Genetics of Athletic Performance

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Athletic ability is considered to be a complex genetic trait involving the interaction of genes with the environment. An understanding of the genetics of human performance is being sought in a number of research studies using laboratory and computer-based strategies. Ultimately, an in-depth understanding of how genes influence human performance has potential for use in talent search programmes and perhaps predicting those who might be predisposed to particular injuries. Many genes have now been identified through association studies to have a possible role in athletic performance but most remain to be confirmed through functional studies. Interest is also moving to novel modes of genetic inheritance including epigenetics and copy number variations. Despite being at the beginning of our understanding of how heritable factors influence athletic performance, there is considerable optimism that the newly developed genomic technologies will identify important genes.

Introduction

Athletic performance is a human trait comparable to height, intelligence and personality. Both nature and nurture can influence athletic ability (**Figure 1**). Nature refers to our genetic makeup or genome. Nurture reflects the effects of the environment including *in utero*, opportunity, parental support, social culture, nutrition and general well being. Other contributors are coaching, training opportunities and, to some extent, luck in terms of talent search. Different sports also impact on the nature versus nurture contribution with some such as archery leaning more towards nurture, whereas nature plays a more significant component in rowing. Therefore, athletic performance is a complex human trait understanding of which is still very preliminary.

One can speculate that most humans do not achieve their full genetic potential for athletic ability, and this becomes evident when individual performance in the non-athlete is measured before and after intensive environmental interventions (**Figure 1**). Feedback in early training can also influence subsequent training. Positive experiences will motivate an individual towards more diligent practice, whereas frustration and failure will do the opposite. Whether genes contributing to athletic performance are rare or common is still to be determined but what can be said with some certainty is that their individual effects are very modest, and it is assumed that their effects are also cumulative. Therefore, modest effects are best detectable at the top elite levels of athletic performance, and *ipso facto* they will always be difficult to identify because by definition top elite athletes are few in numbers. The latter becomes a limitation with current research strategies to detect genes associated with complex traits (see association studies in the later section).

In our current state of knowledge, it is unrealistic to speculate that any single gene or even a mix of genes will transform an individual into an elite athlete, or any single genetic marker will identify who can win an Olympic medal. Nevertheless, the more elite the level of performance, the closer becomes the margins for success and so a small advantage gained from knowledge of genetic makeup might become critical to success. This potential for an incremental change will ensure that research continues looking for clues to explain how genes influence athletic ability. Presently, the hypothesis is that external factors (environment) interacting with internal factors (genome) will produce a particular athletic phenotype comparable to what is thought to occur with complex genetic diseases such as type 2 diabetes. Either can limit or enhance an individual's potential (**Figure 1**). **See also**: Complex Multifactorial Genetic Diseases

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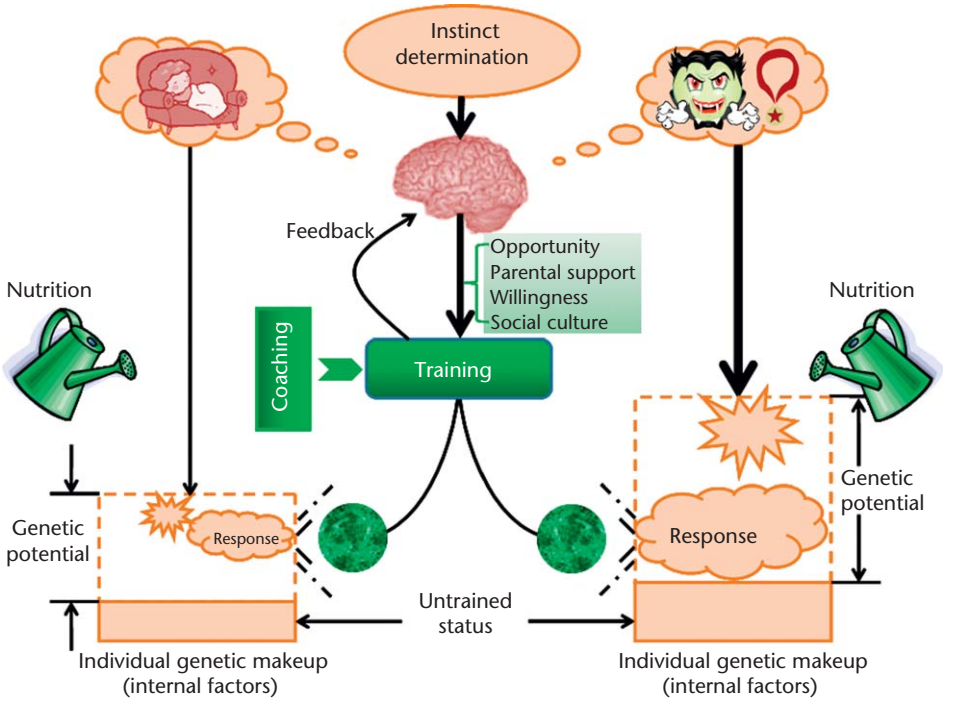

