Heterogeneity of Physical Function Responses to Exercise in Older Adults: Possible Contribution of Variation in the Angiotensin-I Converting Enzyme (ACE) Gene?

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Abstract
Behavioral exercise interventions, aimed at improving either aerobic endurance or muscular strength, are currently the only therapy found, on average, to consistently retard loss of physical function in aging adults. However, not all individuals experience the same magnitude of benefit from a given exercise treatment, and certain persons may respond more favorably to a particular mode of exercise than another. Research now shows that genetic predisposition is one of the factors accounting for interindividual differences in responses to exercise as well as differences in the propensity to engage in exercise. This article discusses how a common variant in a single gene (the angiotensin-I converting enzyme gene) could emerge as a prospective tool to identify older individuals more likely to benefit from and adhere to a specific type of exercise activity over another type.

Keywords
physical function, exercise, genetics, angiotensin-I converting enzyme (ACE)

Personalized medicine, that is, managing a patient’s health based on his/her unique characteristics (including an individual’s genome), is currently most often applied to approved medical therapies for specific diseases, especially those related to medication selection and dosage (e.g., pharmacogenomics). Similarly, a personalized approach to prescribing specific behavioral therapies, including physical activity, may be more beneficial than a global approach. The tailoring of the most recent public health exercise recommendation based on an individual’s age (Nelson et al., 2007) is an example of prescribing a more appropriate behavioral therapy for certain individuals. Yet, despite ever expanding evidence that an individual’s genotype or gene expression profile affects physical performance responses and other health-related parameters and perhaps one’s adherence to physical activity (Bray et al., 2009), in general, current exercise recommendations do not differ by genotype. Although genetic interactions underlying physiological exercise responses and exercise behaviors are complex and presently preclude the practical application of individual exercise recommendations to treat a single health parameter, the purpose of this article is to summarize the available evidence indicative of the plausibility for a single genetic variant to one day be useful for personalizing exercise prescriptions.

Prior to the widespread application of genetically based exercise treatments, strong evidence for an effect of a specific genotype or gene expression profile is warranted. In fact, it would be prudent to establish explicit criteria that are met before prescribing a specific mode or dosage of exercise based on genotype. The first criterion should be that there are highly variable responses among individuals of the exact health outcome needing treatment via exercise. It is important to note that this variability should be at least partially accounted for by genetic factors (e.g., the trait is heritable). A second criterion that should be considered is the biological plausibility of a candidate gene to be involved in the exercise adaptation of the specific outcome. Ideally, the functional consequences of the

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candidate polymorphism will be known, and there should be convincing evidence that it is likely to alter the mechanistic pathway by which exercise affects the health outcome. Thirdly, similar to the interaction between a polymorphism in the serotonin transport protein gene and a preventative behavioral intervention on youth risk behavior (Brody, Beach, Philibert, Chen, & Murray, 2009), there should be data from randomized, controlled trials showing an interaction between a genotype and a preventative exercise intervention. Without this definitive data to support a greatly enhanced response in some individuals of a specific genotype, there would be no clinical reason to prescribe a different exercise treatment.

This article highlights the early, but accumulating, evidence as “proof of concept” for the potential use of a genetic marker for prescribing the type of exercise most likely to prevent disability in an older individual. Presently, both muscle-strengthening and aerobic types of physical activity are recommended for the prevention of disability in older adults (Nelson et al., 2007), even though it is likely that specific individuals may respond more favorably to, and be more likely to engage in, one type over another. Detection of easily identifiable genetic markers of improvement in physiological adaptations to both strength and aerobic modes of exercise in older adults could lead to more effective exercise recommendations geared at maximizing improvements in physical function, ultimately leading to delays in disability for those who choose to exercise. Moreover, based on social cognitive theory, favorable performance responses to exercise enhance self-efficacy and past unfavorable responses (or lack of change) serve to decrease self-efficacy perceptions. This means that older adults with higher levels of self-efficacy should be more likely to attribute exercise gains to circumstances within their control and to exert more effort, and thus, have higher rates of compliance than those individuals with lower levels of self-efficacy (McAuley & Courneya, 1993; McAuley & Mihalko, 1998). Thus, personalized exercise prescriptions based on genotype may ultimately be useful for maximizing exercise efforts and providing incentive to exercise, as well as improving compliance to an exercise treatment.

