

ABSTRACT

Title of Thesis: ASSOCIATION BETWEEN ACE GENOTYPE AND SKELETAL MUSCLE STRENGTH AND VOLUME, AND THEIR RESPONSE TO STRENGTH TRAINING IN OLDER ADULTS

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Introduction: Previous studies have linked an insertion/deletion polymorphism in the angiotensin-converting enzyme (ACE) gene with variability in the response of muscle strength and mass to strength training, though conclusions have been inconsistent across investigations. The purpose of this study was to investigate the possible association between ACE genotype and skeletal muscle strength and volume, and their adaptation to strength training. Methods: A group of older, sedentary adults completed 10-weeks of strength training. Quadriceps muscle strength and volume were measured using one repetition maximum and computed tomography, respectively. Differences were compared among ACE genotype groups (II vs. ID+DD) by sex and race. Results: Baseline and post-training, skeletal muscle strength and volume were not significantly correlated with ACE genotype. ACE genotype was significantly associated with muscle hypertrophy in Caucasian males only ($p=0.02$). Conclusions: The ACE genotype was not associated with skeletal muscle strength, but was associated with muscle hypertrophy in Caucasian males.

ASSOCIATION BETWEEN ACE GENOTYPE AND SKELETAL MUSCLE
STRENGTH AND VOLUME, AND THEIR RESPONSE TO STRENGTH TRAINING
IN OLDER ADULTS

By

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Introduction

Skeletal muscle strength and mass are aspects of health and fitness that play important roles in establishing a person's performance capabilities as well as quality of life. Strength training has been widely documented as resulting in increased muscle strength and hypertrophy. Studies have shown that dynamic strength training (ST) is effective in increasing both skeletal muscle strength and mass in both males and females across the adult age span (53, 117, 165, 281, 285, 314).

Studies have also shown substantial variation among subjects for the adaptation of muscle strength and mass to ST (64, 122, 128, 130, 154), which indicates the potential for a genetic component to ST-induced muscle adaptation. In general, muscle strength and mass are known to be heritable phenotypes. Heritability studies have found skeletal muscle strength to be 14%-80% heritable depending on the muscle group being studied (10, 170, 243, 294, 301, 315, 375) and the type, speed and angle of muscle contraction being measured (300). Similarly, skeletal muscle mass has been shown to be 25%-95% heritable, with the wide range of values being explained by the method of measurement used to calculate muscle mass (9, 26, 161, 263, 299). Finally, a limited number of studies have shown that the adaptation of muscle phenotypes to ST also appears to have a genetic component (288, 293). One study in particular by Thomis et al (292), concluded that strength training-related genetic factors were responsible for approximately 20% of the variation found in response of 1RM and isometric strength measurements to strength training. These studies indicate the importance of genetic influences on muscle strength and mass, as well as the adaptation to strength training.

Despite evidence of the importance of genetic factors, few specific candidate genes have been identified as being important to the response of muscle phenotypes to ST (226). One gene that has emerged recently as a candidate is angiotensin-converting enzyme (ACE). An insertion/deletion polymorphism in this gene has been found to be a marker of activity for this enzyme, with those who carry the deletion (D) allele having higher ACE enzyme activity (46). Studies have found that homozygotes for the I allele (II) have significantly less ACE activity than heterozygotes (ID), with heterozygotes (ID) having lower ACE activity than homozygotes for the D allele (DD) (321, 358). Studies have concluded that ACE genotype is responsible for half of the variation in ACE activity (252, 369).

Skeletal muscle has substantial ACE activity, owing to a local renin-angiotensin system (RAS) (246). Investigators have linked angiotensin II, generated by ACE as the end product of the RAS, to overload-induced cardiac hypertrophy (193, 257, 276) and smooth muscle hypertrophy (23, 101). Gordon et al (109) concluded that ACE inhibitors significantly reduced hypertrophy in overloaded muscles, indicating a role for angiotensin II in skeletal muscle hypertrophy. These findings were supported in a later study by Westerkamp and Gordon (344), in which ACE inhibition attenuated overload-induced increases in muscle weight, muscle protein content and fiber cross-sectional area, each of which were increased in control animals. McBride (183) found that blocking angiotensin II's AT1 receptor attenuated eccentric training-induced hypertrophy and strength gains in Sprague-Dawley rats. These studies provide evidence of the potential importance of the RAS and ACE in particular to skeletal muscle hypertrophy in response to overload.

Studies investigating the effects of ACE genotype on skeletal muscle strength and mass in response to strength training have yielded inconsistent results. Folland et al (82) and Williams et al (357) reported positive associations between the D allele and muscle strength. Moreover, Folland et al (81) showed a gene*training interaction between ACE genotype and ST, such that carriers of the D allele (DD + ID) had greater increases in isometric strength compared to those who were homozygous for the I allele (II). In contrast, Williams et al (356) showed the D-allele carriers to be stronger at baseline, but failed to show a gene*training interaction. More recently, Pescatello et al (215) and Thomis et al (307) failed to support the correlation between the D allele and muscle adaptation to ST. Pescatello et al (217) concluded that subjects with the I allele had greater gains in maximum voluntary contraction in both the trained and untrained arms. This study also concluded that ACE genotype was not related to baseline measures of strength or size (214). Finally, Thomis et al (306) concluded that ACE genotype had no effect on 1RM strength response to 10 weeks of ST.

Given the data indicating a possible role for ACE in muscle overload-induced hypertrophy and the findings of some studies that ACE genotype is associated with muscle phenotypes, the purpose of this study was to investigate the association between ACE genotype and skeletal muscle strength and mass, and their adaptation to strength training in older men and women. Previous investigations have not studied these associations in females or in different race groups. The inconsistencies in the literature may also be due to insufficient sample size and/or measurement techniques, particularly in evaluating muscle size. The current study is a large-scale ST intervention using

careful measures of muscle size and strength designed to more fully test the possible association between ACE genotype and muscle phenotypes.

Hypotheses

Hypothesis 1: ACE genotype will not be correlated with baseline muscle strength or volume regardless of sex or race.

Rationale: Hypothesis 1 was based on the findings of Folland et al (84) and Pescatello et al (222) who independently found no baseline association between muscle strength and ACE genotype, as well as on the findings of Pescatello et al (223) and Thomis et al (305) who found no correlation between ACE genotype and muscle cross-sectional area.

Hypothesis 2: Those subjects who are homozygous for the I allele (II genotype) will have smaller increases in muscle strength and mass in response to strength training than carriers of the D allele (DD + ID) in all sexes and races.

Rationale: Hypothesis 2 was based on the findings of Folland et al (80), who presented greater strength improvements in ID and DD genotypes with isometric and dynamic strength training. Moreover, a biological rationale for greater muscle volume increases in D allele carriers is provided by studies from Gordon et al (108), Westerkamp and Gordon (343), and McBride (182), who collectively show that angiotensin II is required for overload-induced muscle hypertrophy to occur.

Methods

Subjects: The subjects consisted of 261 previously inactive, relatively healthy volunteers between the ages of 50 and 85 years old. Volunteers were recruited through a variety of sources including mailed brochures, newspaper articles and word of mouth from subjects involved in the study. Prior to acceptance into the study, volunteers were exposed to a rigorous screening procedure. This procedure included a phone interview, a medical clearance form to be completed by their primary care physician and an in depth medical history. In order to be considered for the study, volunteers must have been sedentary, as operationally defined as a person who performs less than 20 minutes of vigorous activity per week. Participants in the study were required to be nonsmokers and completely void of significant cardiovascular, metabolic and musculoskeletal maladies that could in any way limit their ability to perform heavy resistance training. Subjects who were already taking medications for more than 3 weeks were included into the study with the understanding that they would maintain the same medicine and dosage for the entirety of the study. After all methods and procedures were explained, volunteers who chose to participate were required to read and sign a written consent form that had been previously approved by the Institutional Review Board of the University of Maryland, College Park. Throughout the study, subjects were continually reminded not to alter their physical activity levels or habitual dietary intake and body weight was measured weekly to confirm the absence of weight loss or gain.