Figure 1 The effects of gene–environment interactions on athletic performance. Individual genetic makeup is represented by an orange rectangle with genetic potential as a dashed line. The interindividual variability for athletic ability will be present in the untrained individual, but the phenotype will not be remarkable. Natural ability reflecting the genome with its physiological response to training, and mental attitude is depicted by the orange colour while nurture is in green. Environmental factors have to interact with the genetic factors to produce a particular phenotype. Genetic makeup sets the limit to athletic potential but environmental factors actualise the individual's potential within that limit.

Genetic Contributions to Athletic Performance

The 'natural-born-athlete' is a familiar term. It implies a strong genetic contribution to athletic performance, and is supported by some evidence dating back to research performed in the early 1970s looking at heritability of athletic ability (Klissouras, 1971, 1973). Genetic contribution has also been noted by Franklin *et al*. (1997) when they reviewed cardiovascular fitness in elite athletes and made the comment that: 'Natural endowment (i.e. 'selecting the right parents'), rather than training per se, plays a major role in producing a gold medal winner in an Olympic endurance event'. What is the evidence to support this claim?

Mendelian inheritance

An extreme and very rare example of how genes influence athletic performance can be found in the case of Eero Mäntyranta, a Finnish cross-country skier who won seven Olympic medals in the 1960s. Why was he so good at his sport? One genetic factor that gave him an edge over his opponents was the finding that he had an inherited mutation in the erythropoietin (*EPO*) receptor. This allowed the gene to over express itself and so increase the individual's oxygen carrying capacity by 25–50% – a distinct physiological advantage for endurance type sport (de la Chapelle *et al*., 1993). Today, EPO is one of the drugs that cheats take to enhance their athletic performance. Because a single defect in a gene such as the *EPO* receptor has caused a major effect on the phenotype (the phenotype is what one sees or measures, i.e. the end point), we call this mendelian inheritance because the effect is significant and can be transmitted to others in the family.

Complex multifactorial inheritance

When we move away from the relatively rare single gene mendelian inheritance we come to the more complex but common modes of inheritance (sometimes called multifactorial). Here nature (gene) and nurture (environment) both play a role in the phenotype.

A strategy used to distinguish nature from nurture in medicine is to take a trait or disease in twins and compare the frequency in monozygotic (MZ) versus dizygotic (DZ) twins. MZ twins have essentially an identical genetic background and so will be more similar (higher intra-pair correlation) for a trait that is under genetic control than DZ twins who share on average only 50% of their genes. In very broad terms both types of twins would be expected to have shared similar environmental exposures. Another strategy to separate nature from nurture involves family studies

to compare similarities between parents, offspring and siblings. These are less informative than twin studies because they can be influenced by age-specific genetic and environmental effects. The family approach permits the identification of genetic and cultural transmission of traits and estimates of maximum heritability. **See also**: Twin Studies