The genetic determinants of physical abilities, responses to physical training and exercise, and compliance to physical activity recommendations are numerous and mostly unknown, with complex genetic interactions likely underlying these traits (Bray et al., 2009). Yet, I provide here an example of a single genetic variant that is accumulating evidence that meets all of the criteria delineated above. Notably, the health outcome requiring exercise therapy—aging-related loss of physical function—is significant from a public health standpoint and shows evidence of heritability. Moreover, on average, regular exercise improves physical function, but there is large variability among individuals in the magnitude of improvement in response to both recommended types of exercise (strength and aerobic) for older adults. There is also knowledge supporting the biologic plausibility for the candidate gene (angiotensin-1 converting enzyme; ACE) to affect functional adaptations to both modes of exercise. Finally, the concept that physical function responses to exercise training are influenced by variation in the ACE gene is favorably supported by association studies in young, elite athletes, and, more importantly, by intervention studies in older adults showing a Genotype × Treatment interaction. Specifically, individuals homozygous for the deletion (D) allele of the ACE I/D variant seem to experience greater improvement in muscle strength in response to strengthening types of exercise, whereas individuals homozygous for the insertion (I) allele appear to experience greater improvement in aerobic capacity and muscle endurance in response to aerobic types of exercise. Early results also suggest that ACE gene variability may also predict adherence to an exercise treatment.

### Aging-Related Decline in Physical Function: A Phenotype of High Prevalence and Health Significance That Is Treatable With Exercise

Aging is associated with declines in physical function that lead to onset of physical disability and loss of independence. Muscle strength, walking speed, and aerobic endurance all decline with age (Fleg & Lakatta, 1988; Forrest, Zmuda, & Cauley, 2005, 2007; Onder et al., 2002), and declines in each of these have been shown to predict a higher incidence of disability, institutionalization, and/or mortality (Newman et al., 2006; Onder et al., 2005). As a greater proportion of the population is surviving to very old ages, the public health burden of disability and related utilization of medical care and need for long-term care have become a critical concern (Waidmann & Liu, 2000). For example, although persons over 65 years of age make up about 13% of the U.S. population, they account for more than 35% of total health care expenditures and the 20% of community-dwelling persons over 72 years of age who were not functionally independent accounted for 46% of health care expenditures (Fried, Bradley, Williams, & Tinetti, 2001). Thus, maximally effective therapies to minimize or retard aging-related loss of physical function are needed to reduce the burden of disability and dependence or institutionalization in the elderly.

Presently, regular exercise is the only therapy known to consistently improve physical function and potentially reduce disability in older adults (Singh, 2002). Recently, a 1-year walking intervention was shown to reduce the overall incidence of major mobility disability in elderly men and women (Pahor et al., 2006). Because both low muscle strength and low aerobic capacity are predictive of future disability, current physical activity recommendations for older adults encourage performing both aerobic and muscle-strengthening activity (Nelson et al., 2007). Prior work at our institution showed that exercise interventions aimed at enhancing either aerobic endurance or musculoskeletal strength, on average, result in improvements in self-reported disability and physical function in older adults (Ettinger et al., 1997). However, as pointed out below, not all individuals respond favorably to nor experience the same magnitude of benefit from a given exercise treatment, and part of this variability is likely due to genetic factors. It is also conceivable that individuals may respond more favorably to one particular mode of exercise than another and may therefore be more
likely to comply with an exercise prescription that results in greater performance benefits. Increasing physical activity in older adults may reduce medical costs within a year after the onset of behavior change (Martinson, Crain, Pronk, O’Connor, & Maciosek, 2003), yet most older adults are not following current exercise recommendations (Centers for Disease Control and Prevention, 2003). Thus, identification of factors, including genotype, that maximize benefits and increase compliance is a crucial area of research.

