Published in final edited form as:
Phys Ther. 2006 April ; 86(4): 585–591.

Association of Genetic Factors With Selected Measures of Physical Performance

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Keywords

Angiotensin-converting enzyme (ACE); Genetics; Rehabilitation

In the last 30 years, the field of genetics has proven to be a highly influential component of nearly all aspects of research and clinical science. Numerous important and interesting discoveries have been made since the Human Genome Project was launched. Among the first accomplishments were the identification of the genes responsible for cystic fibrosis, neurofibromatosis, Marfan syndrome, and xeroderma pigmentosum.[1] Several fields of medicine, such as psychiatry, embryology, and pulmonology, already have incorporated the use of genetics into their practices.[2–4] An individual's genetic makeup may predispose him or her to a specific pathology, such as Alzheimer disease, cystic fibrosis, or diabetes, and influence the response to treatment.[5–7] The possible implications of the use of genetics in physical therapy are profound, and there are many examples in recent literature of genetic markers that are associated with performance and exercise intolerance.[8] Recently, several studies identified an association between the presence of a specific allele of the gene encoding the angiotensin-converting enzyme (ACE) and an individual's endurance or strength capacity.[9–12] Interestingly, some studies have refuted the relationship between the enzyme and increased endurance or strength.[13–15] Understanding the role of the ACE gene and other genes with respect to physical performance and how these genes may alter the ability of subjects to respond to therapeutic exercise may have important implications in designing studies for testing therapeutic interventions, which will in turn have an effect on clinical practice.

Review of Genetics

Each cell in the human body contains 2 copies of each of 23 chromosomes. Chromosomes are tightly packed structures of individual deoxyribonucleic acids (DNAs) and several proteins that help each chromosome maintain its tightly coiled arrangement.[16] Each chromosome is made up of many different genes. A gene is simply a specific sequence of

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DNA that is processed by the cell during transcription and translation, thereby resulting in a single protein.[16]

However, there may be variation in a protein if the chromosome contains more than 1 allele of a specific gene. An allele is an alternative form of the same gene that is located at the same position within the chromosome and that may result in a different phenotype (observable characteristic).[17] For example, many flowers have a gene that produces a protein that affects the color of their petals. The flower may have an allele that creates red petals; however, another flower of the same species may have a different allele of the same gene that produces white petals. This phenomenon often is referred to as a polymorphism.[17]

There are also sequences within a strand of DNA that do not have a direct effect on the formation of proteins and that are excised from the ribonucleic acid (RNA) strand after the DNA is transcribed into RNA. These sequences of RNA are called introns and are excised from the RNA strand by specialized proteins.[18] The remaining segments of RNA, which are all rejoined together by other enzymes, are called exons and make up the part of the DNA that will be the code used to create proteins.[16] The importance of this modification process is that if a sequence is removed, then that sequence will not be expressed as a protein and should not have any physiological effect.

ACE Mechanism of Action

ACE has been the basis of numerous studies related to cardiac and circulatory disorders, such as ventricular hypertrophy, congestive heart failure, and hypertension.[19,20] Jones and colleagues[21] began to investigate the relationship between a specific allele of the ACE gene and human physical performance after the discovery was made that an allele of the gene was associated with exercise-induced left ventricular hypertrophy. ACE is part of the renin-angiotensin system. The inactive form of the angiotensin hormone, angiotensinogen, is cleaved by renin to produce angiotensin I. ACE then catalyzes the conversion of angiotensin I to produce angiotensin II, which is the physiologically active form of the hormone (Figure). Along with several other effects, angiotensin II causes vasoconstriction and regulates salt and water homeostasis through the release of the hormone aldosterone.[21] In addition to converting angiotensin I to angiotensin II, ACE also degrades the potent vasodilator bradykinin.[21]

> This update reviews the role of the angiotensin-converting enzyme gene and other genes with respect to physical performance.