Strength Testing: One repetition maximum strength tests (1RM) were performed on both legs separately prior to and at the completion of the strength training intervention. These tests were performed on the same air powered resistance machines

(Keiser Sports/Health Equipment, Fresno, CA) that were used during the training, and assessed knee extension strength. This exercise could be tested using objective criteria and therefore provided a standardized measure of each subject's strength. These objective criteria involved a light system to indicate a successful attempt when the knee was extended beyond 165 degrees. The 1RM was defined as the maximum resistance that could be moved throughout the full range of motion with proper form one time. Approximately the same number of trials (6-8) and the same amount of rest between trials (about 1 minute) were used to obtain the 1RM both at baseline and post-training. Prior to the baseline test, each subject underwent three familiarization sessions with low resistance and was counseled on proper exercise technique, as well as stretching and an appropriate warm up. These familiarizations served to validate the measured 1RM by preventing the large gains that tend to occur as the subjects learn the testing procedure. They also helped to prevent injuries and muscle soreness in the subjects. Each test was conducted with consistent seat height, body positioning, verbal commands and encouragement. Before each test, the subject rested for 5 minutes and then resting blood pressure was measured. This measurement was followed up with a 1 minute warm up on a cycle ergometer. All subjects wore a seat belt pulled snugly across the pelvis to avoid the recruitment of muscle groups outside of the quadriceps. The 1RM measurement was achieved by gradually increasing the resistance after each successful lift until a maximal load was reached. Following each attempt, the subject was asked to quantify any pain or discomfort they experienced during the lift and to provide the tester with a numerical rating of perceived exertion using the Borg scale.

Muscle Volume Testing: Quadriceps muscle volume was measured on both the trained and untrained thighs at baseline and after ten weeks of unilateral training using computed tomography imaging (CT). Measurements of the untrained leg were taken to account for seasonal and biological variation in muscle volume. Axial sections of each thigh were obtained between the most distal point of the ischial tuberosity and the most proximal boundary of the patella while the subject was placed in the supine position. Each slice was set at 10mm and slices were separated by 40 mm. This protocol was based on previous work done in our lab by Tracy et al (322). Quadriceps muscle volume was estimated using a 4cm interval between the center of each section. Each CT image was obtained at 120kVp with the scanning time set at 1s at 40mA. A 48cm field of view and 512 x 512 matrix was used to obtain a pixel resolution of 0.94mm.

For each section of the thigh, cross-sectional area of the quadriceps muscle group was manually outlined. This manual outlining was done on every section starting from the border of the proximal patella and ending when the quadriceps are no longer distinguishable from the hip flexor and adductor muscle groups. The same number of sections were measured at baseline and post-training for each subject to ensure within subject replication. Investigators were blinded to the identity to the subject, date of scan and training status.

Strength Training Intervention: The strength training intervention consisted of approximately 10 weeks of unilateral (one-legged) knee extensions on the dominant leg. The exercise was performed on the same Keiser air powered resistance machines that were used for the 1RM testing. This machine allows for the easy changing of resistance without interrupting the cadence of the exercise. The untrained leg served as an internal

control for each subject and therefore remained in a relaxed position for the entirety of the training program.

Before each exercise session, the subjects rested for 5 minutes and then resting blood pressure was measured. Any subject whose blood pressure was abnormally elevated was not permitted to train on that day. Once the blood pressure had been measured, the subject warmed up for about 2 minutes on a cycle ergometer. They were then seated in a chair with a seat belt tightly secured across the pelvis to isolate the quadriceps muscle. Seat positioning in the chair was based on the body dimensions of the subject and was uniform for each training session. The training protocol included 5 sets of unilateral knee extensions for those under 75 years of age and 4 sets for those 75 and older. The decreased workload for the older subjects was an effort to avoid overtraining. The first set served as a specific warm up and consisted of 5 repetitions at 50% of the previously determined 1RM. This resistance did not change throughout the course of the training. The second set, or the first working set, consisted of 5 repetitions at the current 5 repetition maximum (5RM). The 5RM was initially estimated based on previous data showing that it corresponds with around 85% of 1RM in most people (120). The 5RM value was increased throughout the training program to account for increases in strength. The third set, or second working set, began with the subject doing repetitions at the 5RM once again. Once they were unable to complete full repetitions (usually around repetition 4-5), the resistance was decreased just enough to allow them to complete one or two more repetitions before once again failing to do a complete repetition. This process continued until 10 repetitions had been completed. This same procedure was continued for the fourth and fifth sets, but the total number of repetitions completed was

increased to 15 and 20 repetitions respectively. This protocol required near maximal effort on every repetition, while still allowing for a high volume of training. The second, third, fourth, and fifth sets were preceded by rest periods of 30, 90, 150, and 180 seconds respectively. Each repetition was comprised of a muscle shortening phase lasting approximately 2 seconds and a muscle lengthening phase of around 3 seconds. The same light system that was used to signal a complete repetition during the 1RM test was also used during training to indicate full range of motion for each repetition. Throughout each set, subjects were provided with verbal motivation and feedback by the investigators. This verbal communication included audible counting of repetitions, reminders to continue breathing normally during the exercise and cues to maintain full range of motion and continue lifting until the light was illuminated. For those subjects who were 75 years or older, the fourth set of 15 repetitions served as their final set. Immediately after the completion of the 20th repetition in the final set (or 15th for those in the older group), peak blood pressure was measured while the subjects remained in the exercise chair. Following the peak blood pressure measurement, subjects performed supervised stretches of the quadriceps, hamstrings, calves and hip flexors. They then sat and rested/recovered for 3 minutes before a final post-exercise blood pressure was measured.

Genotyping: Blood samples were obtained from each subject's antecubital vein prior to the strength training intervention using standard, sterile techniques. DNA was extracted from whole blood samples using standard procedures (Gentra PureGene System). The ACE I/D polymorphism was genotyped using a polymerase chain reaction (PCR)-based DNA amplification using flanking primers. The sense primer sequence was 5' CTGGAGACCACTCCCATCCTTTTCT 3' and the antisense primer was 5'

GATGTGGCCATCACATTCGTCAGAT 3'. The PCR product was a 190 base pair fragment for the deletion (D) genotype and a 490 base pair fragment for the insertion (I) genotype (247). Genotyping was performed by separating the PCR amplicon on a 2% agarose gel with ethidium bromide staining (325). Positive control samples for each genotype were obtained through direct DNA sequencing and used to validate all genotyping assays.

Statistical Analysis: All data for this study were analyzed using SAS computer software for Windows (version 9.1). Statistical analysis for this investigation used analysis of covariance (ANCOVA) to compare the means among ACE D-allele carriers and non-carriers (II genotype vs. ID+DD genotypes). D allele carriers were grouped together to allow for easy comparison with other studies that performed similar analyses. Furthermore, analysis of the data across the three genotype groups showed no difference between ID heterozygotes and DD homozygotes. Covariables included for each measure of muscle strength and volume are presented in the results section. Men and women were analyzed separately given known differences in muscle phenotypes. African Americans and Caucasians were also analyzed separately in sub-analyses. Change in muscle volume was analyzed after subtracting changes in the untrained thigh using the equation: (Post Trained Leg – Post Untrained Leg) – (Baseline Trained Leg – Baseline Untrained Leg). Removing the untrained leg corrected for changes in muscle volume that were not related to the strength training intervention.

Paired T-tests were performed within ACE D-allele carrier and non-carrier groups to confirm that the strength training intervention was adequate to affect the muscle strength and mass phenotypes. Baseline characteristics are presented as least squared

means \pm standard deviation. All other data are presented as least squared means \pm standard error. Statistical significance for all analyses was as accepted at $p \leq 0.05$.

Results

Subject Characteristics: A total of 243 subjects were studied and their characteristics are shown in Table 1; no significant differences were observed.

Table 1: Subject characteristics by sex & ACE genotype

	Men			Women		
	II	ID	DD	II	ID	DD
N	14	29	48	29	50	73
Age	62.8 ± 8.5	63.8 ± 7.9	62.1 ± 8.7	64.9 ± 8.9	62.2 ± 8.2	61.4 ± 9.3
Hgt	173.5 ± 5.7	173.6 ± 7	175.5 ± 7.8	162 ± 6.3	162.5 ± 5.9	162 ± 6.7
Wgt	80.8 ± 10.4	88.9 ± 11.3	92.6 ± 15.4	73.2 ± 14.9	77.3 ± 15.3	75.7 ± 15.7
FM	22 ± 5	26 ± 6.8	26.4 ± 8.1	29.8 ± 9.9	31.8 ± 9.4	30.5 ± 9.8
FFM	58.8 ± 7.1	62.9 ± 6.5	66 ± 9.2	43.4 ± 6.1	45.5 ± 7.2	45.3 ± 6.8

Data presented as means ± standard deviation. N = Number of subjects, Hgt = Height (cm), Wgt = Weight (kg), FM = Fat Mass (kg) and FFM = Fat Free Mass (kg).