### Heterogeneity of Physical Function Responses to Exercise Training: Evidence for a Genetic Contribution

There is no doubt that participation in regular exercise, on average, will improve physical function. Yet, although effects of an exercise intervention are often reported in aggregate, as reviewed by Bouchard and Rankinen (2001), there is large individual variation in the magnitude of change in several performance outcomes with regular exercise. For example, among older adults, changes in aerobic fitness following a highly standardized aerobic training program ranged from 0%–58% (Kohrt et al., 1991). Also, in the largest (N = 633) exercise training study to date, the HERITAGE Family Study, the 5-month exercise stimulus was tightly controlled but still resulted in large variation in fitness responses to the training, with some individuals showing no change at all (Bouchard et al., 1999). Our own data show large heterogeneity in the effectiveness of exercise training (combined aerobic and strengthening exercise three times per week for 6 months) in older men and women (Johnson, You, Messier, Miller, & Nicklas, 2005). Among study participants who attended at least 80% of the prescribed exercise sessions, on average, the training increased 6-min walk distance (208.2 ± 170.7 ft) and knee strength (0.15 ± 0.7 Nm/kg body weight) and decreased stair climb time (–1.3 ± 3.4 s; all p < .001). However, as shown in Table 1, there was a wide range of changes with some participants experiencing little or no change. In fact, our data show that approximately 7.5% of these older adults showed no increase in walking distance (a measure of aerobic fitness) and 58% showed no increase in muscle strength, despite having participated in at least 80% of the exercise sessions. These data provide good evidence for the existence of large variation in interindividual responses to exercise training.

The obvious next step then is to attempt to identify the determinants of these individual differences in exercise effectiveness. Although compliance to an exercise intervention is an obvious important factor in determining its success (van Gool et al., 2005), other factors, including genetics, also affect exercise-induced improvements in physical function (Beunen & Thomis, 2004; Bray et al., 2009). Heritability estimates of grip and arm flexor strength (adjusted for body size and age) range from 36%–65% (Arden & Spector, 1997; Frederiksen et al., 2002; Reed, Fabsitz, Selby, & Carmelli, 1991), and heritability estimates of leg extensor strength and lower-extremity function range from 46%–57% (Arden & Spector, 1997; Carmelli et al., 2000). There are also data to support a relatively large genetic contribution to maximal and submaximal aerobic performance. In young male twins, the heritability of peak aerobic power was 66% after adjustment for body size and hours of sports participation (Fagard, Bielen, & Amery, 1991), and in a family-based study, maximal heritability estimates for aerobic fitness reached 50% (Bouchard et al., 1998). Submaximal aerobic performance, a measure of metabolic or substrate efficiency, is also highly heritable (71%–74%; Perusse et al., 2001).

Studies show that genetic variation also influences exercise training-induced changes in physical function (Bouchard & Rankinen, 2001). For example, monozygotic twins show a higher variance between twin pairs (rather than within pairs) in the responses of several phenotypes to exercise training, including aerobic endurance, substrate use, and body composition (Bouchard et al, 1994). In addition, variation in gains in upper body strength following resistance exercise training was greater in dizygotic twins (intraclass correlation of 0.22) than in monozygotic twins (0.49), suggesting a large genetic influence on this phenotype (Thomis et al., 1998). Results from the HERITAGE family study show that, after 20 weeks of aerobic exercise, there is 2.5 times more variance in changes in aerobic fitness between families than within families (Bouchard et al., 1999). The maximal heritability for change in aerobic fitness was 47%, suggesting that nearly one half of an individual’s ability to increase aerobic fitness with this training protocol was due to genetic determinants. Collectively, these studies confirm that the magnitude of performance responses to exercise training is significantly influenced by genotype. As summarized below, variation in the ACE gene may prove to be one of these genetic determinants.

