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REVIEW ARTICLE

Daniel G. MacArthur · Kathryn N. North

# Genes and human elite athletic performance

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**Abstract** Physical fitness is a complex phenotype influenced by a myriad of environmental and genetic factors, and variation in human physical performance and athletic ability has long been recognised as having a strong heritable component. Recently, the development of technology for rapid DNA sequencing and genotyping has allowed the identification of some of the individual genetic variations that contribute to athletic performance. This review will examine the evidence that has accumulated over the last three decades for a strong genetic influence on human physical performance, with an emphasis on two sets of physical traits, viz. cardiorespiratory and skeletal muscle function, which are particularly important for performance in a variety of sports. We will then review recent studies that have identified individual genetic variants associated with variation in these traits and the polymorphisms that have been directly associated with elite athlete status. Finally, we explore the scientific implications of our rapidly growing understanding of the genetic basis of variation in performance.

## Introduction

Elite athletes, viz. athletes who have competed at a national or international level in their chosen sport, represent a rare convergence of genetic potential and environmental factors (Myburgh 2003). There is no question that environmental factors such as training and nutrition are essential for the development of an elite athlete. However, these factors alone are not sufficient; most of us could never achieve elite athlete status, however hard we trained. Just as genetic predisposition plays a major role in determining one's susceptibility to multifactorial diseases such as diabetes and cancer, elite athletic performance is a complex fitness phenotype substantially determined by genetic potential.

D. G. MacArthur · K. N. North (✉)
Institute for Neuromuscular Research,
Children's Hospital at Westmead, Locked Bag 4001,
Westmead, Sydney, NSW 2145, Australia
E-mail: kathryn@chw.edu.au
Tel.: +61-2-98453011
Fax: +61-2-98453082

D. G. MacArthur · K. N. North
Discipline of Paediatrics and Child Health,
Faculty of Medicine, University of Sydney,
Sydney, Australia

## Heritability of performance-related traits

The first strong evidence for a genetic influence on physical performance came from studies that compared closely related individuals (twin pairs and nuclear families) with unrelated subjects to estimate the heritability (a composite measure of genetic and shared environmental factors) of variation for many aerobic fitness-related and cardiac performance-related traits (reviewed by Bouchard et al. 1997). Much of this data comes from the HERITAGE (health, risk factors, exercise training and genetics) Family Study of 130 two-generation families who were assessed in the sedentary state and in response to a standardised 20-week aerobic exercise-training program (Bouchard et al. 1995). Heritability ranged from 20% to 75% for a number of factors, including maximal oxygen uptake in the sedentary state (Bouchard et al. 1998) and in response to training (Bouchard et al. 1999), oxygen consumption and power output during submaximal exercise (Pérusse et al. 2001), oxygen uptake at the ventilatory threshold (Gaskill et al. 2001), stroke volume and cardiac output during submaximal exercise (An et al. 2000) and the exercise heart rate response to training (An et al. 2003c).

Significant genetic influences have also been identified for measures of skeletal muscle strength and performance, including the response of oxoglutarate dehydrogenase activity to training (Thibault et al. 1986),

muscle adaptation to endurance exercise (Hamel et al. 1986), vertical jump height as a measure of explosive power (Maes et al. 1996), various measures of muscle strength and their response to training (Thomis et al. 1998), anaerobic capacity and explosive power (Calvo et al. 2002), average size of type I (slow oxidative) fibres in the sedentary state and maximal activity of energy production enzymes both in the sedentary state and in response to training (Rico-Sanz et al. 2003b). The genetic contribution to variation in the relative proportions of skeletal muscle fibre types is estimated as lying between 40% and 50% (Simoneau and Bouchard 1995).

Studies by segregation analysis, which involves following the inheritance pattern of specific phenotypes in nuclear families, suggest that single major genes contribute to a substantial fraction of phenotypic variance in at least some performance-related traits. For example, single genes are reported to account for more than 40% of the variance in oxygen uptake at the ventilatory threshold (Feitosa et al. 2002), for 30% of baseline exercise heart rate and for 27% of the variance in the exercise heart rate response to training (An et al. 2003a). These findings have encouraged attempts to identify genetic loci and specific polymorphisms that impact human physical performance.