Table 2 shows the baseline subject characteristics of the two separate genotype groups (II homozygotes and D allele carriers) that were explored in this investigation, separated by males and females. There were significant differences found between genotype groups in the males for baseline weight (kg) ($p = 0.02$) and fat free mass (kg) ($p = 0.02$). There were no significant differences among females for any of the baseline subject characteristics.

Table 2: Subject characteristics by sex and ACE genotype group

	Males		Females	
	DD + ID	II	DD + ID	II
N	77	14	123	29
Age	62.7 ± 0.95	62.8 ± 2.27	61.7 ± 0.79	64.9 ± 1.65
Height	174.8 ± 0.86	173.5 ± 1.58	162.2 ± 0.58	162 ± 1.18
Weight	91.3 ± 1.63 *	80.8 ± 2.9 *	76.3 ± 1.42	73.2 ± 2.76
FM	26.3 ± 0.89	22 ± 1.38	31 ± 0.88	29.8 ± 1.83
FFM	64.9 ± 0.99 *	58.8 ± 1.96 *	45.4 ± 0.63	43.4 ± 1.13

Data presented as means ± standard error. Investigation groups are II homozygotes and D allele carriers. Missing data is due to lack of genotype data available. Significant difference between genotype groups are indicated by a * ($p < 0.05$). N = Number of subjects, Hgt = Height (cm), Wgt = Weight (kg), FM = Fat Mass (kg) and FFM = Fat Free Mass (kg).

Table 3 shows the subject characteristics of the separate sex and race groups that were investigated. The African American males were significantly younger than the Caucasian males ($p = 0.03$) and had significantly more fat free mass than Caucasian males ($p = 0.007$). The African American females were significantly younger ($p = 0.0002$), taller ($p = 0.003$), and heavier ($p = 0.03$) than the Caucasian females.

Table 3: Subject characteristics by sex and race

	Males		Females	
	Caucasian	AA	Caucasian	AA
N	61	25	86	56
Age	64 ± 1.11*	59.8 ± 1.39*	64.4 ± 1.03*	59.1 ± 0.95*
Height (cm)	175.1 ± 0.91	174.4 ± 1.57	161.6 ± 0.7*	164.4 ± 0.61*
Weight (kg)	87.6 ± 1.76	93.5 ± 3.09	74.4 ± 1.77*	80.1 ± 1.81*
FM (kg)	25.1 ± 0.96	25.7 ± 1.55	30.4 ± 1.12	32.3 ± 1.21
FFM (kg)	62.3 ± 1.06*	67.8 ± 1.84*	44 ± 0.75	47.9 ± 0.75

Data presented as means ± standard error. Investigation groups are II homozygotes and D allele carriers. Significant difference between genotype groups are indicated by a * ($p < 0.05$). N = Number of subjects, Hgt = Height (cm), Wgt = Weight (kg), FM = Fat Mass (kg) and FFM = Fat Free Mass (kg).

Genotype Frequency: Table 4 shows the genotype and allele frequencies for all subjects. Of the 243 total subjects involved in the analysis, there were 43 II homozygotes, 79 ID heterozygotes, and 121 DD homozygotes. For analytical purposes, this equated to 43 II homozygotes and 200 D allele carriers. Genotype frequency was further investigated based on race. Our study included 147 Caucasians and 81 African Americans. The Caucasian group included 30, 44, and 73 II, ID and DD genotypes respectively, which equated to 30 II homozygotes versus 117 D allele carriers. The African American group included 13, 27, and 41 II, ID and DD genotypes respectively, which equated to 13 II homozygotes versus 68 D allele carriers.

Table 4: ACE genotype & allele frequencies by race

	II	ID	DD	I allele	D allele
Total (%)	43 (17.7%)	79 (32.5%)	121 (49.8%)	34%	66%
Caucasian	30 (20.4%)	44 (29.9%)	73 (49.7%)	35.4%	64.6%
African American	13 (16.1%)	27 (33.3%)	41 (50.6%)	32.7%	67.3%

Of the 13 African Americans who were II homozygotes, only one was male. This small number of subjects within this genotype group was insufficient to perform any meaningful analysis and therefore the comparisons of muscle phenotypes between African American males who carry the D allele and African American II homozygotes were not used to draw any conclusions.

Muscle Strength: Analysis of the entire cohort by genotype group resulted in no significant differences for 1RM strength at baseline ($p = 0.13$), post training ($p = 0.13$), or change with training ($p = 0.68$; data not shown). No significant differences were observed for muscle strength between genotype groups in either males or females at any point of analysis (Table 5). Analysis of strength measures included covarying for age, height and muscle volume. At baseline, statistical analysis yielded no significant difference in either males ($p = 0.18$) or females ($p = 0.52$). Similarly, there was also no significant difference in 1RM between genotype groups after strength training in males ($p = 0.42$) or females ($p = 0.15$). Finally, there was no significant gene*training interaction between ACE genotype and strength training. This lack of interaction resulted in no significant difference in change in 1RM with training between the groups in either males ($p = 0.52$) or females ($p = 0.77$). Analyses excluding muscle volume as a covariate similarly yielded no significant differences (data not shown). Strength analysis of the entire cohort by genotype (II vs. ID vs. DD) yielded no significant differences for baseline 1RM ($p = 0.24$), post training 1RM ($p = 0.31$) and change in 1RM ($p = 0.64$).

Table 5: Muscle strength in males and females grouped by ACE genotype

	Males		p-Value	Females		p-Value
	DD + ID	II		DD + ID	II	
N	59	12		72	20	
Baseline 1RM	34.05 ± 0.63	36.24 ± 1.49	0.18	18.42 ± 0.38	18.97 ± 0.75	0.52
Post Training 1RM	41.46 ± .76	42.98 ± 1.72	0.42	22.81 ± 0.44	24.19 ± .85	0.15
Δ 1RM	8.25 ± 0.57	7.33 ± 1.31	0.52	5.04 ± 0.34	5.26 ± 0.65	0.77

Data presented as least squares means ± SE. 1RM values are presented in kg.

Muscle Volume: Analysis of the entire cohort showed no significant differences for muscle volume at baseline ($p = 0.06$), post training ($p = 0.6$) or change with training ($p = 0.31$; data not shown). There were no statistically significant differences between the genotype groups for any of the muscle volume measures in either sex group (Table 6). Covariables for the analysis of muscle volume were age and height. At baseline, there was no significant difference in muscle volume in females ($p = 0.27$), though male D-allele carriers tended to have higher muscle volume levels than the II group ($p = 0.07$). Post training muscle volume also lacked a significant difference between genotype groups in males ($p = 0.11$) and females ($p = 0.88$). Finally, there was also no significant difference between groups in change in muscle volume with training in either males ($p = 0.47$) or females ($p = 0.77$). Muscle volume analysis of the entire cohort by genotype (II vs. ID vs. DD) yielded no significant differences for baseline muscle volume ($p = 0.07$), post training muscle volume ($p = 0.52$) and change in muscle volume ($p = 0.92$).

Table 6: Muscle volume in males and females grouped by ACE genotype

	Males		p-Value	Females		p-Value
	DD + ID	II		DD + ID	II	
N	56	13		69	21	
Baseline MV	1882.92 ± 31.74	1738.21 ± 73.75	0.07	1201.06 ± 20.26	1150.23 ± 40.56	0.27
Post Training MV	2029.55 ± 37.02	1887.05 ± 79.61	0.11	1271.32 ± 25.35	1263.43 ± 47.58	0.88
Δ MV	167.19 ± 9.63	185.28 ± 22.88	0.47	91.66 ± 6.25	87.87 ± 11.58	0.77

Data presented as least squares means ± SE. Muscle Volume values are in cm³.