### Table 1. Heterogeneity of Physical Function Responses to Exercise Training Shown by Frequencies of Subjects Who Did Not Improve Physical Function Variables and the Range of Relative Changes

<table>
<thead>
<tr>
<th>Variable (n; X ± SD)</th>
<th>Extent of improvement (# of participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ 6-min walk (n = 54; 16.4 ± 13.6%)</td>
<td>None 0.1%–4.9% 5.0%–9.9% 10.0%–14.9% 15.0%–19.9% 20.0%–24.9% &gt;25.0%</td>
</tr>
<tr>
<td>Δ knee strength (n = 26; 11.4 ± 32.3%)</td>
<td>4 13 10 9 2 13</td>
</tr>
<tr>
<td>Δ stair-climb time (n = 58; –9.7 ± 26.4%)</td>
<td>20 5 5 4 2 17</td>
</tr>
<tr>
<td>Δ disability score (n = 60; –7.7 ± 19%)</td>
<td>24 3 4 9 4 5 11</td>
</tr>
</tbody>
</table>

The obvious next step then is to attempt to identify the determinants of these individual differences in exercise effectiveness. Although compliance to an exercise intervention is an obvious important factor in determining its success (van Gool et al., 2005), other factors, including genetics, also affect exercise-induced improvements in physical function (Beunen & Thomis, 2004; Bray et al., 2009). Heritability estimates of grip and arm flexor strength (adjusted for body size and age) range from 36%–65% (Arden & Spector, 1997; Frederiksen et al., 2002; Reed, Fabsitz, Selby, & Carmelli, 1991), and heritability estimates of leg extensor strength and lower-extremity function range from 46%–57% (Arden & Spector, 1997; Carmelli et al., 2000). There are also data to support a relatively large genetic contribution to maximal and submaximal aerobic performance. In young male twins, the heritability of peak aerobic power was 66% after adjustment for body size and hours of sports participation (Fagard, Bielen, & Amery, 1991), and in a family-based study, maximal heritability estimates for aerobic fitness reached 50% (Bouchard et al., 1998). Submaximal aerobic performance, a measure of metabolic or substrate efficiency, is also highly heritable (71%–74%; Perusse et al., 2001).
Role of the Renin-Angiotensin System in Skeletal Muscle Growth and Metabolism: Evidence for Biologic Plausibility

The renin-angiotensin system regulates the conversion of angiotensinogen to the biologically active molecules bradykinin and angiotensin II (Lavoie & Sigmund, 2003), and this system is a potent regulator of local metabolic function in several tissues, including skeletal muscle (Dietze & Henriksen, 2008; Henriksen & Jacob, 2003). ACE functions to catalyze the conversion of angiotensin I into angiotensin II and to catalyze the breakdown of bradykinin, a vasodilator that also enhances glucose uptake into cells (Henriksen & Jacob, 2003; Jones & Woods, 2003; Taguchi et al., 2000).

The ACE gene localizes to chromosome 17q23 and a common variant (I/D) is the result of either an insertion (I) or deletion (D) of a 287-bp fragment in intron 16 (Rigat et al., 1990). The ACE I/D genotype frequencies in the general population are approximately 25%–30% DD, 45%–50% ID, and 20%–25% II. In comparison with the I allele, the D allele is associated with a higher circulating ACE activity (Agerholm-Larsen, Tybjerg-Hansen, Schnohr, & Nordestgaard, 1999; Kohn et al., 1999; Rigat et al., 1990; Zhu et al., 2001). This higher ACE activity with the D allele is associated with lower bradykinin concentrations, suggestive of less efficient substrate use (Murphey, Gainer, Vaughan, & Brown, 2000) and with greater angiotensin I conversion to angiotensin II, which serves to augment overload-induced hypertrophy of muscle (Gordon, Davis, Carlson, & Booth, 2001; Westerkamp & Gordon, 2005). These findings contribute biologic plausibility for a role of the II genotype in enhancing energy efficiency and muscular endurance and of the DD genotype in enhancing muscle strength when stressed by exercise. However, this variant, although most widely studied in terms of a contribution to physiological and behavioral responses to exercise, may only be a marker of ACE activity, as there are other polymorphisms that are also closely associated with ACE levels (McKenzie et al., 2008).