## Cardiorespiratory and skeletal muscle performance genes

### Genome-wide linkage analyses

Genome-wide linkage analysis has proved invaluable in the identification of causative genes in a vast array of human diseases and other traits (Baron 2001) and have recently been used to identify a number of genetic regions showing significant associations with variation in human physical performance traits. Studies utilising the HERITAGE family cohort (Bouchard et al. 1995) have identified suggestive linkage peaks associated with variation in maximal oxygen uptake (Bouchard et al. 2000; Rico-Sanz et al. 2004), maximal power output (Rico-Sanz et al. 2004), exercise stroke volume and cardiac output (Rankinen et al. 2002a) and blood pressure both in resting subjects (Rice et al. 2002b) and following exercise (Rankinen et al. 2001a). Other studies have identified linkage peaks associated with body composition and fat distribution (Chagnon et al. 2001; Rice et al. 2002a) and glucose and insulin metabolism-related traits (An et al. 2003b).

### Genetic associations with performance-related traits

Genetic association studies are commonly used to test the influence of variation at a candidate locus on specific performance traits. Association studies fall into two major categories: case-control studies involving comparisons of genotype frequencies in cohorts of sedentary controls and elite athletes (discussed in the next section) and cross-sectional association studies, which examine differences in performance-related phenotypic measurements between individuals with different genotypes. The process of identifying and genotyping candidate genetic variations for performance-related traits has accelerated over the last 5 years and the results are catalogued in the 2001, 2002, 2003 and 2004 releases of the human gene map for performance and health-related fitness phenotypes (Pérusse et al. 2003; Rankinen et al. 2001b, 2002b, 2004; Fig.1).

Genetic association studies must always be interpreted with caution (Lewis 2002; Romero et al. 2002). As with any statistical analysis, there is a non-trivial possibility of a false positive result attributable to chance, particularly in studies involving multiple gene-trait analyses or the splitting of cohorts into separately analysed sub-groups (Ioannidis 2003). In addition, studies that have not been carefully controlled for ethnic background and other potential confounding factors carry an additional risk of false positive results (Lewis 2002). Finally, a substantial possibility always exists that the actual causative variant is not the genotyped polymorphism but some other variant in strong linkage disequilibrium. Therefore, all reported genetic associations should remain tentative until there is (1) a biologically plausible and well-supported mechanism by which the variant could influence the trait in question and (2) replication of the association in other independent cohorts. We will restrict discussion in this section to those genes for which there has been independent replication of the finding of a positive genetic association.

Three candidate genes have been reported to be associated with cardiorespiratory function in multiple independent studies. The first of these is the *CKMM* gene, which encodes the cytosolic muscle isoform of creatine kinase, an enzyme responsible for the rapid regeneration of ATP during intensive muscle contraction (Echegaray and Rivera 2001). A positive association between muscle creatine kinase protein variants and exercise performance was first reported by Bouchard

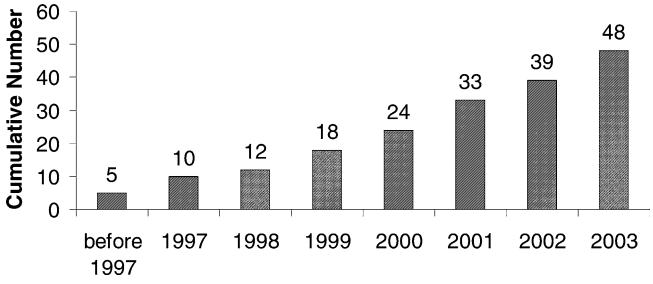


**Fig. 1** Cumulative number of candidate genes associated with health or physical fitness phenotypes each year from 1997 to 2003, as reported by Rankinen et al. (2004). All loci reported to have a significant association with one or more performance or health-related fitness traits (excluding exercise intolerance) are grouped under the year in which the first significant association study was published

et al. (1989). The same group later demonstrated a highly significant association between a restriction fragment length polymorphism (RFLP) in *CKMM* and the response of maximal oxygen uptake to a 20-week endurance training program in 240 unrelated members of the HERITAGE family cohort (Rivera et al. 1997a) and subsequently showed strong evidence of genetic linkage between *CKMM* and the training response of $VO_{2max}$ in 495 individuals from 98 nuclear families (Rivera et al. 1999). However, it is interesting to note that no association was found between the same variations and elite endurance athlete status in another study by the same group (Rivera et al. 1997b).

