, et al. Advances in exercise, fitness, and performance genomics in 2011. Med Sci Sports Exerc 2012; 44: 809–17.

22. Bouchard C. Overcoming barriers to progress in exercise genomics. Exerc Sport Sci Rev 2011; 39: 212–7.

23. Williams AG, Folland JP. Similarity of polygenic profiles limits the potential for elite human physical performance. J Physiol 2008; 586: 113–21.

24. Lucia A, Moran M, Zihong H, Ruiz JR. Elite athletes: are the genes the champions? Int J Sports Physiol Perform 2010; 5: 98–102.

25. Rigat B, Hubert C, Alhenc-Gelas F, et al. An insertion/deletion polymorphism in the angiotensin I converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest 1990; 86: 1343–6.

26. Danser AH, Schalekamp MA, Bax WA, et al. Angiotensin-converting enzyme in the human heart. Effect of the deletion/insertion polymorphism. Circulation 1995; 92: 1387–8.

27. Scott RA, Moran C, Wilson RH, et al. No association between Angiotensin Converting Enzyme (ACE) gene variation and endurance athlete status in Kenyans. Comp Biochem Physiol A Mol Integr Physiol 2005; 141: 169–75.

28. Ma F, Yang Y, Li X, et al. The association of sport performance with ACE and ACTN3 genetic polymorphisms: A systematic review and meta-analysis. PLoS One 2013; 8: e54685.

29. Jones A, Montgomery HE, Woods DR. Human performance: a role for the ACE genotype? Exerc Sport Sci Rev 2002; 30: 184–90.

30. Nazarov IB, Woods DR, Montgomery HE, et al. The angiotensin converting enzyme I/D polymorphism in Russian athletes. Eur J Hum Genet 2001; 9: 797–801.

31. Tsianos G, Sanders J, Dhamrait S, et al. The ACE gene insertion/deletion polymorphism and elite endurance swimming. Eur J Appl Physiol 2004; 92: 360–2.

32. Gayagay G, Yu B, Hambly B, et al. Elite endurance athletes and the ACE I allele-the role of genes in athletic performance. Hum Genet 1998; 103: 48–50.

33. Woods DR, Montgomery HE. Angiotensin-converting enzyme and genetics at high altitude. High Alt Med Biol 2001; 2: 201–10.

34. Thompson J, Raitt J, Hutchings L, et al. Angiotensin-converting enzyme genotype and successful ascent to extreme high altitude. High Alt Med Biol 2007; 8: 278–85.

35. Jones A, Montgomery HE, Woods DR. Human performance: a role for the ACE genotype? Exerc Sport Sci Rev 2002; 30: 184–90.

36. Woods DR, Brull D, Montgomery HE. Endurance and the ACE I/D polymorphism. Sport Prog 2000; 84: 317–36.

37. Scott RA, Moran C, Wilson RH, et al. No association between Angiotensin Converting Enzyme (ACE) gene variation and endurance athlete status in Kenyans. Comp Biochem Physiol Part A Mol Integr Physiol 2005; 141: 169–75.

38. Grealy R, Herruer J, Smith CLE, Hiller D, Haseler LJ, Griffiths LR. Evaluation of a 7-gene genetic profile for athletic endurance phenotype in ironman championship triathletes. PLoS One 2015; 10: e0145171.

39. Yang N, Arthur DG, Gulbin JP, et al. ACTN3 genotype is associated with human elite athletic performance. Am J Hum Genet 2003; 73: 627–31.

40. Yang N, Garton F, North K. Alpha-actinin-3 and performance. Med Sci Sports Exerc 2009; 54: 88–101.

41. Eynon N, Hanson ED, Lucia A, et al. Genes for elite power and sprint performance: ACTN3 leads the way. Sports Med 2013; 43: 803–17.

42. Alfred T, Ben-Shlomo Y, Cooper R, et al. ACTN3 genotype, athletic status, and life course physical capability: meta-analysis of the published literature and findings from nine studies. Hum Mutat 2011; 32: 1008–18.

