Angiotensin-converting enzyme and human physical performance

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Abstract
Genes undoubtedly play a role in the development of a successful athlete. This view has flourished on anecdotes such as the observation of a child who displays the same aptitude for a particular sport as one of their parents, or a pair of sisters who both excel in the same discipline. However, the conclusions made from this type of observation have an obvious limitation: that similar environmental factors may be just as responsible as genetic inheritance in explaining the passage and sharing of talent between family members. Here, we review briefly the salient data showing that genes do play a role in athletic performance, and although the data examining the effect of specific genes are limited, we present data examining the role of the angiotensin-converting enzyme gene in human physical performance.

Keywords: ACE; gene; polymorphism; performance; exercise

Heritability of athletic performance phenotypes

Human musculoskeletal phenotypes are genetically influenced, with greater than 80% of the variation in human skeletal muscle mass being determined by genetics. Consistent with this, variation in strength exists between individuals, and twin studies suggest that 60–80% of individual variation in arm flexor strength and 29–65% of changes in concentric flexor strength are heritable. Similar data apply to bone; in human twin studies, heritability estimates of bone density at the femoral neck and lumbar spine are similar, ranging between 57 and 92%.

Human cardiovascular performance phenotypes have also been examined. Genetic variation accounts for 13–23% of heart rate variability in humans. Even greater indices of heritability have been seen for human blood pressure and pulse pressure. Consistent with these data, the heritability of human carotid artery stiffness is in the order of 20%. Finally, although several studies have conflicted in their conclusions while attempting to examine the heritability of human left ventricular (LV) mass, two larger studies have estimated the heritability of this phenotype to be at least 60%.

Such genetically influenced effects on musculoskeletal and cardiovascular form and function will combine to create more complex performance measures. Not surprisingly, variations in such measures are also genetically determined. For example, Bouchard et al. used a twin study design to show that about 40% of the inter-individual variance in VO2max (maximal oxygen uptake) is dependent on genetic heterogeneity.

Variation of the angiotensin-converting enzyme gene and LV growth

It is clear that many (if not all) performance phenotypes are heritable to varying degrees and although genes are obviously the building blocks of heritability, research attempts to identify the specific genes that alter performance are sparse. To date, many studies have examined the gene encoding angiotensin-converting enzyme (ACE) and so what follows is a brief review of some of the data that implicate this gene with performance.

ACE is a pivotal component in the renin-angiotensin system (RAS). Renin, produced in the kidney, cleaves the relatively inactive angiotensinogen to yield angiotensin I. Angiotensin I is converted into angiotensin II (Ang II) by ACE. Ang II is a potent vasoconstrictor when acting via its type I (AT1) receptor. In addition, Ang II encourages salt and water retention by releasing adrenal aldosterone. ACE also degrades bradykinin...
(BK). BK is a vasodilator when acting via its type 2 (BK2) receptor. Therefore, through Ang II production and BK degradation, increases in ACE activity have an overall effect in raising blood pressure.

In addition to circulating RAS, local RAS also exist. ACE at a local level may rate-limit the synthesis of Ang II in tissues such as skeletal muscle, the human myocardium, and adipose tissue. A common polymorphism of the angiotensin-converting enzyme (ACE) gene exists (with an allele frequency of ~50% in the UK), which results from either the absence (deletion or D allele) or the presence (insertion or I allele) of a 287-bp segment of DNA. The D allele is associated with significantly higher ACE levels in the circulation, as well as locally in tissues including the human myocardium.

In addition to its role in blood pressure regulation, ACE appears to influence LV growth. In animals, there are ample data to suggest that Ang II has growth-promoting effects on the myocardium via the AT1 receptor. In contrast, BK, through BK2 receptor stimulation, may inhibit LV growth. Thus, through Ang II production and BK breakdown, ACE appears to be a regulator of LV growth. The ACE gene I/D polymorphism has been used to examine the role of ACE in human cardiac growth.

Given the theoretical growth-promoting effects of Ang II on human LV muscle, we might expect higher ACE activity (as marked by the D allele of the ACE gene) to be associated with greater LV growth in response to exercise training. This appears to be the case. In 140 British Army recruits, LV mass was determined before and after a 10-week physical training programme. Mean change in LV mass in response to training (or ‘LV growth’) assessed using echocardiography was found to be +2.0, +38.5 and +42.3 g for II, ID and DD genotypes, respectively (P < 0.0001). A second study performed by Myerson et al. confirmed these earlier findings that LV growth in response to training was ACE genotype-dependent. Other studies demonstrate an association of ACE genotype in response not only to physiological stimuli such as exercise, but also to pathological stimuli such as hypertension, aortic stenosis, diabetes and renal failure.

ACE and LV growth: a direct or indirect action?