The M235T missense polymorphism in the angiotensinogen gene *AGT* showed a positive association with several measures of cardiorespiratory performance in 61 healthy postmenopausal women, including 24 elite endurance athletes (McCole et al. 2002), and with left ventricular mass (LVM) in two separate studies on elite endurance athletes: a highly significant association in a cohort of 50 male and 30 female athletes (Karjalainen et al. 1999) and a weak association in a combined analysis with genotype at the *ACE* I/D polymorphism in 83 male athletes (Diet et al. 2001). No evidence of an association was identified in two cohorts of untrained individuals (Linhart et al. 2000; Kauma et al. 1998). Similarly to *CKMM*, the *AGT* M235T variant was not found to be significantly associated with elite endurance athlete status in a case-control study of 60 elite endurance athletes and 400 healthy controls (Alvarez et al. 2000).

Three recent studies have identified associations between missense polymorphisms in the *ADRB2* gene, which encodes the $\beta_2$-adrenergic receptor, and cardiorespiratory performance traits. Analysis of a cohort of 19 sedentary, 20 active and 24 elite endurance athletic postmenopausal women demonstrated significantly lower maximal $O_2$ consumption in women homozygous for the Glu27 allele than in carriers of the Gln27 allele (Moore et al. 2001). Two later studies examined the phenotypic effects of another polymorphism, Arg16Gly: in a study of 267 normotensive adults, Gly16 homozygotes demonstrated higher performance than Arg16 carriers in a number of measures of cardiac left ventricular function (Tang et al. 2003), whereas in a group of 31 healthy adults, Gly16 homozygotes had a significantly greater heart rate response to exercise than Arg16 homozygotes (Eisenach et al. 2004).

Significant genetic associations with variation in cardiorespiratory function have been reported in single studies for several other polymorphisms. These include RFLPs in several mitochondrial genes (Dionne et al. 1991), specific alleles at the *HLA-A* locus (Rodas et al. 1997), RFLP haplotypes of the $Na^+$ –$K^+$ -ATPase α2 gene *ATP1A2* (Rankinen et al. 2000b), common missense variants of the apolipoprotein E gene *APOE* (Thompson et al. 2004) and the common Gly482Ser missense polymorphism in the peroxisome proliferator-activated receptor $\gamma$ coactivator 1 (PGC-1α) gene *PPARGC1* (Franks et al. 2003). For cardiac performance traits, significant associations have been reported for an intronic polymorphism in the peroxisome proliferator-activated receptor α gene *PPARA* (Jamshidi et al. 2002), and for a common nonsense polymorphism in the adenosine monophosphate deaminase 1 gene *AMPD1* (Rico-Sanz et al. 2003a).

To date, only one gene has shown statistically significant associations with skeletal muscle function in multiple independent studies: the vitamin D receptor gene *VDR*. A *Bsm*I RFLP corresponding to a single-nucleotide polymorphism (SNP) in the final intron of the *VDR* gene was significantly associated with quadriceps and grip strength in 307 non-obese women aged over 70 years (Geusens et al. 1997). The same RFLP and a closely linked length polymorphism in a poly-A repeat were analysed in a cohort of 175 healthy women aged 20–39 years, with a weakly significant association with hamstring strength being identified (Grundberg et al. 2004). However, this study failed to replicate the association of the *Bsm*I RFLP with quadriceps and grip strength reported by Geusens et al. (1997).