43. Eynon N, Ruiz JR, Femia P, et al. The ACTN3 R577X polymorphism across three groups of elite male European athletes. PloS One 2012; 7: e43132.

44. Mills M, Yang N, Weinberger R, et al. Differential expression of the actin-binding proteins, alpha-actinin-2 and -3, in different species: implications for the evolution of functional redundancy. Hum Mol Genet 2001; 10: 1335–46.

45. Tremblay S, De Beaumont L, Henry LC, et al. Sports concussions and aging: A neuroimaging investigation. cerebral cortex. 2013; 23: 1159–66.

46. Donix M, Small GW, Bookheimer SY. Family history and APOE-4 genetic risk in Alzheimer’s disease. Neuropsychol Rev 2012; 22: 298–309.

47. Teasdale GM, Nicoll JA, Murray G, Fiddes M. Association of apolipoprotein E polymorphism with outcome after head injury. Lancet 1997; 350: 1069–71.

48. Jordan BD, Relkin NR, Ravdin LD, et al. Apolipoprotein E epsilon 4 allele predispose varsity athletes to concussion? A prospective cohort study. Clin J Sport Med 2008; 18: 322–8.

49. Kanzleiter T, Rath M, Penkov D, et al. Pknox1/Prep1 regulates mitochondrial oxidative phosphorylation components in skeletal muscle. Mol Cell Biol 2014; 34: 290–8.

50. Mano LM, Taylor HG, Ganesalingam K, et al. Apolipoprotein E4 as a predictor of outcomes in pediatric mild traumatic brain injury. J Neurotrauma 2009; 26: 1489–95.