Muscle Strength by Race: Tables 7 and 8 show the strength differences between genotype groups separated by race and sex. Baseline 1RM was not significantly different

between D allele carriers and II homozygotes in either Caucasian males ($p = 0.59$) or Caucasian females ($p = 0.77$). Post training 1RM was also not significantly different between genotype groups in Caucasian males ($p = 0.70$) and females ($p = 0.44$). Change in 1RM was also not significantly different between the genotype groups in either the Caucasian males ($p = 0.89$) or Caucasian females ($p = 0.31$). In African Americans baseline 1RM ($p = 0.42$), post training 1RM ($p = 0.32$) and change with training ($p = 0.35$) were not significantly different between genotype groups in African American females. Once again, the covariables for these statistical analyses were age, height, and muscle volume. Conclusions about African American males could not be drawn do to a lack of II homozygotes in this group.

Table 7: Muscle strength in Caucasian and African American males grouped by ACE genotype

	Caucasian Males		P-Value	African American Males		P-Value
	DD + ID	II		DD + ID	II	
N	42	11		17	1	
Baseline 1RM	33.30 ± 0.71	34.16 ± 1.40	0.59	37.27 ± 1.26	49.79	0.05
Post Training 1RM	40.59 ± 0.85	41.32 ± 1.65	0.70	46.30 ± 1.90	48.28	0.81
Δ 1RM	7.70 ± 0.52	7.53 ± 1.02	0.89	10.67 ± 0.8	-0.31	0.19

Data presented as least squares means ± SE. 1RM values are presented in kg.

Table 8: Muscle strength in Caucasian and African American females grouped by ACE genotype

	Caucasian Females		p-Value	African American Females		p-Value
	DD + ID	II		DD + ID	II	
N	49	12		23	8	
Baseline 1RM	16.67 ± 0.43	16.39 ± .83	0.77	22.22 ± .82	23.69 ± 1.57	0.42
Post Training 1RM	21.04 ± 0.49	21.92 ± 1.0	0.44	27.3 ± 0.93	29.18 ± 1.57	0.32
Δ 1RM	4.77 ± 0.40	5.69 ± .81	0.31	6.14 ± 0.74	4.73 ± 1.25	0.35

*Data presented as least squares means ± SE. 1RM values are presented in kg. Significant difference between genotype groups are indicated by a * ($p < 0.05$).*

Muscle Volume by Race: Baseline muscle volume was not significantly different between the genotype groups in Caucasian males ($p = 0.24$), Caucasian females ($p = 0.20$), or African American females ($p = 0.26$; Tables 9 and 10). Similarly, post training muscle volume was not significantly different between genotype groups in Caucasian males ($p = 0.30$), Caucasian females ($p = 0.90$), or African American females ($p = 0.46$). Change in muscle volume with strength training was significantly different in Caucasian males ($p = 0.02$) with the D allele carriers demonstrating greater hypertrophy with training than II homozygotes. This difference was not observed in Caucasian females ($p = 0.77$), or African American females ($p = 0.71$). All of the statistical analyses performed on the muscle volume data were covaried for age and height. Once again, the number of II homozygotes among African American males was inadequate to draw any conclusions about this group.

Table 9: Muscle volume in Caucasian and African American males grouped by ACE genotype

	Caucasian Males		p-Value	African American Males		p-Value
	DD + ID	II		DD + ID	II	
	39	12		17	1	
Baseline MV	1801.68 ± 31.24	1718.79 ± 61.1	0.24	2094.13 ± 77.26	1960.77	0.72
Post Training MV	1949.71 ± 39.51	1863.32 ± 71.90	0.30	2246.11 ± 86.60	2202.14	0.91
Δ MV	174.64 ± 9.92	124.88 ± 18.06	0.02*	193.59 ± 20.70	280.18	0.36

Data presented as least squares means ± SE. Muscle Volume values are in cm³. Significant difference between genotype groups are indicated by a * (p < 0.05).

Table 10: Muscle volume in Caucasian and African American females grouped by ACE genotype

	Caucasian Females		p-Value	African American Females		p-Value
	DD + ID	II		DD + ID	II	
	46	13		23	8	
Baseline MV	1114.09 ± 21.90	1050.87 ± 42.75	0.20	1404.41 ± 35.12	1316.27 ± 67.64	0.26
Post Training MV	1187.11 ± 25.88	1180.08 ± 50.19	0.90	1490.55 ± 48.31	1419.21 ± 80.9	0.46
Δ MV	87.39 ± 6.31	87.35 ± 12.0	0.77	105.32 ± 15.82	93.47 ± 26.5	0.71

Data presented as least squares means ± SE. Muscle Volume values are in cm³. Significant difference between genotype groups are indicated by a * (p < 0.05).

Discussion

The results of this investigation indicate no clear association of the ACE I/D genotype with skeletal muscle strength before or after strength training in older adults. The results do provide evidence of a minor association between ACE genotype and muscle volume in males, possibly limited to Caucasian males. Based on previous studies, we had hypothesized that the D allele of the ACE gene would not be associated with baseline measures of skeletal muscle strength or muscle volume. This hypothesis was partially supported, in that baseline muscle strength was not associated with ACE genotype. However, this investigation revealed a tendency for male carriers of the D allele to have greater baseline muscle volume than II homozygotes. The second hypothesis was that carriers of the D allele would exhibit greater increases in muscle strength and volume after strength training compared to the II genotype group. Once again, this hypothesis was only partially upheld by the data, in that Caucasian males who carried at least one D allele exhibited significantly more hypertrophy than II homozygotes. When considered within the context of previous studies, the present investigation suggests that ACE genotype play a minor role in skeletal muscle size and its adaptation to strength training, but potentially only in certain subgroups within the population.

The lack of association between ACE genotype and baseline strength reported here supports earlier findings by both Folland et al (79) and Pescatello et al (213). These previous studies concluded that baseline isokinetic, isometric, and isotonic muscle strength were not associated with ACE genotype in either the upper arm (212) or the leg (78). In contrast, Williams et al (355) reported a significant association between ACE

genotype and pretraining isometric and isokinetic strength in the knee extensors. Specifically, this study concluded that those with the most circulating ACE, DD homozygotes, were the strongest, whereas those with lower ACE levels, II homozygotes, were the weakest (354).

The lack of gene*training interaction affecting muscle strength was contrary to our a priori hypothesis. Folland et al (85) tested the interaction of ACE genotype with isometric strength training as well as the interaction of ACE genotype with isotonic strength training. Subjects in this study performed isometric strength training on one leg and isotonic strength training on the other leg. Strength was then tested using both isometric and isokinetic knee extension tests. The authors found that the response to isometric strength training was strongly associated with ACE genotype and that the carriers of at least one D allele experienced significantly greater strength increases than II homozygotes. They also found a similar, but non-significant, tendency for the response of isometric strength to isotonic strength training to be greater in the D allele carriers vs. the II genotype group (77). The authors explained this non-significant strength gain on less uniformity and duration of loading during the isotonic training (76). However it seems likely that some strength gain was masked by a disconnect between the isotonic training stimulus and the isometric strength testing. Pescatello et al's (211) study of upper arm strength reported a gene*training interaction that was different than the one found by Folland et al: greater increases in maximal voluntary contraction with training in carriers of the I allele than in DD homozygotes. Pescatello et al also observed that biceps 1RM increased more in the carriers of the D allele when testing the untrained arm, indicating a potential gene*training interaction that is involved with muscle cross-

education (210). These two previous studies thus present conflicting results regarding the nature of a gene*training interaction that links ACE genotype with strength training, though the findings of Folland et al are more consistent with the biological rationale for ACE genotype. The results of the present study did not support any of the findings of these studies, in that we failed to observe a significant difference in increases of dynamic muscle strength with strength training between D allele carriers and II homozygotes. Furthermore, our data revealed no significant difference between groups regarding muscle strength both when muscle volume was and was not corrected for as a covariate.

The present investigation observed a tendency for males who carried the D allele to have greater baseline muscle volume. Although these results did not reach statistical significance, they were in line with our hypothesis that the D allele would provide an advantage in tests of muscle size and may represent an important association. It was also observed that Caucasian males who carried the D allele had a greater hypertrophic response to strength training than the Caucasian males who were II homozygotes. Previous studies that have investigated the association of ACE genotype with the muscle size response to strength training have also concluded that there is no association (209, 304). However, both of these studies used muscle cross-sectional area to assess muscle size. In the present investigation, muscle size was assessed using muscle volume which is a more effective technique in that it measures the size of the entire muscle rather than relying on a representative slice (255).