In any research looking at athletic performance, it is necessary to have an unequivocal phenotype. An example of such a phenotype is maximal oxygen uptake (VO_{2max}) or aerobic power. This is a frequently used measure for endurance performance since it represents fitness of the oxygen transport and cardiorespiratory systems. In an early study of a small group of twins, it was found that MZ twins were more alike than DZ twins for VO_{2max} relative to body mass (Klissouras, 1971). Later twin studies confirmed that VO_{2max} is partially genetic determined with the heritability between 0.40 and 0.70 (Bouchard *et al*., 1986; Malina and Bouchard, 1986). After adjustment for environmental factors and body weight, it was proposed that heritability estimates for VO_{2max} could reach 0.71 and 0.67 for male and female twins, respectively (Maes *et al*., 1996). Mean intraclass correlations of MZ twins vary between 0.60 and 0.80, and the same mean correlations of DZ twins vary between 0.30 and 0.50 (similar to the estimates for biological siblings). VO_{2max} is well known to vary considerably among sedentary adults. **See also**: Genotype-Phenotype Relationships

The HERITAGE family study found that there was significant familial resemblance for VO_{2max} in the sedentary state even when the data are adjusted for age, gender, body mass and body composition (Bouchard *et al*., 1998). Maximal heritability estimates were as high as 0.50 of the total phenotypic variance although such a value could be inflated by undetermined nongenetic factors. Heritability has been reported in other measures of athletic performance. Maximal anaerobic power and capacity have heritability factors that range from 0.70 to 0.99 (Komi *et al*., 1973; Malina and Bouchard, 1986; Simoneau *et al*., 1986). The heritability of human heights ranges from 0.69 to 0.90 (Bouchard *et al*., 1997), whereas the genetic control for the body mass and body mass index are less with the heritability of 0.40–0.70 (Katzmarzk and Bouchard, 2005).

Gene and environment effects are difficult to measure since they are dynamic and evolving (**Figure 1**). Similar to baseline VO_{2max} as discussed previously, the ability to improve VO_{2max} has a strong genetic component. In a twin study, total power output during a 90-min maximal cycle ergometer test was monitored before and after 15 weeks of training (Hamel *et al*., 1986). Members of the same MZ pairs were shown to be significantly more alike ($r = 0.83$) than unrelated individuals in their VO_{2max} increase following exposure to the above training programme (Hamel *et al*., 1986; Prud'homme *et al*., 1984; Simoneau *et al*., 1986). The intrapair correlations for the resemblance in the VO_{2max} changes with training range from 0.65 to 0.70. Family studies have also shown that there was over 2.5 times or more variance between families than within families in the VO_{2max} response variance. **See also**: Gene–Environment Interaction

Molecular Insights into Athletic Performance

Heritability is one way to describe in broad terms the proportion of phenotypic variance attributable to underlying genetic factors. However, a top-down approach such as this cannot reveal the actual genetic factors involved. To understand better the responsible genes and how they work requires a bottom-up approach, that is from genotype to phenotype. Since current evidence suggests that athletic performance has a multifactorial basis, the major strategies needed for gene discovery are linkage analysis and genetic association studies (also called case-control studies). **See also**: Linkage and Association Studies

Linkage analysis and association studies

Linkage analysis is a family-based strategy that looks for co-segregation of genetic markers with the phenotype and different alleles of a gene on a chromosome. Linkage analysis can identify broad genomic regions based on identity by descent. One such genome-wide linkage analysis has been performed to screen the genes contributing to human variation in VO_{2max} in the untrained state and its trainability (Bouchard *et al*., 2000). This study found suggestive linkages for baseline VO_{2max} at chromosomes 4q12, 8q24, 11q15 and 14q21.3. Suggestive loci were also identified on chromosomes 1p11.2, 2p16, 4q26, 6p21 and 11p14.1 for the change in VO_{2max} in response to a 20-week endurance training programme. Although useful, the linkage analysis approach has limited capacity for detecting genes with a modest effect and low penetrance.