Several other genetic variations linked to skeletal muscle function have been identified in cohorts of elderly individuals. These variations include a null allele in the *CNTF* gene encoding ciliary neurotrophic factor (Roth et al. 2001), a SNP in the 3′-untranslated region of the CNTF-specific α-receptor subunit gene *CNTFR* (Roth et al. 2003), an *Apa*I RFLP in the *IGF2* gene encoding insulin-like growth factor II (Sayer et al. 2002), the K153R amino acid polymorphism in the myostatin gene *GDF-8* (Seibert et al. 2001) and a SNP in the promoter region of the *COL1A1* gene encoding the type I collagen $\alpha_1$ chain (van Pottelbergh et al. 2001).

## Case-control studies of candidate genes in elite athletes

### *ACE* I/D polymorphism

A common polymorphism in the angiotensin converting enzyme I gene (the *ACE* I/D variant) represents one of the first characterised, and certainly the most widely studied, genetic variant in the context of elite athlete status and performance-related traits. The features and known biological functions of ACE have been summarised in a recent review (Coates 2003). The human *ACE* gene has two alleles differing in the presence (insertion or I allele) or absence (deletion or D allele) of a 287-bp *Alu* repeat element in intron 16 (Rieder et al. 1999). The I allele is associated with lower *ACE* activity in both serum (Rigat et al. 1990) and tissue (Danser et al. 1995) compared with the D allele. The health implications of this polymorphism have been intensively explored in more than 100 separate studies; the homozygous DD genotype has been associated with disorders as diverse as heart disease (Danser et al. 1995), systemic lupus erythematosus (Pullmann Jr et al. 1999), obstetric cholestasis (Heiskanen et al. 2001), affective

disorders (Arinami et al. 1996), the pathological outcomes of immunoglobulin A nephropathy (Chen et al. 1997) and meningococcal disease in children (Harding et al. 2002).

Several case-control studies have shown a significant association between *ACE* genotype and elite athlete status. The first such study reported an increased frequency of the I allele in 25 British high-altitude mountaineers compared with 1,906 sedentary controls (Montgomery et al. 1998) and, concurrently, similar results were reported in 64 Australian endurance rowers compared with 114 healthy controls (Gayagay et al. 1998). Conversely, an increased frequency of the D allele was found in 35 elite short-distance ( ≤ 400 m) swimmers (Woods et al. 2001), suggesting that the two alleles at the *ACE* I/D polymorphism have differing effects on athletic performance, with the I allele favouring endurance ability and the D allele improving performance in sprint or power events. Two further studies have supported this interpretation. A cohort of 91 British Olympic-standard runners displayed a significant linear trend between *ACE* genotype and length of specialist event, with a skew towards the D allele for events of ≤ 200 m and a skew towards the I allele for events of ≥5,000 m (Myerson et al. 1999). A later study of 141 elite Russian athletes, divided into three groups according to the average duration of their specialist event, showed a significant excess of the D allele in 30 short-distance athletes (events lasting less than 1 min) and a similar excess of the I allele in 35 middle-distance athletes (events lasting 1–20 min; Nazarov et al. 2001). Surprisingly, a relatively large group of 76 long-distance athletes had genotype frequencies indistinguishable from controls, rather than the expected skew towards the increased frequency of the I allele. This puzzling result may be partly attributable to each group containing athletes from multiple different sporting disciplines, thereby introducing heterogeneity that may have obscured an association.

Whereas the presence of so many positive association studies suggests that there is an influence of *ACE* genotype on athletic performance, it should be noted that all of the studies described above consisted of comparatively small cohorts and that two sizeable studies have found no evidence for the association. An early study by Taylor et al. (1999) compared 120 mixed elite athletes with 685 healthy controls and found no difference in *ACE* genotype frequencies between the two groups. This study was compromised, however, by the sheer heterogeneity of the athlete cohort, which included hockey players, cyclists, skiers, track and field athletes, swimmers, rowers, gymnasts and ''others,'' many of whom did not clearly fall into either pure sprint or endurance categories. Given the apparently opposing directions of effect of the D and I alleles on performance in sprint and endurance events, it is not surprising that such a mixed cohort failed to reveal an association. A larger and better-controlled study was carried out by Rankinen et al. (2000c) who examined genotype frequencies in 192 males elite endurance athletes with a maximal oxygen uptake of ≥75 mL/kg per minute compared with 189 sedentary controls and found no difference in genotype frequencies between the two groups. However, despite the careful selection of athletes competing in endurance events, the athlete cohort was still drawn from a heterogeneous range of sporting disciplines, including cross-country skiing, biathlon, long-distance and middle-distance running and road cycling.