51. Terrell TR, Bostick RM, Abramson R, et al. APOE, APOE
promoter, and Tau genotypes and risk for concussion in college athletes. Clin J Sport Med 2008; 18: 10–7.
52. Jordan BD, Relkin NR, Ravdin LD, Jacobs AR, Bennett A, Gandy S. Apolipoprotein E epsilon4 associated with chronic traumatic brain injury in boxing. J Am Med Assoc 1997; 278: 136–40.
53. Jordan BD. Genetic susceptibility to brain injury in sports: a role for genetic testing in athletes? Phys Sportsmed 1998; 26: 25–6.
54. Gao YL, Wang N, Sun FR, Cao XP, Zhang W, Yu JT. Tau in neurodegenerative disease. Ann Transl Med 2018; 6: 175.
55. Neselius S, Zetterberg H, Blennow K, et al. Linking genes with exercise: where is the cut-off? Eur J Appl Physiol 2010; 110: 258–64.
56. Murakami H, Ota A, Simojo H, et al. Unique among unique. Is it genetically determined? Br J Sports Med 2009; 43: 307–9.
57. Kambouris M, Ntalouka F, Ziogas G, et al. Myostatin pathway genes with knee strength in humans. Physiol Genomics 2004; 17: 264–70.
58. Rankinen T, Bray MS, Hagberg JM, et al. The human gene map for performance and health-related fitness phenotypes: the 2005 update. Med Sci Sports Exerc 2006; 38: 1863–88.
59. Rankinen T, Church T, Rice T, et al. Effect of endothelin 1 genotype on blood pressure is dependent on physical activity or fitness levels. Hypertension 2007; 50: 1120–25.
60. Kostek M, Hubal MJ, Pescatello LS. The role of genetic variation in muscle strength. Am J Lifestyle Med 2011; 5: 156–70.
61. Schuelke M, Wagner KR, Stolz LE, et al. Myostatin mutation associated with gross muscle hypertrophy in a child. N Engl J Med 2004; 350: 2682–8.
62. Huygens W, Thomsis M, Peeters M, et al. Linkage of myostatin pathway genes with knee strength in humans. Physiol Genomics 2004; 17: 264–70.
63. de la Chapelle A, Traskelin AL, Juvenon E. Truncated erythropoietin receptor causes dominantly inherited benign human erythrocytosis. Proc Natl Acad Sci USA 1993; 90: 4495–9.
64. Rankinen T, Church T, Rice T, et al. Unique among unique. Is it genetically determined? Br J Sports Med 2009; 43: 307–9.
65. Flueck M, Vaughan D, Westerblad H. Does the polygenic profile determine the potential for becoming a world-class athlete? Insights from the sport of rowing. Scand J Med Sci Sports 2010; 20: e188–94.
66. Eynon N, Ruiz JR, Meckel Y, et al. Does the polygenic profile determine the potential for becoming a world-class athlete? Insights from the sport of rowing. Scand J Med Sci Sports 2010; 20: e188–94.
67. Eynon N, Ruiz JR, Meckel Y, et al. mitochondrial biogenesis related endurance genotype score and sports performance in athletes. Mitochondrion 2011; 11: 64–9.
68. Dias RG. Genetics, human physical performance and gene doping: common sense versus the scientific reality. RevBras Med Esporte 2011; 17: 62–70.
69. Thornton PM, Wagnert KR, Stolz LE, et al. Myostatin mutation associated with gross muscle hypertrophy in a child. N Engl J Med 2004; 350: 2682–8.
70. Montgomery HE, Marshall R, Hemingway H, et al. Human gene for physical performance. Nature 1998; 393: 221–2.
71. Roth SM. Critical overview of applications of genetic testing in sport talent identification. Recent Pat DNA Gene Seq 2012: 6: 247–55.
initial fitness, and response to training: The HERITAGE Family Study. J Appl Physiol 2001; 90: 1770–6.
86. Saunders CJ, de Milander L, Hew-Butler T, et al. Lipidogenic genes associated with weight changes during Ironman Triathlons. Hum Mol Genet 2006; 15: 2980–7.
87. Silventoinen K, Magnusson PKE, Tynelius P, et al. Heritability of body size and muscle strength in young adulthood: a study of one million Swedish men. Genet Epidemiol 2008; 32: 341–9.
88. Stubbe JH, Boomsma DI, De Geus EJ. Sports participation during adolescence: a shift from environmental to genetic factors. Med Sci Sports Exerc 2005; 37: 563–70.
89. Ahmetov II, Egorova E, Gabdrakhmanova LJ, Fedotovska ON. Genes and athletic performance: an update. Med Sport Sci 2016; 61: 41–54.
90. Williams CJ, Williams MG, Eynon N, et al. Genes to predict VO2max trainability: a systematic review. BMC Genomics 2017; 18: 831.
91. Houweling PJ, Papadimitriou ID, Seto JT, et al. Is evolutionary loss our gain? The role of ACTN3p.Arg577Ter (R577X) genotype in athletic performance, aging, and disease. Hum Mutat 2018; 39: 1774–87.
92. Wolfarth B, Rankinen T, Mühlbauer S, et al. Association between a beta2-adrenergic receptor polymorphism and elite endurance performance. Metabolism 2007; 56: 1649–51.