It is tempting to conclude that ACE acts directly through myocardial production of Ang II and degradation of BK to alter LV mass. However, it is known that local RAS also exist in tissues such as skeletal muscle. Such an observation suggests that variations in ACE activity may alter skeletal muscle in a way that changes the demand placed on the left ventricle. In this way, ACE may alter LV mass indirectly through changes in skeletal muscle. This hypothesis has been tested in several studies, some using the army exercise model.

Williams et al. used exercising army recruits to assess whether ACE genotype altered the efficiency of energy use. They measured how ‘Delta efficiency’ (the ratio of the change in muscle work performed/min to the change in energy expended/min, analogous to miles travelled per gallon of petrol consumed) changed in response to a 10-week exercise training programme. They found change in Delta efficiency to be ACE genotype-dependent, being +8.62 and −0.39% in those of II and DD genotype, respectively. Thus, the I allele and reduced ACE activity were associated with the greatest gains in metabolic efficiency. This outcome was consistent with the hypothesis that low ACE activity resulted in greater improvement in skeletal muscle efficiency and so placed less demand on the left ventricle, resulting in a reduced LV hypertrophic response.

Although enlightening, the metabolic efficiency study described above was examining a relatively global measure of skeletal muscle performance. In contrast, Montgomery et al. chose to examine the effect of physical training on the ability of the biceps muscle to withstand fatigue. ACE genotype was determined in 123 male UK army recruits. Seventy-eight completed an identical 10-week physical training programme. Before and after training the maximum duration (in s) for which the recruits could perform repetitive elbow flexion while holding a 15-kg barbell was assessed. In contrast to pre-training performance, the improvement seen in duration that the recruits could continue this exercise was ACE genotype-dependent, being 79.4 ± 25.2, 24.7 ± 8.8 and 7.1 ± 14.9 s for II, ID and DD genotypes, respectively. Therefore, improvement was eleven-fold greater (P < 0.001) for those of II than for those of DD genotype.

The effect of ACE on skeletal muscle strength has also been examined. Folland et al. examined the effect of ACE genotype on changes in strength of the quadriceps muscle in response to 9 weeks of strength training in 33 young, adult, male volunteers. Greater strength gains were associated with the D allele, with the mean being 9.0, 17.6 and 14.9% for II, ID and DD genotypes, respectively. Consistent with these data, Hopkinson et al. examined the effect of the ACE gene on quadriceps weakness in 103 patients with chronic obstructive pulmonary disease, a condition associated with skeletal muscle weakness. They found mean isometric quadriceps strength to be 31.4, 34.1 and 38.3 kg for II, ID and DD genotypes, respectively (P = 0.04 for linear trend).

So, low ACE activity appears to be associated with both skeletal muscle metabolic efficiency and fatigue resistance, but with an inferior increase in strength.
in response to training. This dichotomy may have some consistency with the possible influence of ACE on skeletal muscle fibre type. Zhang et al.\textsuperscript{50} tested the hypothesis that the I allele may be associated with increased number of slow-twitch fibres, which are more efficient than fast-twitch fibres in low-velocity contraction. They examined the association between ACE genotype and skeletal muscle fibre types in 41 untrained, healthy, young volunteer subjects. II subjects had a significantly higher percentage of type I fibres (50.1 vs. 30.5\%) and a lower percentage of type IIb fibres (16.2 vs. 32.9\%) than DD subjects.

So, these data associating the ACE gene and ACE activity with muscle performance suggest that the skeletal muscle RAS may be changing demands placed on the left ventricle and, in doing so, altering the LV growth response to training. Alternatively, the association of ACE activity with skeletal muscle performance may simply mirror changes in metabolic efficiency and/or fatigue resistance in cardiac muscle (which also has a local RAS), and so associates with, rather than causes, the LV growth response.

**ACE genotype and elite athlete status**

Ultimately, a combination of superior performance phenotypes is required for success in athletic competition at a high level. If ACE genotype is influencing performance phenotypes, we might expect individuals who are successful at endurance sports to be more likely to possess the I allele. Conversely, the D allele may predominate in athletes competing successfully in power-based sports. This hypothesis has been tested by several investigators\textsuperscript{39,47,51–61}.

Gayagay et al.\textsuperscript{51} compared the ACE genotype distribution in 64 Australian national rowers with 118 age- and race-matched controls. The I-allele frequency was significantly greater in the rowers compared with the controls, being 0.57 and 0.43, respectively. Attempting a similar strategy, Myerson et al.\textsuperscript{39} collected DNA from nearly 500 British, Olympic-standard athletes. In the 91 runners in this group, I-allele frequency increased with distance run, being 0.35, 0.53 and 0.62 amongst those running \( \leq 200\), 400–3000 and \( \geq 5000\) m, respectively \((P = 0.009\) for linear trend)\textsuperscript{52}. Similar findings were reported for Russian athletes\textsuperscript{53} and elite long-distance cyclists\textsuperscript{54}, implying that ability to run longer distances may be partly linked to the presence of the I allele and associated low ACE activity.