The polymorphism of the ACE gene is classified by the presence (insertion [I]) or absence (deletion [D]) of a 287-base-pair DNA sequence within the ACE gene. With this notation, each I or D represents a single allele. Because each gene has 2 alleles, there are 3 combinations of the gene: II, ID, and DD. The distributions of these genotypes among whites are 25%, 50%, and 25%, respectively.[21] The polymorphism occurs in an intron and therefore is thought to be nonfunctional; however, it has been shown that the presence of the D allele is associated with higher ACE activity than is that of the I allele.[20,21] The reason for this phenomenon is unclear.

ACE and Endurance Performance

Investigators began examining the possible associations of the ACE polymorphism to determine whether either of the 2 alleles provides an advantage for athletic performance. Studies originally were designed to examine the presence of the polymorphism among "elite athletes"[9] by use of a population association approach; these studies attempted to determine whether a specific polymorphism or allele occurred more frequently in a specific population of athletes than in a control group.[21] Gayagay and colleagues[9] demonstrated a significant excess of the II and ID ACE genotypes among Australian national rowers attending the pre-Olympic trials in 1996; this group was selected because rowing requires a very high endurance level. A similar association was demonstrated in a study involving high-altitude mountaineers; this study explored the ACE I/D polymorphism relationship among 25 elite, unrelated British mountaineers who frequently had ascended above 7,000 m without supplemental oxygen.[22] The frequency of the I allele and the presence of the II genotype were significantly greater among the high-altitude mountaineers than among a control group of 1,906 men who were healthy.[22] Fifteen of these climbers previously had ascended above 8,000 m without auxiliary oxygen. Among this group, none possessed the DD genotype (6 had the II allele and 9 had the ID allele). Furthermore, the top performer in this group (who had the largest number of ascents above 8,000 m) was homozygous for the I allele.[22]

A few studies also have shown an increased association of the I allele among athletes who perform long-distance events and an increase in the frequency of the I allele as the distance of the event increases.[23,24] Myerson and colleagues[23] studied the ACE I/D polymorphism association among 91 potential Olympic runners and showed that the frequency of the I allele was significantly greater among long-distance runners (distances of >5,000 m) than among the control group (404 Olympic-standard athletes from 19 different sporting events); furthermore, they showed an increase in the frequency of the I allele with increasing distance. Tsianos and colleagues[24] investigated the frequency of the ACE I/D polymorphism among elite endurance swimmers. The study involved 35 elite long-distance swimmers who were classified as being either better at 1- to 10-km races or better at 25-km races. The percentage of swimmers in the long-distance group who possessed the I allele was significantly higher than that in the shorter-distance group.[24] The genotype distributions also reflected this trend, with only 1 of the 19 subjects in the shorter-distance group displaying the II genotype and only 1 of the 15 subjects competing over longer distances having the DD genotype. These data support the previous findings that as the distance of the competition increases, the frequency of the I allele among athletes increases. Tsianos and colleagues[24] also found a significant excess of the D allele among subjects competing in 1- to 10-km races, which may require more strength or power.

ACE and Strength Performance

The association of the I allele with increased endurance performance led investigators to examine possible relationships of the D allele of the ACE gene with other measures of human physical performance. Previous studies revealed an association of the D allele with the growth of vascular smooth muscle at the site of coronary angioplasty[25] and human cardiac hypertrophy following exercise.[26] Furthermore, Reneland and Lithell[27] found

considerable ACE activity in skeletal muscle. These studies prompted Folland and colleagues[11] to investigate the influence of the D allele on the response of human quadriceps muscles to specific strength training programs in young men who were healthy; they hypothesized that if the D allele were associated with skeletal muscle hypertrophy, then subjects with the D allele would respond with a greater strength increase than would those without this allele. The subjects of the study participated 3 times per week for 9 weeks in strength training protocols that involved isometric knee extension training with 1 leg and dynamic knee extension training with the other leg. Several different measurements were used to evaluate strength gains. The study showed significantly greater strength enhancement among subjects who possessed the D allele. The group with the ID genotype showed the greatest strength improvement, followed by the group with the DD genotype and then the group with the II genotype. The subjects with the ID and DD genotypes improved their quadriceps muscle strength 97% and 66% more than did the subjects with the II genotype, respectively.[11] Folland and colleagues[11] speculated that the ACE genotype that regulates hypertrophic responses in other tissues has a similar effect in skeletal muscle. The D allele has been associated with higher systemic[28] and cardiac tissue[29] ACE activities. ACE produces angiotensin II, which is a potent growth factor in cardiac and vascular tissues[30] and which degrades kinins that inhibit growth in cardiac myocytes.[31,32] The interaction of ACE in the same fashion in skeletal muscle may represent a possible mechanism for the greater strength gains associated with the D allele.[11] However, hypertrophy may not be the only measure of strength gain, as there have been reports of inconsistencies in the relationship between muscle size and strength.[33]