93. Tsianos GI, Evangelou E, Boot A, et al. Associations of polymorphisms of eight muscle- or metabolism-related genes with performance in Mount Olympus marathon runners. J Appl Physiol (1985) 2010; 108: 567–74.
94. McCole SD, Shuldiner AR, Brown MD, et al. Beta2- and beta3-adrenergic receptor polymorphisms and exercise hemodynamics in postmenopausal women. J Appl Physiol (1985) 2004; 96: 526–30.
95. Posthumus M, Schwelius MP, Collins M. The COL5A1 gene: a novel marker of endurance running performance. Med Sci Sports Exerc 2011; 43: 584–9.
96. Brown JC, Miller CJ, Posthumus M, Schwelius MP, Collins M. The COL5A1 gene, ultra-marathon running performance, and range of motion. Int J Sports Physiol Perform. 2011;6(4):485- 496.
97. Obisesan TO, Leeuwenburgh C, Phillips T, et al. C-reactive protein genotypes affect baseline, but not exercise training-induced changes, in C-reactive protein levels. Arterioscler Thromb Vasc Biol 2004; 24: 1874–9.
98. Kuo HK, Yen CJ, Chen JH, Yu YH, Bean JF. Association of cardiorespiratory fitness and levels of C-reactive protein: data from the National Health and Nutrition Examination Survey 1999–2002. Int J Cardiol 2007; 114: 28.
99. Eynon N, Sagiv M, Meckel Y, et al. NRF2 intron 3 A/G polymorphism is associated with endurance athletes’ status. J Appl Physiol (1985) 2009; 107: 76–9.
100. Ahmetov II, Gavrilov DN, Astratenkova IV, et al. The association of ACE, ACTN3 and PPARα gene variants with strength phenotypes in middle school-age children. J Physiol Sci 2013; 63: 79–85.
101. Lopez-Leon S, Tuvblad C, Forero DA. Sports genetics: the PPARα gene and athletes’ high ability in endurance sports. A systematic review and meta-analysis. Biol Sport 2016; 33: 3–6.
102. Lucia A, Gómez-Gallego F, Barroso I, et al. PPARC1A genotype (Gly482Ser) predicts exceptional endurance capacity in European men. J Appl Physiol (1985) 2005; 99: 344–8.
103. Maciejewska A, Sawczuk M, Cieszczyk P, Mozhayskaya IA, Ahmetov II. The PPARC1A gene Gly482Ser in Polish and Russian athletes. J Sports Sci 2012; 30: 101–13.
104. Prior SJ, Hagberg JM, Paton CM, et al. DNA sequence variation in the promoter region of the VEGF gene impacts VEGF gene expression and maximal oxygen consumption. Am J Physiol Heart Circ Physiol 2006; 290: 1848–55.
105. Ahmetov II, Khakimullina AM, Popov DV, Missina SS, Vinogradova OL, Rogozkin VA. Polymorphism of the vascular endothelial growth factor gene (VEGF) and aerobic performance in athletes. HumPhysiol 2008; 34: 477–81.
106. Gomez-Gallego F, Santiago C, González-Freire M, et al. The C allele of the AGT Met235Thr polymorphism is associated with power sports performance. Appl Physiol Nutr Metab 2009; 34: 1108–11.
107. Zarbska A, Sawczyn S, Kaczmarczyk M, et al. Association of rs699 (M235T) polymorphism in the AGT gene with power but not endurance athlete status. J Strength Cond Res 2013; 27: 2898-903.
108. Ruiz JR, Buxens A, Artieda M, et al. The -174 G/C polymorphism of the IL6 gene is associated with elite power performance. J Sci Med Sport 2010; 13: 549–53.
109. Eider J, Cieszczyk P, Leoshska-Duniec A, et al. Association of the 174 G/C polymorphism of the IL6 gene in Polish power-orientated athletes. J Sports Med Phys Fitness 2013; 53: 88-92.
110. Liu XG, Tan LJ, Lei SF, et al. Genome-wide association andreplication studies identified TRHR as an important gene for lean body mass. Am J Hum Genet 2009; 84: 418–23.
111. Wang P, Ma LH, Wang HY, et al. Association between polymorphisms of vitamin D receptor gene Apal, BsmI and TaqI and muscular strength in young Chinese women. Int J Sports Med 2006; 27: 182–6.
112. Windelinckx A, De Mars G, Beunen G, et al. Polymorphisms in the vitamin D receptor gene are associated with muscle strength in men and women. Osteoporos Int 2007; 18: 1235–42.
113. Ginevičienė V, Jakaitiene A, Aksenov MO, et al. Association analysis of ACE, ACTN3 and PPARC1A gene polymorphisms in two cohorts of European strength and power athletes. Biol Sport 2016; 33: 199–206.
114. Iachenko DS, Galeeva AA, Kulemin NA, et al. Genomewide association study of elite power athlete status. Eur J Hum Genet 2015; 23: 472.
115. Ahmetov II, Mozhayskaya IA, Flavell DM, et al. PPARa-
pha gene variation and physical performance in Russian athletes. Eur J Appl Physiol 2006; 97: 103–8.