These case-control studies, although conflicting in their conclusions, fit into a general pattern: the studies that obtained a positive association were generally relatively small studies on well-defined athlete cohorts, whereas the negative studies were larger in size but contained more heterogeneous athlete groups. Whereas the balance of evidence appears to favour the notion that some association exists between *ACE* genotype and elite athlete status, the methodological differences between the positive and negative studies make it difficult to draw firm conclusions.

A number of mechanism(s) exists by which *ACE* expression might influence athletic performance. Initially, the influence was proposed to act on cardiorespiratory function, a hypothesis supported by a study in postmenopausal women suggesting that *ACE* genotype influenced maximal oxygen uptake (Hagberg et al. 1998), which is a reasonable predictor of endurance athlete performance (Bassett and Howley 2000; Myburgh 2003). However, in a study of 476 sedentary Caucasian subjects there was no evidence for an association between *ACE* genotype and any of 54 measures of pre-training cardiorespiratory function (Rankinen et al. 2000a). A later study (Woods et al. 2002) found no link between the *ACE* I/D polymorphism and the cardiorespiratory response to training in 58 army recruits. A number of studies have linked the *ACE* I/D polymorphism with various cardiac diseases, although many of these associations remain contentious (for reviews, see Crisan and Carr 2000; van Berlo and Pinto 2003). The association between *ACE* genotype and left ventricular growth in response to exercise, both in diseased patients and in elite athletes, is slightly better established (van Berlo and Pinto 2003). Significant associations between the D allele of *ACE* and LVM have been reported in several studies of athletes (Fatini et al. 2000; Hernández et al. 2003; Nagashima et al. 2000; Rizzo et al. 2003) and individuals exposed to physical training (Montgomery et al. 1997), although, in other athlete cohorts, the association between the *ACE* D allele and LVM was only significant in combination with other genetic variants (Diet et al. 2001) or was not identified at all (Karjalainen et al. 1999). The association does not appear to be present in untrained healthy controls (Kauma et al. 1998; Linhart et al. 2000) suggesting that any influence of *ACE* genotype on cardiac function involves an interaction between genotype and training.

The *ACE* I/D polymorphism could also influence athletic performance via local effects on skeletal muscle function (Jones and Woods 2003). The I allele has been

associated with significantly greater improvements in muscle endurance (Montgomery et al. 1998) and efficiency of muscle contraction (Williams et al. 2000) in response to training, and with an increased proportion of type I (slow) fibres in the vastus lateralis muscle in untrained individuals (Zhang et al. 2003). In contrast, the D allele has been associated with a greater increase in quadriceps strength in response to a 9-week isometric strength-training program (Folland et al. 2000). Jones and Woods (2003) suggest that the I allele boosts endurance performance through an increase in skeletal muscle efficiency, perhaps in part because of effects on fibre type proportions (Zhang et al. 2003), whereas the D allele may enhance sprint/power activity through an increase in muscle strength, potentially via the muscle hypertrophic effects of increased angiotensin II (Jones and Woods 2003).