Studies also have shown a greater frequency of the D allele among athletes who compete in shorter-distance events.[23,24,34] Myerson and colleagues[23] found a significantly greater frequency of the D allele among Olympic sprinters running 200 m or less. These findings led Woods and colleagues[34] to investigate this relationship in elite swimmers. Sixty-six percent of the 103 white elite swimmers who were examined in the study exhibited the presence of the D allele; this percentage was significantly higher than those in the 4 largest control populations used.[34] Tsianos and colleagues[24] drew the same conclusion by showing a significant excess of the D allele among subjects competing in swimming competitions of 1 to 10 km as opposed to those competing in races of 25 km.

Limitations of Association Studies

Jones and colleagues[21] noted that even if an association is found between the ACE I/D polymorphism and human performance, there is more than 1 possible explanation for the relationship. The polymorphism itself, the locus within which the polymorphism is located, or another locus that is tightly linked to the polymorphism may be responsible for the association.[21] Furthermore, an association does not imply causation; that is, an association between a gene and a certain physical characteristic does not mean that the gene caused or created the physical attribute. In addition, population association studies are prone to other difficulties. For example, in the case of attempting to associate the presence of the ACE I allele with elite athlete status, the definition of what constitutes an elite athlete is subjective and varies across studies. Furthermore, variation within the control group can be a

confounding factor, especially when the frequency of the polymorphism varies among control populations.[21]

Studies Not Showing an ACE-Performance Relationship

Although numerous studies have shown a correlation of the ACE I/D polymorphism with enhanced physical performance, other studies have found no such association.[13–15] Taylor and colleagues[14] investigated 120 white Australian national athletes from several different sporting disciplines classified as requiring a high level of aerobic fitness; they found no difference in the ACE genotype and allele frequency between this group and the control group that was recruited randomly from the community. Similarly, Karjalainen and colleagues[13] studied 80 long-distance runners, orienteers and crosscountry skiers, and triathletes from the Finnish national teams and found no significant association among the athletes with regard to the ACE I/D polymorphism. Unfortunately, the study of Karjalainen and colleagues did not include a control group against which the athletes' genotypes could be compared.

A study involving 192 male endurance athletes from the sporting disciplines of cross-country skiing, biathlon, Nordic combined, long-distance running, middle-distance running, and road cycling found no excess of the I allele among the athletes within the highest quartile (>80 $mL \cdot kg^{-1} \cdot min^{-1}$) or decile (>83 $mL \cdot kg^{-1} \cdot min^{-1}$) of maximum oxygen uptake ($\dot{V}o_2max$).[15] The authors[15] concluded that these data suggested that the ACE I/D polymorphism may not be associated with increased cardiorespiratory endurance performance.

Sonna and colleagues[35] recently noted that studies that have found an association of the ACE genotype with physical performance in young athletes typically have involved populations consisting of limited ethnic or geographic diversity. They suggested that these types of cohorts may result in an overestimation of the effect of the polymorphism on physical performance. Sonna and colleagues therefore studied the effect of the ACE I/D polymorphism on the $\dot{V}o_2max$ and physical performance responses of 147 (84 white, 37 African American, 20 Hispanic, 5 Asian, and 1 Native American) US Army recruits during basic training. This population was chosen because of the ethnic and geographic diversity of young American soldiers. Subjects participated daily in 1 to 1.5 hours of physical training, which consisted, on average, of 2 days of aerobic training and 2 days of strength training per week for 8 weeks. The study showed no statistically significant association of the ACE genotype with $\dot{V}o_2max$, minute ventilation, CO_2 output, or maximum heart rate achieved before or after basic training.[35]