116. Miciejewska-Karlowska A, Sawczuk M, Cieszczyk P, Zarebska A, Sawczyn S. Association between the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor gamma gene and strength athlete status. PLoS One 2013; 8: e67172.

117. Drozdovska SB, Dosenko VE, Ahmetov II, Ilyin VN. The association of gene polymorphisms with athlete status in Ukrainians. Biol Sport 2013; 30: 163–7.

118. Cieszczyk P, Eider J, Arczewska A, et al. The HIF1A gene Pro582Ser polymorphism in Polish power-orientated athletes. Biol Sport 2011; 28: 111–4.

119. Kumanogoh A, Shikina T, Suzuki K, et al. Nonredundant roles of Sema4A in the immune system: defective Th cell priming and Th1/Th2 regulation in Sema4A-deficient mice. Immunity 2005; 22: 305–16.

120. Pickering C, Suraci B, Semenova EA, et al. DNA damage responses. Proc Natl Acad Sci U S A 2005; 102: 8222–7.

121. Masutomi K, Possemato R, Wong JM, et al. The telomerase reverse transcriptase regulates chromatin state and DNA damage responses. Proc Natl Acad Sci U S A 2005; 102: 8222–7.

122. Pickering C, Suraci B, Semenova EA, et al. Trans-eQTLs reveal that independent genetic variants associated with a complex phenotype converge on intermediate genes, with a major role for the HLA. PLoS Genet 2011; 7: e1002197.

123. GTEx Consortium. Genetic effects on gene expression across human tissues. Nature 2017; 550: 204–13.

124. Henderson J, Withford-Cave JM, Duffy DL, et al. The EPAS1 gene influences the aerobic-anaerobic contribution in elite endurance athletes. Hum Genet 2005; 118: 416–23.

125. Popov DV, Ahmetov II, Shikhova JV, et al. NFATC4 gene polymorphism and aerobic performance in athletes. Eur J Hum Genet 2008; 16: 336.

126. Saunders CJ, Xenophontos SL, Carloulo MA, et al. The bradykinin b2 receptor (BDKRB2) and endothelial nitric oxide synthase 3 (NOS3) genes and endurance performance during Ironman Triathlons. Hum Mol Genet 2006; 15: 979–87.

127. Williams AG, Wackerhage H, Day SH. Genetic testing for sports performance, responses to training and injury risk: practical and ethical considerations. Med Sci Sports Exerc 2016; 48: 10519.

128. Joyner MJ. Genetic approaches for sports performance: how far away are we? Sports Med 2019; 49: 199–204.

129. Juvonen E, Ikkala E, Fyhriquist F, Ruutu T. Autosomal dominant erythrocytosis caused by increased sensitivity to erythropoietin. Blood 1991; 78: 3066–9.

130. Vincent D. The amazing story of Priscilla Lopes-Schlep and Iowa mom. https://www.thestar.com/news/world/2016/01/28/the-amazing-story-of-priscilla-lopes-schlep-and-the-iowa-mom.html

131. Ling, C.; Rönn, T. Epigenetic adaptation to regular exercise in humans. Drug Discov Today 2014; 19: 1015–8.

132. Moran CN, Pitsiladis YP. Tour de France Champions born or made: Where do we take the genetics of performance? J Sports Sci 2017; 35: 1411–9.

133. Widmann M, Nieß AM, Munz B. Physical exercise and epigenetic modifications in skeletal muscle. Sports Med 2019; 49: 509–23.

134. Voisin S, Eynon N, Yan X, Bishop DJ. Exercise training and DNA methylation in humans. Acta Physiol 2015; 213: 39–59.

135. Pareja-Galeano H, Sanchis-Gomar F, García-Giménez JL. Physical exercise and epigenetic modulation: Elucidating intricate mechanisms. Sports Med 2014; 44: 429–36.