For the past 10–15 years gene discovery in complex traits has increasingly turned to an alternative approach involving candidate gene association studies. These have usually been restricted to a few dozen genes. The aim in genetic association studies is to detect trait-related alleles that are more or less common in an extreme group such as elite athletes than they are in the general population. In contrast to linkage analysis, the association study has more power to detect modest effects predicted for complex traits. Gene-centred association studies can also be performed to analyse further linkage-identified loci. For example, the earlier described genome-wide linkage analysis (Bouchard *et al*., 2000) was not convincing but it did identify five suggestive loci for the VO_{2max} changes in response to an endurance training programme. Our research group took the poorly defined genomic region of chromosome 2p16 and searched for potential genes using a computer-based *in silico* approach (Yu, 2008). We were able to identify 40 putative genes for this region. Nearly half were unknown at the time and remainder was scrutinised for their functions. From this, four plausible candidate genes emerged

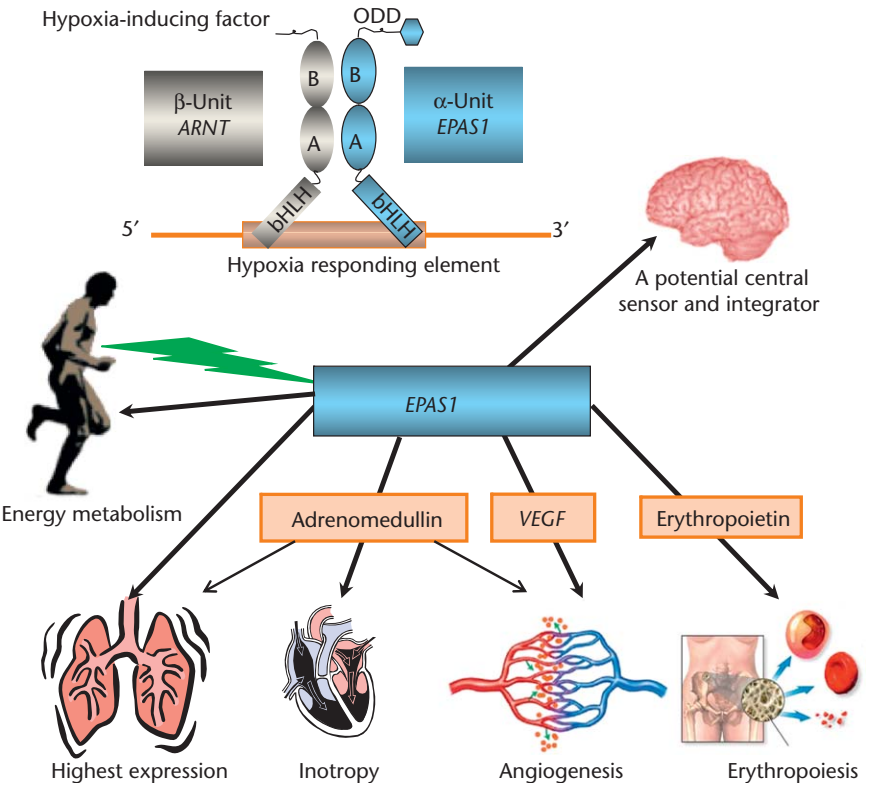

Figure 2 Potential molecular mechanisms by which *EPAS1* can influence athletic performance. The *EPAS1* gene is the α-unit of the hypoxia-inducing factor and dimerises with the β-unit – aryl hydrocarbon receptor nuclear translocator (*ARNT*). *EPAS1* has an oxygen-dependent degradation (ODD) unit, which facilitates the protein degradation in the presence of oxygen. Hypoxia-inducing factor via the basic helix–loop–helix (bHLH) domains interacts with the hypoxia responding element in its down-stream target genes. Endurance training and competition are likely to cause oxygen deficiency in the body, which can subsequently stimulate the expression of the *EPAS1* gene. This represents a gene–environment interaction. *EPAS1* expression in brain can be a potential central sensor. Its highest expression in the lungs enhances the efficient oxygen intake. *EPAS1* can improve cardiovascular function via the adrenomedullin gene; enhance angiogenesis by upregulation of both adrenomedullin and vascular endothelial growth factor (*VEGF*) genes; and increase oxygen-carrying capacity through its stimulatory effect on the erythropoietin gene. *EPAS1* also enhances energy metabolism in skeletal muscle (Oie *et al.*, 2010; Yanagawa and Nagaya, 2007). The *EPO* gene is the down-stream target gene of *EPAS1* and is relevants to oxygen-carrying capacity as previously discussed. These biological effects of *EPAS1* would be particularly beneficial for endurance athletes.