Interaction of ACE I/D Genotype With Mode of Exercise on Physical Function in the Elderly: Evidence From Observational Studies in Young Athletes

Historical observational data from young athletes support the concept that physical function responses to exercise training may be influenced by variation in the ACE gene (Jones, Montgomery, & Woods, 2002). In comparison with controls, there is an excess of the I allele and the II genotype in elite rowers (Gayagay et al., 1998), triathletes (Collins et al., 2004), marathon runners (Hruskovicova et al., 2006), and mountaineers (Tsianos, Eleftheriou, et al., 2004; Woods & Montgomery, 2001). In addition, a large study of British Olympic competitors showed a linear increase in the number of I alleles with running distance (35% for less than 200 meters, 53% for 400–3000 meters, and 62% for more than 5000 meters; Myerson et al., 2003). The advantage of the I allele for aerobic performance is likely due to enhanced aerobic efficiency for a given workload leading to greater muscular endurance (Montgomery et al., 1998; Woods et al., 2002; Zhang, Wang, Dai, Lin, & Zhang, 2008). As these associations are seen only in the most highly trained athletes, they are suggestive of an interaction between ACE genotype and exercise behavior. However, not all studies show an excess of the I allele in elite endurance athletes (Rankinen et al., 2000). On the other hand, studies show an excess of the D allele in short-distance, sprint (less than 1 min in duration) athletes compared to controls (Myerson et al., 1999; Nazarov et al., 2001; Tsianos, Sanders, et al., 2004; Woods et al., 2001). In two of these studies, combining the elite athletes with less-trained competitors eliminated any differences in genotype frequencies, again supporting the concept of a Gene × Training interaction.

Longitudinal intervention studies in young adults do point to an ACE I/D by exercise training interaction on aerobic performance. Aerobic exercise training in young male army recruits improved muscle endurance in those with the II and ID genotype only (Montgomery et al., 1998), whereas preexercise training values were not genotype dependent (Williams et al., 2000). Moreover, in young women, the ACE II genotype was associated with greater improvement in longer duration aerobic performance following aerobic exercise training (Cam, Colakoglu, Colakoglu, Sekuri, & Berdeli, 2007). Two published intervention studies in young adults show disparate findings regarding the effects of strength training on muscle size and strength gains (Folland et al., 2000; Pescatello et al., 2007). But results consistently show that the D allele is predictive of exercise-induced cardiac muscle hypertrophy (Fatini et al., 2000; Hernandez et al., 2003; Montgomery et al., 1999). Although the physiological basis for potentially greater strength gains in individuals with the D allele is not definitely known yet, it is most likely due to the effects of their increased angiotensin II level, a growth factor that augments overload-induced hypertrophy of muscle (Gordon et al., 2001; Westerkamp & Gordon, 2005).

Collectively, these studies show that, in young persons, the interaction of ACE I/D genotype with exercise is more important than the genotype alone in predicting individual differences in physical performance. Also, the direction of the genotype effect depends on the type of exercise performed (aerobic or strengthening). Next, I point out that these findings are also evident in older adults.

Interaction of ACE I/D Genotype With Mode of Exercise on Physical Function in the Elderly: Evidence From Intervention Studies in Older Adults

To date, only a few studies examined the association of the ACE gene variant with physical function in the elderly. In one study, ACE I/D allele frequencies between the strongest and weakest groups of elderly women were similar (Walston, 1999).
Seibert, Johnson, & Fried, 1999). Likewise, in a study of elderly twins, neither physical function at baseline, nor changes in function over time, were associated with ACE I/D genotype (Frederiksen, Gaist, et al., 2003). Another paper reports retrospective data from four exercise trials in elderly adults that show no effect of the ACE I/D variant on function (Frederiksen, Bathum, Worm, Christensen, & Puggard, 2003). However, the exercise programs consisted of a combination of aerobic, resistive, and balance training, and because the direction of the genotype effect depends on the type of exercise performed, this may be why no effect was noted. In older heart disease patients, peak oxygen uptake (aerobic function) was found to be higher in those with an I allele (Abraham et al., 2002), and aerobic exercise training elicited a greater increase in peak oxygen uptake in II patients than in ID or DD patients (Defoor et al., 2006). Also, older men and women homozygous for the D allele were found to have higher total and leaner mass and larger muscle volume at baseline than I genotype carriers, but there was no ACE genotype effect for muscle or strength gains following unilateral knee strength training (Charbonneau et al., 2008).