Several, more recent studies, which included populations with limited ethnic and geographic diversity, also do not support the previously reported associations of the ACE polymorphism with increased endurance or strength. Thomis and colleagues[36] recruited both members of 16 pairs of dizygotic twins and 1 individual who was a monozygotic twin to participate in a 10-week training session of bicep curls. Training sessions included 5 sets of bicep curls performed 3 times per week. Each week the load was adjusted to a percentage of each subject's maximum for 1 repetition. On the basis of previous studies, Thomis and

colleagues[36] hypothesized that the D allele of the ACE gene would correlate with greater strength gains; however, they demonstrated no evidence of an association of the ACE I/D polymorphism with gains in elbow flexor muscle cross-sectional area, maximum strength, or isometric and concentric strength after the high-resistance strength training program.

In addition, a study of 67 nonsmoking Chinese men who were healthy with no previous exercise or military training revealed that the ACE DD genotype was associated with higher $\dot{V}o_2$max than were the II and ID genotypes.[37] These findings conflict with those of previous studies suggesting that the I allele is associated with greater endurance capacity.[9,22,23,24] Finally, Scott and colleagues[38] compared the incidence of the ACE I/D polymorphism in 291 elite Kenyan endurance athletes and the incidence in 85 control subjects. Seventy of these athletes had competed internationally and either held world records or were Olympic, World, or Commonwealth champions. The study showed no association between the ACE I/D polymorphism and the classification as an elite endurance athlete.[38]

Possible Mechanisms Underlying the Association of ACE With Increased Performance

Two primary theories have been posed regarding the possible physiological mechanisms involving the ACE I/D polymorphism.[39] The first is that the ACE polymorphism may alter physical performance through a metabolic response associated with the I allele, resulting in greater metabolic efficiency.[39] The second theory is that there is a cardiorespiratory mechanism underlying the increased endurance capacity observed among subjects possessing the I allele.[40] Subjects involved in activities requiring a high level of endurance rely greatly on fatty acids as an energy source. At the start of strenuous activity, these fatty acids are sent to the tissue more quickly among subjects who participate in endurance training than among those who are untrained.[41] Montgomery and colleagues[39] investigated the metabolic effects of the human local renin-angiotensin system within subjects involved in an intensive exercise program and showed that those with the II genotype had a greater anabolic response for fat mass than did those with either the ID or the DD genotype. These data are consistent with those of Katsuya and colleagues,[42] who found an association of the ACE I allele with increased body mass index. Montgomery and colleagues[39] stated that the association of the increased storage of fatty acids with improved physical performance may suggest that the ACE II genotype allows for the conservation of energy, thereby enhancing metabolic efficiency by maximizing the use of oxidative fuel for metabolism.

In addition, Montgomery and colleagues[39] suggested 3 primary means by which the increased metabolic efficiency may occur. First, the ACE I/D polymorphism may be linked to a nearby gene allowing the endocrine system to alter metabolism systemically.[39] Montgomery and colleagues[39] suggested that the ACE polymorphism may be linked to the growth hormone gene; however, other research indicated that the I/D polymorphism is not linked to other genes.[43] Furthermore, differences in the renin-angiotensin system within the central nervous system may alter appetite and physical effort,[44] and the renin-angiotensin system within the intestines may modify the absorptive capability of the gut.[45]

Second, metabolism may be affected if the mobilization of fat stores is altered. This process may be possible through a local adipose renin-angiotensin system.[39] The angiotensin gene is expressed readily within adipose tissue and also can be influenced by the body's nutritional state.[46] The up-regulation (associated with the presence of the D allele) or down-regulation (associated with the presence of the I allele) of ACE, therefore, will alter the local concentration of angiotensin and thus have an effect on metabolism. Additionally, angiotensin II[46] and kinins[47] may be involved in the regulation of metabolism. Kinins have been found to increase insulin-stimulated hexone transport within adipocytes,[48] and ACE inhibition increases insulin suppression of non-esterified fatty acid flux.[39,49]