(Yu, 2008). The endothelial PAS domain protein 1 (*EPAS1*) gene was finally selected as the most likely candidate because it had clear interaction with the environment through oxygen sensing and influenced down-stream gene expression through transcriptional regulation.

EPAS1 candidate gene

A genetic association study using *EPAS1* as the candidate gene was performed involving 492 elite Australian athletes (cases) and 444 matched normal subjects (controls) with 12 selected deoxyribonucleic acid (DNA) markers called SNPs (single nucleotide polymorphisms). This confirmed that the *EPAS1* gene is, at least, one of the training-responsive genes at 2p16 (Henderson *et al.*, 2005). One haplotype, consisting of four SNPs in the *EPAS1* gene's first intron, was over-represented in athletes involved in high-intensity maximal exercise (i.e. power-time maximum) with odds ratio of 1.75. Another haplotype of the same region differentiated the athletes involved in a sustained steady-state effort from those of power-time maximum. As suggested by the odds ratio (<2.0), the haplotype effect is quite modest, which is consistent with most genetic effects observed in complex traits or diseases. Is *EPAS1* a plausible gene and likely to contribute to athletic ability? The answer is yes because this gene has relevant functions as demonstrated by its gene–environment and gene–gene interactions (**Figure 2**).

ACE candidate gene

Another extensively studied gene is the angiotensin I converting enzyme (*ACE*) gene. *ACE* is an important member of the renin-angiotensin system and so plays a key role in cardiovascular function. The presence or absence of a 287-bp Alu repeat sequence in intron 16 of the *ACE* gene, characterises the I-allele (insertion) and D-allele (deletion), leading to three genotypes (II, ID and DD). We genotyped the ACE I/D polymorphism in 64 Australian rowers participating in pre-Olympics selection trials. We found that the *ACE* gene was associated with athletic performance (Gayagay *et al.*, 1998) with the I-allele and the II genotype

over-presented in these caucasian elite endurance athletes. Their elite status can be confirmed as 41 won rowing medals in the 1996 Olympics. This study was followed by a further report demonstrating an excess of I-alleles and II genotypes in 33 British mountaineers who had ascended to 8000 m without oxygen (Montgomery *et al*., 1998). Subsequently, this gene has been extensively studied in relation to athletic performance and has created considerable debate and controversy with many studies failing to replicate the results of others. The problem with reproducibility is not uncommon in the association-type studies because the gene effects are small and so phenotypes can be inaccurate. It is also often difficult to control for elite status, homogeneous sporting discipline and the effects of ethnic admixture (Woods, 2009).

ACTN3 candidate gene

The association study involving human α-actinin 3 (*ACTN3*) gene has also attracted a lot of interest. *ACTN3* is a structural component of the Z line of the sarcomere and plays a key role in the maintenance and regulation of the cytoskeleton. A coding SNP (cSNP, rs1815739) is found in *ACTN3*. This converts the arginine (R, CGA) at amino acid position 577 into a premature stop codon (X, TGA). This cSNP appears to be nonpathogenic since it is commonly found with a frequency of up to 18% in Caucasians. A candidate gene-based association study with R577X polymorphism was initially performed in 2003 (Yang *et al*., 2003) with the same cohorts of Australian elite athletes as the *ACE* and *EPAS1* studies (Gayagay *et al*., 1998; Henderson *et al*., 2005). The sprint/power athletes had a significantly lower frequency of the XX genotype (5% compared with 18% in controls) and a higher frequency of the RR genotype (50% compared with 30% in controls). This distribution was more prominent in females and in sprint/power Olympians (25 males and 7 females), none of whom had the XX genotypes.

The XX-deficient marker in sprint/power athletes has now been reproduced in Finnish, American, Greek, British and Russian athletes (Druzhevskaya *et al*., 2008; Niemi and Majamaa, 2005; Papadimitriou *et al*., 2008; Roth *et al*., 2008; Santiago *et al*., 2008). Interestingly, a recent association study (Eynon *et al*., 2010) found that the combination of *ACTN3* RR genotype with the PP (P582S, rs1154965) genotype of the hypoxia inducing factor 1A (*HIF1A*) gene was significantly higher in sprinters with the odds ratio of 2.25. In contrast, elite endurance athletes had relatively higher frequency of the XX genotype (Yang *et al*., 2003).