136. Seaborn RA, Strauss J, Cocks M, et al. Human skeletal muscle possesses an epigenetic memory of hypertrophy. Sci Rep 2018; 8: 1898.

137. Pandorf CE, Haddad F, Wright C, Bodell PW, Baldwin KM. Differential epigenetic modifications of histones on the myosin heavy chain genes in fast and slow skeletal muscle fibers and in response to muscle unloading. Am J Physiol Cell Physiol 2009; 297: C6–16.

138. Mooren FC, Viereck J, Krüger K, Thum T. Circulating microRNAs as potential biomarkers of aerobic exercise capacity. Am J Physiol Heart Circ Physiol 2013; 306: H557–63.

139. Baggis AL, Park J, Min PK, et al. Rapid upregulation and clearance of distinct circulating microRNAs after prolonged aerobic exercise. J Appl Physiol 2014; 116: 522–31.

140. Dennis C. Rugby team converts to give gene tests a try. Nature 2005; 434: 260.

141. Vlahovich N, Hughes DC, Griffiths LR, et al. Genetic testing for exercise prescription and injury prevention: AIS–Athlome consortium–FIMS joint statement. BMC Genomics 2017; 18: 818.

142. Vlahovich N, Fricker PA, Brown MA, Hughes D. Ethics of genetic testing and research in sport: a position statement from the Australian Institute of Sport. Br J Sports Med 2017; 51: 5–11.

143. Karanikolou A, Wang G, Pitsiladis Y. Letter to the editor: a genetic-based algorithm for personalized resistance training. Biol Sport 2017; 34: 31–3.

144. Hogarth S, Javitt G, Melzer D. The current landscape for direct-to-consumer genetic testing: legal, ethical, and policy issues. Annu Rev Genomics Hum Genet 2008; 9: 161–82.

145. Hopkins WG. Genes and training for athletic performance. Sport science 2001; 5.

146. https://www.dnafit.com/downloads/DNAFit%20Clinical%20Study%20V1.pdf

147. Persi A, Maltese PE, Bertelli M, et al. Polymorphisms of alpha-actinin-3 and ciliary neurotrophic factor in national-level Italian athletes. Panninerva Med 2013; 55: 217–24.

148. Pickering C, Kiely J. Exercise genetics: seeking clarity from noise. BMJ Open Sport Exerc Med 2017; 3: e000309.
149. Maltese PE, Venturini L, Poplavskaya E, et al. Genetic evaluation of AMPD1, CPT2, and PGYM metabolic enzymes in patients with chronic fatigue syndrome. Genet Mol Res 2016; 15: 10.4238/gmr.15038717.

150. Castellanos-Rubio A, Ghosh S. Disease-associated SNPs in inflammation-related lncRNAs. Front Immunol 2019; 10: 420.

151. Haas U, Sczakiel G, Laufer SD. MicroRNA-mediated regulation of gene expression is affected by disease-associated SNPs within the 3’-UTR via altered RNA structure. RNA Biol 2012; 9: 924-37.

152. Elfaki I, Mir R, Mir MM, AbuDuhier FM, Bahakr AT, Barnawi J. Potential impact of microRNA gene polymorphisms in the pathogenesis of diabetes and atherosclerotic cardiovascular disease. J Pers Med 2019; 9: 51.

153. Windelinckx A, De Mars G, Huygens W, et al. Comprehensive fine mapping of chr12q12-14 and follow-up replication identify activin receptor 1B (ACVR1B) as a muscle strength gene. Eur J Hum Genet 2011; 19: 208-15.

154. Maltese PE, Michelini S, Baronio M, Bertelli M. Molecular foundations of chiropractic therapy. Acta Biomed 2019; 90: 93-102.

155. Santiago C, Ruiz JR, Rodriguez-Romo G, et al. The K153R polymorphism in the myostatin gene and muscle power phenotypes in young, non-athletic men. PLoS One 2011; 6: e16323.

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