Other sporting disciplines have also been examined. In 56 swimmers from the European and Commonwealth championships, D-allele frequency was significantly greater (0.66) than in over 1000 healthy army recruits acting as controls (0.51; \( P = 0.004\))\textsuperscript{55}. Furthermore, Tsianos et al.\textsuperscript{56} studied 35 elite long-distance swimmers and found I-allele frequency to be 0.29 for those classified as being best at 1–10 km distances, and 0.59 for those considered best at 25 km distance \((P = 0.01)\). In 27 mountaineers with a history of ascending to above 7000 m without supplementary oxygen, I-allele frequency was markedly greater compared with controls \((0.25 \text{ vs. } 0.48; P = 0.005)\textsuperscript{57}. Indeed, the authors also reported that of those 15 climbers who had ascended to 8000 m, none were of the DD genotype.

A strong case can be made to support the existence of an association between ACE genotype and human physical performance. However, conflicting results have been reported. Three studies have failed to find an association between the I allele and elite endurance performance\textsuperscript{57–59}. A common feature of these studies has been the selection of athletes from mixed sporting disciplines. For example, one of these studies included 81 men and 39 women who excelled in a variety of sports: hockey \((n = 26)\), cycling \((n = 25)\), skiing \((n = 21)\), track and field \((n = 15)\), swimming \((n = 13)\), rowing \((n = 7)\), gymnastics \((n = 5)\) and other \((n = 8)\textsuperscript{57}. Phenotype heterogeneity may underlie such inconsistencies\textsuperscript{57–61}. Strengthening this argument, those studies associating ACE genotype and endurance collected data from one sporting discipline\textsuperscript{57,51,52}.

**Possible mediators of ACE: bradykinin**

The advent of a functional polymorphism of the BK2 receptor gene has allowed investigators to assess the role of this RAS component on performance measures. The polymorphism exists as either the absence \((-9)\) or the presence \(+9\) of a 9-bp insertion. The \(-9\) polymorphism is associated with higher BK2 receptor response to BK\textsuperscript{62}. Although the data are not as comprehensive as those for the ACE gene I/D polymorphism, the results are nevertheless impressive.

In 141 army recruits, Brull et al.\textsuperscript{63} showed that exercise-induced LV growth was BK2 receptor genotype-dependent, being 4.6 \(\pm\) 2.6, 8.3 \(\pm\) 1.7 and 13.7 \(\pm\) 2.4 g for the 16, 60 and 33 individuals of \(-9/-9\), \(-9/+9\) and \(+9/+9\) genotype, respectively \((P = 0.01\) for linear trend). Skeletal muscle metabolic efficiency also appears to be dependent on the genotype of the BK2 receptor gene. In 115 sedentary men and women, Delta efficiency was 23.8 \(\pm\) 2.8, 24.2 \(\pm\) 2.81 and 26.0 \(\pm\) 2.26\% for those of \(+9/+9\), \(+9/-9\) and \(-9/-9\) genotype, respectively \((P = 0.003\) by analysis of variance)\textsuperscript{64}. Finally, in a study of 81 British Olympic-standard runners, an association was found between running distance at which the runner excelled and BK2 receptor genotype allele frequency. The \(-9\) allele frequency was 0.38, 0.41 and 0.57 for those athletes running \(\leq 200\), 400–3000 and \(\geq 5000\) m, respectively \((P = 0.06\) for linear...
trend; $P = 0.04$ for comparison of $\leq 5000$ vs. $> 5000$ m$^{-2}$. Thus, high BK2 receptor activity marked by the $\sim 9$ allele is associated with reduced LV growth, increased metabolic efficiency and increased endurance running ability in much the same way as the I allele of the ACE gene (again associated with high BK activity$^{65}$) is associated with these performance phenotypes. Unfortunately, specific data examining the role of Ang II and its receptors on performance phenotypes are not available yet.

**Selection of future athletes by genotype?**

A common question arising from this type of research is ‘Will selection of athletes of the future be based on genetic testing of children?’ We think the answer is no. The example gene we have used here, ACE, is probably one of many candidates that have a role in altering performance ability. Similarly, any gene may have one or more functioning polymorphisms that may contribute to inter-individual performance variation. These loci have yet to be identified and such a quest is not merely a matter of applying modern rapid-throughput genotyping to a hundred individuals; collection of phenotype data in the sport of interest is also necessary, costly and time-consuming. Even if all this takes place, would the creation of a powerful database linking genotype to sporting phenotype be of any use in selecting the athletes of the future? We think not. Not only would a child have to be genotyped for many gene polymorphisms, there is no reason why these data should be better than observing the performance of a child at a local athletics meeting or school football match. Indeed, the latter approach allows the selector to observe the composite phenotype (for example, running or goal-scoring ability). Finally, psychological factors are crucial for success in sport, not only in maintaining motivation during training, but also in remaining focused during competition. The studies required to identify the specific gene polymorphisms that alter such mental fortitude are likely to be even more difficult than those examining the conventional (physical) sporting phenotypes already mentioned.

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