Genome-wide association studies (GWAS)

The association studies described earlier were directed to one or several candidate genes and so examined only a minute fraction of the genome. Recently, GWAS looking at the entire genome have become feasible because of developments in genotyping technology and bioinformatics. This approach does not require a hypothesis about the exact position of the relevant SNP to detect an association with a genetic trait. Another important development for GWAS has been the finding that there is extensive linkage disequilibrium (LD) across the genome which meant that a smaller set of DNA markers (SNPs) can be used and they will provide information not only about the variants tested but also about all other variants that are in strong LD with the ones tested. Even with the GWAS approach, it still requires thousands of cases with an extreme phenotype and an equal or preferably double the number of controls to boast the statistical power in detecting genes that have a small phenotypic effect. The large number of controls required would be limited by the costs although costs are falling. However, it would not be possible to collect around a thousand elite athletes in the same sport let alone with the same ethnic background. Therefore, to date, there have been no GWAS looking at athletic performance. **See also**: Genome-Wide Association Studies

A genome map of human performance

The human gene map for performance and health-related fitness phenotypes has been published seven times since 2001. This map is derived from a summary of published data. The most recent map collected 214 autosomal gene entries and quantitative trait loci plus seven other loci on the X-chromosome, as well as 18 mitochondrial genes (Bray *et al*., 2009). Although not all that is on the map is accurate because many of the studies particularly association ones have not been replicated, it gives a taste of how heterogenous are likely to be the genetic components involved in human performance. **Table 1** lists the various entries in the genome map of human performance in terms of where they are found in the chromosomes.

Functional analysis of gene activity

After finding a likely gene in an association study, the critical next step is to show how a change in the gene can alter the phenotype. The *ACTN3* story has taken this step by making a knockout mouse model. A potential molecular mechanism has been suggested in the *actn3* knockout mice that α-actinin 3 deficiency is associated with a shift in characteristics of fast, glycolytic IIb muscle fibres towards a slow phenotype. Along with the shift, there is a reduction in muscle mass and fibre diameter, slower contractile properties, and an increase in fatigue resistance and oxidative metabolism efficiency. These changes are detrimental to sprint performance, but there could be a 'trade-off' in performance traits for speed versus endurance (MacArthur *et al*., 2008).

The ability to take the *actn3* model on to *in vivo* functional studies is perhaps not surprising because the mutation in the *ACTN3* gene results in a significant reduction in gene output. In contrast, the other genes implicated in athletic performance are likely to have more subtle effects

Table 1 Summary of chromosomal location of genes and markers for human performance and health-related fitness phenotypes 2006–2007[a]

Chromosome	Loci[a]	Chromosome	Loci[a]	Chromosome	Loci[a]
1	28	9	7	17	9
2	15	10	12	18	10
3	11	11	18	19	7
4	12	12	8	20	5
5	7	13	9	21	1
6	12	14	8	22	3
7	19	15	7	X	7
8	3	16	5	Y	0

[a]Loci include actual genes or DNA markers such as SNPs.
Source: Bray *et al*. (2009).

and it might not be possible to test these changes through the traditional *in vitro* or *in vivo* approaches such as the mouse model just described.

Epigenetic inheritance

Many studies have demonstrated significant heritability for human performance characteristics including motor function, neuromuscular coordination, muscle fibre-type distributions, cardiovascular function, glucose metabolism, substrate utilisation, pulmonary function, as well as hormones and hormonal response to training. However, what has not been explained is how these genetic contributions arise. Are they reflecting changes in genes or genetic regulatory elements controlling how genes function as demonstrated by the *EPO* receptor example? Little is known because athletic ability is a complex trait and direct gene effects, let alone how they interact with the environment, are difficult to define or measure.