### Other variants linked to elite athlete status

Several studies have been carried out on associations between elite athlete status and genes for adrenergic receptors. A weak association ($0.05 > P > 0.01$) between an RFLP in the $\alpha_{2a}$-adrenoceptor gene (*ADRA2A*) and elite endurance athlete status was identified in a cohort of 148 Caucasian male elite endurance athletes and 148 Caucasian sedentary male controls (Wolfarth et al. 2000). The same study found no evidence for an association between athlete status and an RFLP in the $\beta_2$-adrenoceptor gene *ADRB2*, whereas a later study of a missense polymorphism (Gln27Glu) in the *ADRB2* gene showed slightly different genotype frequencies between a cohort of 39 sedentary and active postmenopausal women and a group of 24 postmenopausal female elite endurance athletes (Moore et al. 2001). Although Moore et al. (2001) did not explicitly compare genotype frequencies between the two groups, their data demonstrated a small but significant difference (exact Pearson's $\chi^2$ test, $P = 0.036$). The Glu/Glu genotype was less common in the athlete group and was weakly associated with lower maximal oxygen uptake and higher body mass index values (Moore et al. 2001).

More recently, a correlation was demonstrated between a 9-bp insertion/deletion polymorphism (denoted +9/−9) in exon 1 of the bradykinin $\beta_2$ receptor gene *BDKBR2* and running distance in 81 Olympic-standard track athletes (Williams et al. 2004). The study showed a weakly significant linear trend of increasing frequency of the −9 allele with running distance in the athletes ($P = 0.04$ for comparison of ≤ 5,000 vs. ≥5,000 m) and a more highly significant trend in combination with *ACE* I/D allele frequencies ($P = 0.001$). The *BDKBR2* genotype alone and in combination with the *ACE* genotype also showed highly significant associations with a measure of the efficiency of skeletal muscle contraction in 115 healthy controls (Williams et al. 2004). There was no difference in *BDKBR2* genotype or allele frequencies between the Olympic athlete and control groups, possibly because of the same problems with the mixed athlete cohorts described above for the *ACE* association. The −9 allele of *BDKBR2* had previously been associated with higher transcriptional activity of the *BDKBR2* gene (Braun et al. 1996) and with a reduced left-ventricular growth response to a 10-week exercise program (Brull et al. 2001). Since the bradykinin $\beta_2$ receptor is a downstream effector of ACE, the finding of similar phenotypic associations for the *ACE* I/D and *BDKBR2* +9/−9 polymorphisms lends indirect support to the reported associations of *ACE* I/D with elite athlete status and other performance-related phenotypes and suggests that at least some of the effects of the *ACE* genotype on performance are related to downstream effects on the bradykinin pathway (Williams et al. 2004).

Recently, our group reported an association between elite athlete status and a common null polymorphism (R577X) in the *ACTN3* gene encoding the fast-fibre-specific Z line protein α-actinin-3 (North et al. 1999). R577X genotype frequencies were examined in 436 healthy controls compared with two cohorts of elite Australian athletes (107 sprint/power athletes and 194 endurance athletes; Yang et al. 2003). In sprint/power athletes, the frequency of the XX (α-actinin-3 deficient) genotype was approximately three-fold lower than the frequency in controls for both males ($P < 0.001$) and females ($P < 0.01$), suggesting that deficiency of α-actinin-3 impairs fast muscle fibre function. The opposite trend was seen in endurance athletes, who had significantly higher frequencies of the XX genotype than controls in females ($P < 0.05$) but not in males, suggesting that the absence of α-actinin-3 may be beneficial for endurance performance and that this effect is gender-specific. The negative association with sprint performance has biological plausibility given that the R577X polymorphism abolishes the expression of a fast-fibre-specific protein in skeletal muscle. However, comparatively little is known about the precise functions of α-actinin-3 (MacArthur and North 2004) and the association has not yet been independently replicated.

## Scientific implications

### Implications for sports science

The field of sports science encompasses the multitude of biological and environmental factors that determine athletic success. Ultimately, the findings and recommendations of sports scientists are used to guide the decisions of sporting bodies, coaches and athletes in two major areas: (1) talent identification, the process of selecting individuals with the potential of becoming champion athletes, and (2) the formulation of training programs that will maximise an individual's potential.