The likely mechanism through which ACE genotype affects skeletal muscle size is through production of angiotensin II. ACE is responsible for producing angiotensin II, which acts as a growth factor in cardiac (186, 260) and smooth muscle cells (22, 102).

Montgomery et al (190) showed left ventricular hypertrophy in response to exercise was greater in carriers of the D allele compared to II homozygotes. This indicates a potential interaction between exercise-induced overload and ACE genotype that affects muscle hypertrophy. As discussed previously, the presence of a local RAS in skeletal muscle and the consistent association of the D-allele with higher ACE levels provides a rationale for the hypothesis that ACE genotype may influence angiotensin II levels in skeletal muscle. Further biological support for a potential gene*training interaction comes from studies that have shown an interaction between angiotensin II and overload-induced skeletal muscle hypertrophy in animal models (107, 342). These studies found that decreased levels of angiotensin II, resulting from ACE inhibition, effectively attenuated skeletal muscle hypertrophy that normally occurred under overload (106, 341). Another study has shown that blocking the AT₁ receptors, through which angiotensin II signals muscle cells, can attenuate exercise-induced skeletal muscle hypertrophy (181). These studies provide a biological rationale for explaining a potential role for ACE genotype in affecting muscle size. In these animal studies, ACE inhibition was used to decrease the production of angiotensin II through the renin-angiotensin system. Similarly, in people who are II homozygotes for the ACE gene, the conversion of angiotensin I into angiotensin II is lower than in those who carry the D allele (35). Therefore, these studies provide support for the hypothesis that II homozygotes would have an attenuated hypertrophic response to overload, much like the animal models injected with ACE inhibitors. In the current study, Caucasian male carriers of the D allele demonstrated greater overload-induced hypertrophy compared to II genotype carriers, consistent with expectations derived from these studies. The effect of ACE on skeletal muscle size has

been disputed in the literature. Some previous studies have found that ACE inhibition resulted in reduced muscle atrophy rather than being associated with decreased muscle size as would be expected from the work described above (31, 268, 280). However, these studies were commonly performed on diseased subjects. It is possible that in these populations ACE inhibitors allowed subjects to better tolerate physical activity which could act to decrease muscle wasting caused by a sedentary lifestyle (49).

The results of the present study as well as those that have previously studied ACE genotype and strength training indicate that the ACE I/D genotype is not a major determinant of skeletal muscle strength or size or their response to strength training, but it may play a minor role in some sub-groups. It is possible that the influence of ACE genotype is only observed in males, and perhaps may be further limited to Caucasian males, though sample size limitations in the present study preclude strong conclusions in this regard. Folland et al (75) showed a gene*training interaction regarding muscle strength in a cohort of Caucasian males. Similarly the only significant finding of the current study, increased hypertrophy among D allele carriers, was also limited to Caucasian males. Given the inconclusive nature of the results of various studies, it seems unlikely that ACE I/D genotype is more than just a minor contributor in the determination of skeletal muscle strength and size response to training.

To the best of our knowledge, this investigation is the first large-scale study of the association between ACE genotype and skeletal muscle strength and size using muscles in the lower body. The two previous studies that investigated this association in the knee extensors only had 33 and 44 subjects, respectively, who completed the training protocol (74, 353). The current investigation is also the first to study these associations in an

older population. All of the prior studies that investigated ACE genotype and strength training involved subjects who were 30 years old or younger (73, 216, 312, 352). Finally, other than the study by Pescatello et al (208), no previous study examined females or racial minorities (72, 303, 360) and Pescatello et al did not report separate analyses for sex- or race-based subgroups. Thus, to the best of our knowledge, the current study is the first to perform separate gender and race based analyses of the effect of ACE genotype on skeletal muscle strength and muscle volume.

ACE genotype frequencies have been shown to differ among race groups (17, 20, 173). Commonly, the allele frequency among Caucasians for this insertion/deletion polymorphism is approximately 50% for both the I and D alleles compared to 41% I alleles and 59% D alleles in African Americans (172). However, in the present study, the allele frequency of the Caucasian subjects was 35% for the I allele and 65% for the D allele. The African American subjects had an allele frequency of 32.7% for the I allele and 67.3% for the D allele, which was much closer to the expected distribution within this population. The atypical genotype distribution among Caucasian subjects and the typical distribution among African Americans resulted in the total group having allele frequencies that were high for the D allele (34% I allele and 66% D allele frequencies). We are uncertain why our subject group had this abnormal allele frequency. Our genotyping protocol has been validated and is a commonly accepted and utilized protocol. However, it seems unlikely that this atypical allele distribution among the Caucasian subjects were relevant to our results. The statistical analysis between genotype groups within Caucasians resulted in p-values that did not approach significance in any measures of muscle strength or size except for change in muscle

volume in Caucasian males. It seems unlikely that the increased number of D allele carriers were able to cause such a high level of non-significance.

The main limitation of this study was the inability to draw conclusions about African American males. This population subgroup had to be removed from the analysis due to an insufficient number of II homozygotes among that group. This limitation hinders our ability to conclude if the ACE gene is associated with muscle strength and size in all males or only in Caucasian males. Further limitations were that subjects were responsible for maintaining their habitual dietary intake and remain sedentary throughout the entire study. It is possible that some subjects may have unknowingly altered these variables.

In summary, the present study observed no clear association between ACE genotype and baseline or post training skeletal muscle strength in untrained older adults. The present study did show an association between ACE genotype and skeletal muscle volume adaptations as a result of strength training in Caucasian males, with carriers of the D allele having greater muscle hypertrophy than the II homozygotes. There was also a tendency among all male subjects for the D allele carriers to have greater baseline muscle volume than their II counterparts. However when subjects were divided by race, this association at baseline no longer approached significance. These results are generally supportive of animal studies that have shown ACE inhibition to attenuate hypertrophic response in the face of muscle overload. Further research needs to be done to investigate this association in other male populations, particularly African Americans who typically have a higher frequency of D allele carriers but were lacking in the present investigation. There should also be further investigation into the association of ACE

genotype with baseline muscle volume in males that approached significance in the present study. Our results, in combination with those of others, do provide evidence that at most the ACE I/D genotype is contributing only a small fraction of the variation in muscle phenotypes. Further research is clearly necessary to identify and investigate other candidate genes that may be important in determining muscle strength and size and their response to strength training.

Conclusions

Conclusion 1: It was hypothesized that ACE genotype would not be correlated with either baseline muscle strength or baseline muscle volume. Our data indicated no significant difference between ACE genotype groups regarding muscle strength and muscle volume. Therefore, this hypothesis was supported by our data. However, there was a tendency that approached significance for males who carry the D allele to have greater baseline muscle volume than II homozygote males.

Conclusion 2: The second hypothesis that we investigated was that II homozygotes would have smaller increases in muscle strength and volume after the completion of a strength training intervention compared to D allele carriers. Instead, the data indicated that there was no difference in strength increases with strength training between ACE genotype groups. Furthermore, most groups showed no significant difference in muscle volume increases with strength training between ACE genotype groups. However, there was a significant difference in change in muscle volume among Caucasian males that was supportive of our hypothesis. Therefore, this hypothesis was partially supported by our data.

Appendix A – Limitations of Study

Delimitations:

1. The scope of the race analysis of this study was delimited to 147 Caucasians and 81 African Americans and the scope of the sex analysis was delimited to 91 males and 152 females. The subjects were further delimited to people between the ages of 50 and 85 years.
2. Participation in the study was delimited to healthy participants free of musculoskeletal or cardiovascular disease and maintained a level of independence that allowed them to attend training sessions at our facility three times per week.
3. Subjects were delimited to volunteers who lived within 20 minutes of the training/testing facility and responded to mailed advertisements.

Limitations:

1. This study is limited to drawing conclusions about the population from which the subjects were selected. This population includes older adult males and females characterized by two racial groups, African Americans and Caucasians. The ability to generalize our conclusions is further limited to people of similar age, health status, level of physical activity and motivational status as our subjects.
2. Subjects self-reported physical activity level, dietary habits, medication intake and medical conditions. Some of these factors may have been under-reported. However, with the large sample size of this study it is unlikely that any errors in these self reports would significantly affect our results.
3. Subjects were asked to maintain their dietary intake and refrain from increased physical activity outside of the strength training intervention that this study

provided. Some subjects may have unknowingly altered one or both of these variables. Once again however, with the large sample size of this study, it is unlikely that any changes in physical activity or nutritional intake would significantly affect our results.