Interest is also shifting to alternative mechanisms for mediating genetic effects such as epigenetics. Although MZ twins have a near to identical genome, the potential for superimposed epigenetic effects can modulate the genetic effects and so ultimately the phenotype. An example of this might be found in a case study involving a set of MZ twins who reached the elite level in walking. A significant difference in the twin's personality profile was reported and it was suggested that this might explain their different outcomes for the 20-km walking race with one twin consistently performing at the highest level and winning, whereas the second twin was much less successful although showing the ability to perform as an elite athlete (Klissouras and Pigozzi, 2009). External factors such as training, diet, even uterine nutrition can make an imprint on genes and influence the epigenetic switches. Thus, epigenetics could lead to beneficial or suboptimal responses regardless of the underlying genotypes. The role for epigenetics in athletic performance remains to be identified but it is a plausible explanation for variability and perhaps 'trainability' of athletes. **See also**: Epigenetic Variation in Humans

Copy number variation

Apart from epigenetics, another genetic mechanism needs to be explored to see if it contributes to the athletic phenotype. This is variation in the genome brought about by changes in copy number, that is it is now recognised that two individuals differ more in gene copy number than in their actual nucleotide sequence (Sebat, 2007). Copy number variants could play a role in athletic performance, particularly if the variants are found in the known molecular pathways related to the trait. **See also**: Copy Number Variation in the Human Genome

Applications of Genetic Knowledge

Predictive genetics is well established in clinical practice and works because changes in DNA that are inherited (germline DNA) can be detected at any time in life including before these changes lead to clinical disease. Examples of predictive genetics include testing for Huntington disease in at-risk adults. Predictive testing can be undertaken decades before clinical changes are detectable. Recently the concept of avoiding drug-related complications or optimising the dose of a drug depending on an individual's genetic makeup is being promoted through pharmacogenetics. Predictive genetics in terms of athletic performance is considered potentially relevant in two major areas.

Talent search and training

Not surprisingly in the very competitive sporting environment, the question is asked whether predictive genetics could be used in talent search to identify potential elite athletes, particularly at a young age so that the appropriate training can be started early? Could such prediction also be extended to an even more difficult question and that is how likely will a selected athlete respond to a training programme, that is can improvement to training be predetermined? A related question is: can training be individualised to reflect an individual's genetic makeup? As well as improving outcomes, the concept of an

individualised training programme is attractive because of the potential to avoid unnecessary fatigue and even premature 'burn out', which comes from excessive training without the expected gains.

The answers to these questions are 'yes' but only if genes can be identified and their effect on the phenotype understood. So far the complexities at the genome, and perhaps epigenome levels, are such that definitive answers are awaited. Objections based on ethical and social considerations have also been raised about the use of genetic information in talent search but it is basically no different to the current approach using talent search programmes based on anthropometric measurements, physiological data and track records and attempting to pick 'winners'. There are clearly issues about privacy and what else could be sought through DNA testing but if conducted appropriately a DNA test might provide a lot of useful information.

The *ACTN3* gene story illustrates how inappropriate DNA testing can highlight ethical and social concerns. This gene test is now commercially available as a marker for 'athletic ability' and has been targeted in some advertising to young children. This is unfortunate because the scientific data are solid but based on population studies as well as an animal model, but little if anything is known how this single gene change will impact on an *individual's* ability given the other factors (genetic and environment) that are also important.

Injury prevention

Sports-related injuries are common and can affect both performances as well as shortening the athlete's professional lifetime. Some of these injuries are directly related to the sport but others may also reflect an underlying genetic predisposition. An example would be ankle injuries to the Achilles tendon. These can be caused by many factors including likely genetic components. In one study, the *COL5A1* gene was investigated as a candidate because it is known that mutations in this gene lead to a severe connective tissue disorder called Ehlers–Danlos syndrome. Although only preliminary evidence, the association study suggested that some individuals did have subtle gene changes that affected the expression of this gene and so collagen would not be as strong. These individuals would then be more likely to have injuries to this tendon (Mokone *et al.*, 2006).

Summary

Steady but slow progress has allowed the identification of a number of genes likely to be involved in human performance. The genetic approaches have now expanded to involve genomic-based research strategies allowing multiple genes to be investigated simultaneously. A limitation remains the ability to detect small gene effects and to understand how the environment can influence gene function. As these challenges are overcome we will know more about athletic ability and how it can be influenced by heritability. As is already happening, this will also highlight a number of ethical, legal and social issues that the community as well as the scientists will need to consider to ensure that genetic information is used appropriately.

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