Although some of these data are suggestive that genetic variation in the ACE gene influences physical responses to exercise training, most of the findings come from smaller studies of low statistical power and are from secondary, retrospective analyses. In addition, none of the prior mentioned studies in older adults report significant Gene (I vs. D genotype) × Environment (exercise behavior) interactions that would provide the best evidence for a definitive effect of this genotype on exercise responses, and such information is critical before more individually effective exercise regimens may be able to be prescribed based on one’s ACE I/D genotype. However, well-designed and controlled research from our group does consistently show that ACE I/D genotype interacts with mode of exercise to affect physical function in the elderly. Next, I report findings from three different studies, all of which show a significant interaction between participation in either aerobic or strengthening exercise and ACE I/D.

**Interaction Between ACE I/D Genotype and Reported Exercise Behavior on Incident Mobility Limitation in the Health, Aging, and Body Composition (HABC) Study**

Researchers have previously reported that the ACE I/D genotype modifies the beneficial effects of exercise on risk for mobility limitation in older men and women enrolled in the HABC study (Kritchevsky et al., 2005). HABC is a cohort study with 3,075 well-functioning men and women aged 70–79 years. Individuals were eligible for the study if they reported no difficulty walking one quarter of a mile, climbing 10 steps, or performing basic activities of daily living. The primary outcome of HABC was the onset of persistent lower extremity mobility limitation, defined as self-reported difficulty or inability to walk one quarter of a mile or climb 10 steps during two consecutive semianual assessments. After an average of 4.1 years of follow-up, 40.6% of HABC participants reported incident mobility limitation.

Among Caucasians, 32.7% of the HABC population was homozygous for the D allele, 46.9% were heterozygous, and 20.4% were homozygous for the I allele of the ACE I/D variant. The genotype frequencies did not differ by race (in Black participants, DD = 34.9%, ID = 46.6%, II = 18.5%), nor were there racial differences in genotype–phenotype associations, so the researchers combined races for analyses. The ACE I/D marker was not associated with any physical, demographic, or health status variable at baseline. In addition, there were no associations between ACE I/D and changes in body composition or measures of physical function over the 4-year follow-up. ACE I/D alone was not predictive of mortality or of onset of mobility limitation in the entire cohort (39.9% of DD, 40.0% of ID, and 43.1% of II developed mobility limitation).

There were no differences among genotypes in frequency of participants who reported engaging in strengthening exercise or walking, and as expected, there was a protective effect of both strengthening exercise and walking on mobility limitation regardless of genotype. It is important to note, however, that the ACE I/D genotype modified the beneficial effects of exercise on incident mobility limitation in this cohort, and the gene effects were strongest among participants reporting engaging in strengthening exercise. Table 2 shows the incidence rates and hazard ratios for mobility limitation stratified by strengthening exercise status and genotype. There was no genotype difference in the rate of mobility limitation onset among those reporting no exercise. When stratified according to self-reported participation in exercise, there was a significant genotype effect such that the II individuals developed functional limitation approximately 2.5 times faster than individuals with a D allele. In fact, the incidence rate of 14.9 approached that of the II genotype individuals who reported performing no exercise (17.8). Using proportional hazards modeling, the interaction between the genotype (modeled as number of I alleles) and strengthening exercise status was significant in an unadjusted model ($p = .049$), and it tended to be significant in a model adjusting

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Incident cases</th>
<th>Person years</th>
<th>Incidence rate (per 1,000 person years)</th>
<th>Adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No exercise</td>
<td>DD/ID</td>
<td>936</td>
<td>472</td>
<td>2,527</td>
<td>18.68</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>231</td>
<td>115</td>
<td>647</td>
<td>17.78</td>
</tr>
<tr>
<td>Strengthening exercise</td>
<td>DD/ID</td>
<td>186</td>
<td>44</td>
<td>634</td>
<td>6.94</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>38</td>
<td>17</td>
<td>114</td>
<td>14.90</td>
</tr>
<tr>
<td>Walking</td>
<td>DD/ID</td>
<td>569</td>
<td>195</td>
<td>1,820</td>
<td>10.71</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>135</td>
<td>58</td>
<td>396</td>
<td>14.65</td>
</tr>
</tbody>
</table>

Note: Adjusted for age, race, gender, site, education, smoking, alcohol use, knee pain, diabetes, cardiovascular disease, hypertension.
for age, race, gender, site, education, smoking status, knee pain, diabetes, cardiovascular disease, and hypertension ($p = .17$). Thus, it is apparent that among older individuals who perform strengthening exercise, there is a much higher risk of functional limitation in those with the $II$ genotype.