4. Another potential limitation of this study is the abnormal distribution of ACE I/D genotype frequencies among the Caucasians in our subject group. Our subjects included many more carriers of the D allele than would be expected based on previous literature. We are confident that this uncommon genotype distribution occurred within this subject pool and was not caused by error during the genotyping process. Prior to genotyping subject samples, sequence-verified control samples were performed to ensure the accuracy of the genotyping methods employed during this study. This atypical distribution may have masked an association between ACE genotype and the phenotypes being investigated.
5. Finally, the division of the subject pool by race and sex may have caused some of the analyses to lose some statistical power.

Appendix B – Abbreviations

1RM – 1 Repetition Maximum

ACE – Angiotensin Converting Enzyme

ACE I/D – Angiotensin Converting Enzyme Insertion/Deletion Polymorphism

Ang II – Angiotensin II

cc³ – Cubic Centimeters

CT – Computed Tomography

DD – Homozygotes with 2 deletion alleles

ID – Heterozygotes with 1 insertion allele and 1 deletion allele

ID + DD – ID Heterozygotes and DD Homozygotes joined into one group

II – Homozygotes with 2 insertion alleles

kg – Kilograms

PCR – Polymerase Chain Reaction

ST – Strength Training

TL – Trained Leg

UL – Untrained Leg

Appendix C – Statistical Power

The statistical power calculations for this project were based on the number of subjects for whom muscle phenotype data and DNA samples exist. The effect size for differences in muscle strength was set at 2.37 kg in 1RM. This effect size represents ~12% of the typical 1RM measurements reported in other studies who tested subjects similar to ours (142, 145, 150). The standard deviation for this measurement was 7.02 based on the same prior studies (141, 145, 149). We chose 12% of typical 1RM values as the effect size based on several studies that have reported that after the age of 50 yr., people lose an average of 12-14% of their muscle strength per decade (153, 156, 166, 187). Therefore, this 12% difference is the average loss in muscle strength per decade that has been found in most people. As can be seen in Table C1, this project will have a power of 96.6% when using 2.37 kg as the effect size to test the 252 subjects for whom baseline 1RM data exist. The power to test the gene*training interaction will be 90.4% when analyzing the data of the 188 subjects who completed all aspects of the training program. The alpha level for both of these tests was set at 0.05.

Table C1 – Muscle strength statistical power calculations.

Analysis	Alpha	Subjects	Power
Baseline Strength	0.05	252	96.6%
Change in Strength	0.05	188	90.4%

The effect size for muscle volume was set at a difference of 52.5 cm³, which represents ~5% of the muscle volume values reported in two studies by Tesch et al (286, 287) and a study by Reeves et al (244). The standard deviation for this measure was 71.1 based on the findings of studies by Reeves et al (244), Tesch et al (286, 287) and a

previous study from our lab (143). A longitudinal study by Frontera et al (87) concluded that after 12 years, subjects had lost 12.5-16.1% or a little over 1% per year. Two studies by Visser et al (335, 336) concluded that a 5% change in muscle volume is functionally significant. Therefore, the 5% effect size for this study is physiologically significant as well as roughly translating to the amount of change that could occur in half a decade in the later stages of adult life. By employing an effect size of 52.5 cm³ this project will have a power of 99% for both the baseline analysis (232 subjects) and the analysis of the training effect (180 subjects). The alpha level for both of these tests was set at 0.05 (Table C2).

Table C2 – Muscle volume statistical power calculations

Analysis	Alpha	Subjects	Power
Baseline Muscle Volume	0.05	232	99%
Change in Volume	0.05	180	99%

Tables C3 and C4 present the statistical power for each analysis that was performed as part of the present study. The effect sizes and standard deviations were the same as those described above.

Table C3: Muscle strength statistical power calculations by sex and race

	Alpha	Subjects	Power
Males	0.05	71	0.62
Females	0.05	92	0.83
Caucasians			
Males	0.05	53	0.60
Females	0.05	61	0.46
African Americans			
Males	0.05	18	0.22
Females	0.05	31	0.43

Table C4: Muscle volume statistical power calculations by sex and race

	Alpha	Subjects	Power
Males	0.05	69	0.99
Females	0.05	90	0.99
Caucasians			
Males	0.05	51	0.96
Females	0.05	59	0.98
African Americans			
Males	0.05	18	0.58
Females	0.05	31	0.80

Appendix D - Review of Literature

This review will begin with a discussion of skeletal muscle and its importance to physical function. This discussion of physical function will focus on the importance skeletal muscle has in characterizing and maintaining quality of life and functional capacity as people age. Along with this discussion of quality of life and functional capacity will be a brief discussion of sarcopenia. That will be followed by a review of strength training interventions and their effect on skeletal muscle strength and mass, including the use of strength training in older populations and its effectiveness as a treatment for sarcopenia. After a brief section on the variability in the effectiveness of strength training, this review will move to the heritability of muscle strength, mass, and strength training responses. From there, the discussion will move to the candidate gene: angiotensin converting enzyme (ACE). Discussion of this gene will review the physiology of its involvement in the cardiovascular system and skeletal muscle. The genetics of the key polymorphism within ACE will then be presented followed by a review of its relation to cardiovascular phenotypes. Finally, this review will be completed with a section describing the exercise studies that have been completed regarding ACE genotype and endurance, sprint, and strength training performance.

Importance of Skeletal Muscle:

Skeletal muscle is an important tissue that serves many functions in the body. The most obvious of these functions is muscle strength and power and their significant influence over a person's ability to perform physical tasks. These physical tasks include performance in athletic and leisure activities, execution of work related duties, chores

around the home and anything else that involves movement (e.g., speech, eye movement and most importantly respiration). Skeletal muscle is also important in metabolism, as the majority of calories are burned by muscle. Thus, people who have more skeletal muscle mass maintain a higher metabolic rate. Furthermore, developing strength in the skeletal muscles in the younger ages tends to promote a healthier lifestyle as a person ages.

Quality of Life/Functional Capacity: Skeletal muscle strength and mass are important in maintaining functional capacity and thus quality of life, especially in older adults. Studies have concluded that the decline of muscle strength with age is an important risk factor of increased disability, morbidity and mortality (148, 232). Muscular strength is also largely responsible for the reduced independence and quality of life that many elderly adults experience. This diminished quality of life stems from the decreased walking speed, impaired mobility and increased risk and fear of falls that comes with a loss of muscle strength (41, 88, 152, 203). A paper by Young stated that increasing muscle weakness in older adults may lead to the inability to perform everyday activities like rising from a seated position, which will lead to further inactivity and deterioration of functional status (373). Fiatarone et al (63) showed that in people living in nursing homes, time required to stand from a chair was inversely correlated with dominant quadriceps strength. This same paper also stated that a similar correlation existed between 6 meter walk time and dominant leg 1-repetition maximum (1RM) strength (62). Visser et al (337) showed that leg muscle mass was inversely related with lower extremity performance in older adults. They also concluded that leg muscle strength is directly associated with lower extremity performance. A study by Lamoureux

et al (147) tested the effect of lower body strength on performance in a walking obstacle course. They found that knee extensor strength could predict performance of 15 gait variables and that the importance of muscle strength increased as the gait obstructions became more challenging. These findings led Lamoureux et al to draw the conclusion that enhanced lower body strength through resistance training could aid older people in maintaining their functional mobility and thus independence (146). A study by Schenkman et al (272) investigated the importance of muscle strength and balance in the completion of a series of chair rise tests. They concluded that successfully rising from a seated position was most significantly predicted by lower body muscle strength (273). A study by Rantanen et al (234) concluded that older adults with lower levels of muscle strength had more difficulty with motor tasks. They also reported that within groups with similar activity levels, lower levels of muscle strength were associated with more difficulty completing functional tasks (235).