The process of talent identification could, in principle, be revolutionised by the discovery and characterisation of genetic variants that strongly influence athletic performance, with routine genetic analysis being added

to the existing battery of physiological, biochemical and psychological tests that form the current basis for selecting talented young athletes for further training. However, there is still no evidence that any of these variants have any substantial predictive value for prospectively identifying potential elite athletes. The detailed analyses of physiological parameters currently used actually represent integrated measurements of the effects of multiple genes and environmental influences on the phenotype, whereas genetic tests examine only single isolated determinants. This said, however, there may be situations in which genetic tests will provide invaluable predictive information: for instance, if a gene influences performance through a physiological pathway that is poorly characterised or difficult to measure directly or for analysis of the athletic potential of young children in whom some physiological tests are only weakly predictive of adult performance. We will only be able to evaluate the true benefits of genetic testing when geneticists and sports scientists can collaborate in large prospective cohort studies, which empirically determine the utility of genetic analyses in predicting future performance.

The potential benefit of genetic testing for optimising training programmes is also currently unclear, although selection of the optimal sport for a young athlete could benefit from genetic information. Several of the genetic factors for which positive associations have been reported in elite athlete cohorts (including both the *ACE* I/D and the *ACTN3* R577X polymorphisms discussed above) do not appear to influence whether someone can become an elite athlete but instead may influence in which sport an elite athlete can compete successfully. In the case of both *ACE* and *ACTN3*, one allele at the polymorphic site appears to favour performance in sprint or power events (the *ACE* D and *ACTN3* R allele), whereas the other appears to benefit the ability to compete in endurance sports (the *ACE* I and *ACTN3* X allele), findings that are consistent with the observation of ''trade-offs'' between sprint and endurance performance in elite decathletes (van Damme et al. 2002). This suggests that some genetic factors might not be useful in predicting whether a young amateur athlete has elite potential but may help to guide the choices of young athletes and their coaches in determining the events to which they would be best suited. In other cases, such as the finding that a variation in the *APOE* gene increases the probability of serious brain damage in boxers (Jordan et al. 1997), genetic testing might serve to steer young athletes with an increased genetic potential for serious injury away from particular sports.

However, the question of added utility still arises: can genetic testing provide an extra advantage over existing testing methods in determining sports selection in young athletes? It may well turn out that genetic testing provides no added benefit over the combination of self-guided sports selection and existing talent identification programmes based on physiological tests. As is the case for talent identification, this question can only be resolved by well-controlled prospective studies in large cohorts of young athletes.

## Implications for human health

Genetic variants influencing athletic performance are likely to have wider significance for human health and biology. In many cases, the variants associated with performance traits and elite athlete status are reasonably common in the general population; for instance, both the *ACTN3* 577X allele and the *ACE* I allele have frequencies of more than 30% in a variety of human populations (Mills et al. 2001; Sagnella et al. 1999). Whereas some variants may only have a phenotypic impact under specific environmental conditions, such as in response to the heavy physical training experienced by elite athletes, many genetic variations probably have a significant impact on the wide variation in physical traits within the general community.

If the influence of genetic variants on athletic performance were limited to traits such as muscle strength and running speed, their influence on daily life in most modern humans would be trivial. However, many performance-associated genetic variants are thought to influence physical traits such as energy metabolism, response to exercise and cardiovascular fitness, which are just as crucial to health and fitness in the general population as they are to the performance of elite athletes. Some ''athlete genes'' might have a positive effect on health; for instance, genetic variants that boost the response to training of athletes may well increase the health benefits of regular exercise in less athletic humans. Conversely, and perhaps counter-intuitively, factors that help athletes could actually have a strong negative effect on health in others; for instance, genes that allow a long-distance runner to conserve energy over long periods of intense physical activity might be disastrous to less physically active individuals, leading to obesity, diabetes and heart disease. Similarly, a polymorphism that boosts the cardiac function of sprinting champions may lead to a greater incidence of cardiac disease in the general population, as has been suggested for the D allele of the *ACE* gene (Crisan and Carr 2000; van Berlo and Pinto 2003). Thus, although the relationships will not always be simple, research into the genetic factors influencing physical fitness in elite athletes should boost our understanding of genetic influences on health in the general population.

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