**Association Between ACE I/D Genotype and Changes in Muscle Strength and Walking Endurance in the Arthritis, Diet, and Activity Promotion Trial (ADAPT)**

The ADAPT study was a single-site, randomized, controlled trial designed to determine the effects of exercise and dietary-induced weight loss, alone and in combination, on self-reported physical function and disability. 316 older (60 years and over), overweight/obese, and sedentary individuals with radiographic evidence of knee osteoarthritis were randomized to four 18-month treatments: lifestyle control, dietary-induced weight loss, exercise, and diet and exercise. The exercise intervention consisted of combined weight training and walking for 1 hr, three times per week. The diet intervention consisted of a weekly session with a registered diettian to provide education for lowering energy intake with a target weight loss goal of 5%.

A total of 252 participants completed the trial (63 diet, 64 exercise, 58 diet and exercise, 67 control). The primary results showed that the combination of dietary-induced weight loss and exercise resulted in greater improvement in self-reported function and objective measures of mobility than either intervention alone (Messier et al., 2004). However, there were large interindividual responses to the ADAPT treatments, not totally accounted for by compliance, that prompted researchers to examine whether this variation was related to genetic factors. Thus, the researchers recontacted all ADAPT participants for permission to obtain a DNA sample, and 213 participants agreed to provide a blood sample for extraction of DNA. As published earlier, and described below, the researchers found a significant interaction between ACE $I/D$ genotype and exercise training on knee extensor muscle strength (Giaccaglia et al., 2008).

The ACE $I/D$ genotype frequencies in ADAPT were 38% $DD$, 39% $ID$, and 23% $II$, and there were no associations between genotype and baseline measures of obesity, physical function (6-min walk distance, knee extensor muscle strength, self-reported disability), or severity of osteoarthritis. There was no association between ACE $I/D$ genotype and exercise compliance ($DD = 61\% \pm 24\% ; ID = 66\% \pm 23\% ; II = 68\% \pm 24\% ; p = .65$). In analyses conducted in the 176 genotyped participants who completed the exercise intervention ($n = 87$ for exercise; $n = 89$ for no exercise), individuals with the $DD$ genotype showed greater gains in knee extensor strength compared to $II$ individuals. There was a significant ($p = .014$) interaction between ACE $I/D$ genotype and exercise treatment on percent change in knee strength (Fig. 1). In addition, there was a trend towards greater improvement in the self-reported disability score in $DD$ genotypes ($p = .13$). On the other hand, although not statistically significant, changes in 6-min walk distance tended to be higher in the $II$ (increase of $185 \pm 211$ ft) genotype than in the $DD$ (increase of $128 \pm 215$ ft) genotype in response to the combined walking and resistance exercise intervention.

These data indicate that changes in physical function and disability status with exercise training in older individuals may be dependent on ACE $I/D$ genotype. Tasks requiring muscle strength may improve more in $DD$ individuals, whereas tasks requiring endurance may improve more in $II$ individuals. It is likely that these differences would be exaggerated if the exercise stimulus and compliance to exercise were greater than that of the ADAPT study and perhaps if the type of exercise were tailored toward the ACE $I/D$ genotype rather than a combination of the two exercise modes.

**Association Between ACE I/D Genotype and Changes in 400-M Walk Performance With Exercise Training in the Lifestyle Intervention and Independence for Elders Pilot (LIFE-P)**

This ancillary analysis (unpublished) to a recently completed randomized clinical trial of physical activity in 267 elderly (70–89 years of age) men and women at risk for disability (LIFE-P; Pahor et al., 2006) determined whether the ACE $I/D$ genotype influenced improvement in walking endurance (assessed by a 400-m walk test) in response to the exercise intervention. The physical activity intervention was composed...
primarily of walking (~150 min/week), and a successful aging intervention consisting of stretching, education and social support served as the control group.