Sarcopenia, which is defined as the age related reduction in muscle mass, has been translated into the main reason for the lack of skeletal muscle strength that characterizes the majority of older people (33, 89, 177, 240). Muscle strength commonly reaches its peak between the ages of 25 and 35 years, is maintained during the fifth decade and then begins to decline at a pace of approximately 12-14% per decade starting at age 50 yr. (151, 157, 168, 187). Despite some evidence that intrinsic muscle factors are reduced with advanced age, the strength loss that occurs after the age of 50 years is highly correlated with this age-related loss of muscle mass (90, 137, 167, 176, 239). The consequences of sarcopenia can be numerous and extensive. They may include increased susceptibility to falls, increased likelihood of fractures, impairments in thermoregulation,

reduced metabolic rate, glucose regulation deficiencies and loss of overall functional capacity and ability to perform everyday tasks (178).

Sarcopenia also increases the risk of mortality both indirectly through the list of consequences discussed above and directly through decreased muscle mass and strength. Studies have shown in various populations who experience muscle wasting, that a loss of more than 40% of baseline lean mass is fatal (144, 282, 364). Baseline is typically defined as the mean for adults aged 20-30 years old (139). Muscle strength has a greater correlation with mortality than muscle mass. Rantanen et al (237) found handgrip strength to be associated with cause-specific and total mortality in older, disabled females. This study concluded that grip strength is a good predictor of mortality due to cardiovascular disease, respiratory disease, other diseases (except cancer) and total mortality. In the case of each of these associations, those with the lowest grip strength had a significantly higher relative risk of mortality (236). A study by Sasaki et al (270) supported an association between grip strength and mortality in both sexes and over a wide age range. This study investigated grip strength in males and females divided into three age groups (35-54 yrs, 55-64 yrs, and 65-74 yrs) and then followed up on mortality rate of these subjects for more than 20 years. They found that both males and females who scored best on the grip strength test had the lowest relative risk for all cause mortality. This conclusion was true for both the middle and older age groups (269). Grip strength is believed to be representative of overall muscular strength due to its high correlation to other strength measures including elbow flexion, knee extension, trunk flexion and trunk extension (233). Therefore, these studies indicate that muscle strength is important not only for maintaining quality of life, but also lengthening life in general.

Thus, the muscle strength that is lost due to sarcopenia increases the risk of death for older adults.

Strength Training Interventions:

Effects of Strength Training: Strength training has been widely documented as resulting in increased muscle strength and hypertrophy. Muscle hypertrophy, which is characterized as greater muscle cross-sectional area, is primarily the result of increased individual muscle fiber size (54, 116, 313). A study by Haggmark et al (115) investigated the use of computed tomography in measuring muscle area in subjects ranging from sedentary to elite athletes. They found that the largest muscle areas belonged to the heavy weight lifters involved in the study (114). A study by Tesch (283) found that long-term heavy strength training resulted in increased synthesis of myofiber proteins. The result of this increase was larger muscle cross-sectional area, mainly brought about by hypertrophy in the fast twitch muscle fibers (284). A study by Dons et al (52) studied the effect of dynamic strength training at 80% of 1RM in young males. They found that this type of training was effective at increasing dynamic muscle strength as subjects increased strength by 42%. The authors also observed significant muscle hypertrophy with this type of strength training (51). Similar results have been shown in females who underwent heavy strength training. A study by Staron et al (281) showed consistent and significant increases in 1RM throughout 16 weeks of heavy strength training. This training also resulted in significant decreases in body fat and increases in muscle mass such that overall thigh circumference remained unchanged (281). Finally, a

study by Luthi et al (164) found strength training led to increases in strength up to 84% in the knee extensors, as well as increases in midhigh cross-sectional area.

Clearly, it is well documented that strength training is an effective intervention for increasing muscle strength and muscle size. Studies have shown that both muscle strength increases and muscle hypertrophy are achievable in both males and females. Once these conclusions were drawn, researchers turned to studying strength training in older adults as a potential method of maintaining function and as a treatment for sarcopenia.

Older Populations: Many studies have shown that older adults can achieve many of the benefits of strength training, including increased muscle strength. Hurley et al (127) showed that older adults are able to perform strength training intense enough to promote increases in muscle strength and hypertrophy without resulting in significant muscle damage or soreness. Subjects in this study, underwent 16 weeks of strength training, which resulted in a 43% increase in total muscle strength (126). A study by Hakkinen et al (119) showed that elderly men and women, averaging 70 years of age, were able to increase muscle strength after 6-months of heavy strength training. In this study, strength increases were exhibited in tests for maximal isometric force as well as 1RM strength. The authors concluded that this increase in strength was caused by neural improvements, in the form of increases in maximal voluntary activation of the agonist muscles, and muscular hypertrophy (118). Frontera et al (94) found that dynamic strength training can increase both 1RM strength as well as isokinetic strength. These strength improvements were in part due to growth of muscle fibers (93).

Studies have also shown that muscle size responses to strength training are not limited by aging. A study by Roth et al (254) reported the effects of 6-months of full body strength training on muscle volume in a sample of young and old males and females. They concluded that muscle volume response to this type of strength training was independent of age and gender (253). Hurley et al (125) showed that full-body, heavy resistance training can cause muscle hypertrophy in older men. In this study, strength training yielded a 7.2% increase in midthigh muscle cross-sectional area (124). A study by Treuth et al (324) showed that strength training can significantly alter body composition in older males (average 60 yrs). In that study, 16 weeks of strength training resulted in subjects significantly decreasing fat mass in their arms, legs and trunk as well as decreasing their overall body fat percentage. These losses in fat mass were countered with increases in fat free mass in the arms, legs and trunk, such that total body weight remained unchanged. Magnetic resonance imaging was used to confirm that these increases in fat free mass were due to muscle hypertrophy (323). Charette et al (43) showed that older women are also able to experience strength training-related hypertrophy. In this study, females (average age 69.9 yrs) completed 12 weeks of strength training that resulted in a significant increase in type II muscle fiber area. This increase in area was accompanied by significant increases in strength for each exercise included in the strength training protocol (42). Frontera et al (92) also found that increased muscle strength was related to muscle hypertrophy. However, in their subjects both type I and type II muscle fibers underwent similar amounts (33.5% and 27.6% respectively) of training induced hypertrophy (91).

Despite many studies showing strength training is an effective intervention for improving muscle mass and strength in older adults, questions remain about the optimal training protocols for such interventions. For example, uncertainty still remains about the appropriate number of sets and repetitions, and resistance to prescribe to maximize these gains in an older population. A study by Galvão and Taaffe (95) compared the effectiveness of 1-set and 3-set strength training programs in building muscle strength in older adults (average age 68.9 yrs). They found that both volumes of training resulted in significant increases in strength for all seven exercises that were involved in the training (96). These findings indicate that the typical older adult is detrained to the point that even low volume strength training, represented by the 1-set program, is effective in increasing muscle strength. Vincent et al (334) studied the effects of 6 months of high-intensity (80% of 1RM) and low-intensity (50% of 1RM) strength training of older adults (60-83 yrs). They found that both groups significantly increased their 1RM strength for all of the exercises involved, with no significant difference between the groups. Both intensity levels also resulted in significant and similar increases in muscle endurance (333). A study by Kalapotharakos et al (136) also investigated the effects of intensity on the effectiveness of strength training protocols in older adults. They found that both moderate and high resistance strength training led to significant increases in muscle strength, but that the high resistance protocol resulted in increases that were significantly greater than the moderate protocol (135). These findings are similar to those made by Vincent et al (332) in that both studies concluded that any strength training, regardless of intensity, is effective in increasing muscle strength in older adults. However, unlike

Vincent et al, Kalapotharakos et al found that higher intensity training is more effective than less challenging protocols.