Third, a local skeletal muscle renin-angiotensin system[50] may alter the way in which fatty acids are used.[39] For example, ACE inhibition causes increases in skeletal muscle glucose uptake, insulin sensitivity, glycogen storage, glucose transporter GLUT-4 synthase activity, hexokinase activity, and the modification of specific enzymes for the breakdown of glucose.[39,51]

The association of the I allele with increased endurance poses the question of the possible association of the allele with increased aerobic capacity. Maximum oxygen uptake has been a widely used indicator of overall aerobic function[40] and has been found to be influenced significantly by genetic factors.[52] Furthermore, the ability to alter $\dot{V}o_2$max varies greatly among subjects. Improvements in $\dot{V}o_2$max in response to identical training protocols have been demonstrated to range from nearly 0 to 1 L per minute.[53] A few studies have suggested an association of the ACE I/D polymorphism with $\dot{V}o_2$max. A study done among postmenopausal women showed that those homozygous for the I allele (II genotype) had a significantly higher $\dot{V}o_2$max than did those homozygous for the D allele (DD genotype).[54] In contrast, a study by Rankinen and colleagues[55] involving 4 different groups of subjects (white parents, their offspring, black parents, and their offspring) showed no differences in the baseline $\dot{V}o_2$max among genotypes but did show significant increases in $\dot{V}o_2$max after 20 weeks of training for the white offspring who were homozygous for the D allele. These conflicting reports prompted Woods and colleagues[40] to investigate the possible association of the ACE I/D polymorphism with $\dot{V}o_2$max among 108 white British military recruits before and after an 11-week aerobic endurance program. They found a significant increase in $\dot{V}o_2$max for those homozygous for the D allele; however, this association was negated after adjustment for baseline differences. They therefore concluded that there was no significant association of $\dot{V}o_2$max with the ACE I/D polymorphism, suggesting that the influence of the ACE I allele on endurance performance is not mediated by differences in the aerobic training response.[40] Woods and colleagues[40] therefore suggested that differences in muscular efficiency, and not cardiorespiratory fitness, accounted for the increased endurance characteristics mediated by way of the ACE I allele.

Implications for Rehabilitation Specialists

The information presented in this brief review and the results of future work may have tremendous implications regarding the design of clinical studies to evaluate interventions. As an example, if investigators can identify subpopulations of subjects who respond favorably to strength training protocols or other populations who do not respond readily to

these programs, then it may be helpful to include the genetic makeup of the subjects as a covariant to stratify the sample during data analysis. Similarly, it may be possible to identify subjects (eg, which ACE genotype) who will be the most and least responsive to exercise and to predict the best treatment parameters for each subject. Finally, as more is learned about the effects of genetics on rehabilitation, physical therapy educational programs will need to require that students attain a sufficient level of competence so that the students can use information regarding a subject's genetic makeup to prescribe appropriate therapeutic exercise.

Acknowledgments

Both authors provided concept/idea/project design and writing. The authors acknowledge Allon Goldberg, PT, PhD, for his helpful comments and suggestions regarding the manuscript.

Funding for this project was provided by NIH grants HD36797, HD7490, and RR1658.

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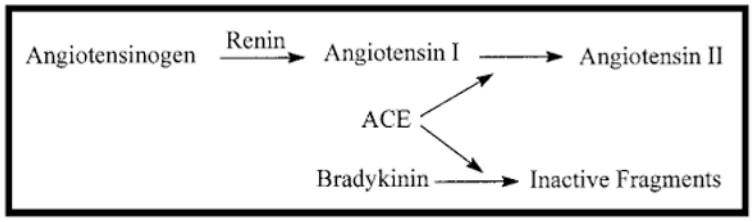

Figure.

The renin-angiotensin system. ACE=angiotensin-converting enzyme. Adapted and reprinted by permission of Lippincott Williams & Wilkins from: Jones A, Montgomery HE, Woods DR. Human performance: a role for the ACE genotype? *Exerc Sport Sci Rev*. 2002;30:184–190.