The ACE I/D genotype frequencies were 38% II, 42% ID, and 20% DD in this sample. After adjustment for gender, clinical site, baseline walking endurance (400-m walk time), and ACE inhibitor use, 400-m walk time after 6 months tended to be faster in the physical activity group than in the successful aging group ($p = .08$). Again, there was substantial variability in changes in walk time in response to physical activity, and researchers found a significant interaction between intervention assignment and ACE I/D genotype (II + ID vs. DD, $p = .03$). In the physical activity group, improvement in 400-m walk time tended to be greater in individuals with an I allele than in DD individuals (−37 s vs. −14 s, $p = .14$), whereas in the SA group, 400-m walk time tended to be slower in the DD homozygotes (+20 s vs. −6 s, $p = .18$). These data indicate that the I allele of the ACE I/D gene variant may be a marker for greater improvement in walking performance with aerobic exercise training in older adults. These results are consistent with findings in young athletes showing enhanced aerobic capacity in those with the ACE I allele.

**Association of ACE I/D Genotype With Exercise Adherence**

It is clear from observation that certain individuals are more physically active and/or engage in sports or purposeful regular exercise more frequently than others. Knowledge of the factors that contribute to individual differences in exercise habits is essential for motivating individuals to engage in exercise. The frequency, intensity, and type of exercise chosen by an individual could all be modified by several factors, including physiological, biomechanical, social, or cultural factors (Perusse, Tremblay, Leblanc, & Bouchard, 1989). In addition, there is a growing body of evidence indicating that there are genetic determinants underlying exercise behavior. Twin studies show high heritability estimates for various physical activity behaviors (Carlsson, Andersson, Lichtenstein, Michaelsson, & Ahlbom, 2006; Duncan et al., 2008; Lauderdale et al., 1997). Moreover, a genome-wide linkage scan identified loci linked to human physical activity behavior in the Quebec Family Study (Simonen et al., 2003). To our knowledge, there are currently no data on the heritability of adherence to a prescribed exercise intervention, most likely due to the difficulty in obtaining such data (i.e., enrolling related family members in an intervention). However, there is some evidence from two genetic association studies indicating that the ACE I/D genotype may be predictive of adherence to aerobic exercise treatments. First, it was reported that sedentary lifestyle was more common among DD than II hypertensive individuals among whom resistance exercise is contraindicated, suggesting that the DD individuals were less likely to engage in aerobic exercise (Winnicki et al., 2004). Moreover, adherence to a 6-month aerobic exercise training intervention was found to be higher in carriers of an I allele, compared to D homozygotes (Thompson et al., 2006). Clearly, additional work is needed to expand and confirm these results; however, because individuals who respond more favorably to an intervention are more likely to adhere to it (McAuley & Courneya, 1993; McAuley & Mihalko, 1998), the ACE I/D genotype may also be found to be a marker of adherence to specific modes of exercise. If this genotype does indeed predict propensity to adhere to an exercise regimen, this knowledge would be a valuable tool to use to increase successful implementation of exercise treatments aimed at preventing or delaying physical disability.

**Summary**

Given the importance of maintaining physical function in older adults, knowledge regarding the effects of the ACE I/D genotype on physical responses to exercise training in the elderly has great clinical relevance and, potentially, a vast impact on public health. A priori knowledge and prescription of the most effective mode of exercise for improving physical function based on a person’s genotype should ultimately lead to more individually effective treatments for physical disability in the elderly. Because of the biologic plausibility for a role of the ACE gene in affecting muscle metabolism, and the consistent findings of an ACE I/D variant by physical activity interaction on both endurance and strength abilities, this easily identifiable genotype represents a prospective screening tool to identify individuals more likely to benefit from a specific type of exercise or least likely to benefit from an alternative mode of exercise. Although additional evidence is needed before screening is put into practice, the accumulated knowledge to date points to the potential for the use of this genetic marker in predicting probability of success to exercise therapy. Thus, older adults may eventually be encouraged to “tailor” their mode of exercise based on their genotype in order to maximize improvement and adherence. In turn, this may lead to more individually effective therapeutic approaches to delaying physical disability in the elderly.

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