Treatment for Sarcopenia and loss of function: Resistance exercise has been shown to be effective in maintaining physical function that is usually lost as part of aging, particularly in those afflicted with sarcopenia. Galvão and Taaffe showed that 20 weeks of a single set strength training protocol could cause significant improvement in many common functional tasks including chair rise, 6-m backwards walk, the 400-m walk, and stair climb tests. This study also showed that a 3-set protocol improves performance in 6-m walk time and floor rise to standing tests in addition to all of the functional tests which improved with single set strength training (97). Vincent et al (331) found that strength training, regardless of intensity, improves stair climbing performance. Furthermore, they found significant inverse correlations between stair climbing time and leg press, leg curl, and leg extension 1RM strength values (-0.73, -0.67, and -0.78 respectively) (330). Similarly, Kalapotharakos et al (134) found that, when compared to control subjects, those who underwent strength training improved functional performance regardless of intensity. The functional tests in this study included 6-m walk time, chair rise, stair climb and sit and reach (133). A study by Fiatarone et al (61) showed that strength training can be effective in improving functional capacity in frail individuals at an extremely advanced age. This study investigated the effects of strength training on people living in nursing homes (average age 90 yrs). The 8 week, high intensity strength training resulted in significant increases in 1RM strength as well as increased total midthigh muscle area (9%), quadriceps area (10.9%) and hamstring and adductor area (8.4%). These physiological increases translated into functional improvements, as walking time

increased, some subjects needing walking aids (canes or walkers) at baseline no longer required these devices, and some subjects who could not stand from a chair without the use of arms at baseline became able to complete this task (60). Another study by Fiatarone et al (65) in a similar subject group also showed that strength training can increase muscle strength and cross-sectional area which in turn improves gait speed and stair climbing ability. This study also found that the strength training intervention increased spontaneous physical activity (66). Lord et al (162) investigated the effects of exercise training on the incidence of falls in older women (average age 71.6 yrs). They found that exercise greatly decreased the frequency of falls and those who attended more than 75% of the exercise sessions suffered fewer falls than less dedicated exercisers and controls. Furthermore, half as many high adherers (6.3%) experienced multiple falls when compared to low adherers (14.8%) and controls (12.8%) (163).

Variability in Results: Despite the very strong evidence for the effectiveness of strength training for improving muscle mass and strength both in general and in the elderly, there is evidence for a high degree of inter-individual variability in the results of strength training, even in people who are performing the same exercise protocol. In a study by Fiatarone et al (59), 8 weeks of strength training in elderly people resulted in strength gains ranging from 61% to 374%. A study by Hubal et al (123) displayed the wide variation in muscle growth that occurs as a result of strength training. In this study, subjects experienced muscle cross-sectional area changes ranging from -2% to 59%. The training in this study also resulted in extremely variable strength changes. Specifically 1RM changes ranged from 0 to 250% and maximum voluntary contraction varied from -32% to 149% (121). Studies from our laboratory have shown variation in strength

increases ranging from <5 to >100% and muscle volume from 0 to >25% after resistance training (129, 131, 155). One potential explanation for this variation that is present in every study, no matter how well controlled, is genetic variation.

Muscle Heritability:

Heritability of Strength: Performance-related muscle phenotypes, including skeletal muscle strength and mass, have been shown through twin and family studies to be heritable. One such study by Thomis et al (296) showed high levels of heritability for various types of muscle strength, concluding that genetic factors are responsible for up to 77% of pretraining 1RM strength, 69% of isometric strength and 65-77% of eccentric strength in the elbow flexors(295). Another study by Thomis et al (298) concluded that arm muscle strength has a 30-80% genetic contribution depending on the angle, type and velocity of the contraction being performed. Furthermore, the genetic contribution for a dynamic 1RM test was concluded to be 80% (297). In a study of 10 year old twins, Maes et al (169) found that 72% of static arm strength was under genetic influence. A study of sibling pairs by Zhai et al (374) found that leg muscle strength ranged from 42-59% heritable. A study by Reed et al (242) found that grip strength also has a genetic aspect. In their study of older adults, Reed et al found that grip strength is up to 65% heritable when adjusting for age and various body size variables (241). A study by Arden and Spector (8) found what they considered to be a moderate genetic component involved with knee extensor strength and a small genetic component for grip strength in adult twins who were in their late 50s. Specifically, they found knee extensor strength to be 46% heritable and grip strength to be 30% heritable (7). Furthermore, the influence of genetics on these muscle phenotypes remains significant even at an advanced age. A

study by Tiainen et al (315) investigated the heritability of muscle strength in older twins who were an average of 68 years old. They concluded that there is a genetic component that accounts for 14% of handgrip strength and 31% of knee extensor strength (315).

Heritability of Muscle Mass: Skeletal muscle mass has also been shown to be a highly heritable phenotype. According to Bouchard et al (26) biological inheritance accounts for 25-30% of the variance of fat-free mass. A later study by Arden and Spector (6) found that genetic factors are responsible for approximately half of the total variance of lean body mass. Specifically, they found that lean body mass was between 52 and 56% heritable depending on the covariates included in the analysis (11). A study by Loos et al (160) concluded that up to 87-95% of the variance for muscle circumferences in the arms and legs was due to additive genetic factors. A study by Sanchez-Andres and Mesa (262) investigated various measures of body composition. They found that upper arm circumference was up to 68% heritable, thigh circumference was 58% heritable and calf circumference was 67% heritable. Furthermore, they found arm muscle area to be up to 58% heritable (264). Thomis et al (291) found that 85% of pretraining muscle cross-sectional area can be attributed to genetic factors. A second study by Thomis et al (302) found that arm cross-sectional area has a heritability greater than 85%.

Heritability of Strength Training Adaptation: There is also limited evidence of a moderate interaction between genetic factors and strength training stimulus that appears to explain some of the variation in muscle adaptation that occurs as a result of strength training. Monozygotic twins, involved in a study by Thomis et al (290), had a correlation of 0.46 for 1RM response to training. There was also a correlation of 0.30 in isometric strength increases with training. Thomis et al concluded that these correlations meant

that training-specific genetic factors accounted for 20% of the variance found in post-training measures of 1RM and isometric strength (289). A study of the heritability of muscle enzyme adaptation to strength training by Thibault et al (288) found that the adaptation of some enzymes to strength training was highly variable. The authors concluded that this variability was most likely due to genetics (288).

In summary, there is strong evidence supporting a significant genetic influence over skeletal muscle strength and mass. There is also evidence showing an interaction between genetic factors and strength training that affects muscle adaptation to strength training. An important next step is to investigate specific genetic influences through the examination of specific candidate genes that may underlie this genetic influence. However, according to the gene map for performance and fitness phenotypes (227), very few studies have investigated the effect that specific candidate genes have over strength training response. Those studies that did investigate the genetic component of strength training adaptation have successfully found genes that are partially responsible for the accumulation of strength (44, 140). However, strength is a complex phenotype and more candidate genes are likely to exist. Therefore, further investigation remains necessary.

Angiotensin Converting Enzyme (ACE):

One potential candidate gene is the angiotensin converting enzyme. This enzyme is involved in the renin-angiotensin system (RAS). This system is best known for its role in the maintenance of cardiovascular homeostasis and blood pressure regulation. However, research also indicates that RAS, and specifically ACE, may be involved with cell growth and muscle hypertrophy. This indicates a potential role of ACE activity, as

dictated by ACE genotype, in skeletal muscle mass and muscle strength. ACE may also be responsible for some of the genetic variation involved with strength training adaptation.

Renin-Angiotensin System: The angiotensin converting enzyme plays a major role in maintaining cardiovascular homeostasis due to its contribution to blood pressure regulation. ACE is an important participant in both increasing vasoconstriction and decreasing vasodilatation. As part of the RAS, ACE is responsible for converting angiotensin I to angiotensin II: a potent vasoconstrictor. ACE is also involved in breaking down bradykinin, a powerful vasodilator, into inactive fragments. This means that ACE is involved in simultaneously stimulating vasoconstriction and inhibiting vasodilatation which results in increased vascular resistance and a rise in blood pressure. Brown et al (34) concluded that there is an inverse relationship between the half life of bradykinin and both serum ACE activity and angiotensin II production. Therefore, higher levels of ACE cause increases in blood pressure. While the renin-angiotensin system is considered to be a critical component to central cardiovascular regulation, many tissues within the human body also have a localized renin-angiotensin system including the heart, kidneys, and lungs (56), as well as skeletal muscle (245). These tissues contain kallikrein, and therefore are able to locally produce kinins such as ACE, which means that they are able to down regulate the activity of bradykinin (55).

Skeletal Muscle Hypertrophy: The local renin-angiotensin system in skeletal muscle is a hormonal pathway through which muscle cell growth and hypertrophy may be activated. Berk et al (21) and Geisterfer et al (100) have shown that adding angiotensin II to cultured smooth muscle cells causes increases in protein synthesis and

cell hypertrophy. Angiotensin II is also a mediator of smooth muscle cell proliferation after vascular injury (224). Furthermore, the extent of angiotensin II stimulating smooth muscle cell proliferation is greater in hypertensive rats when compared to normotensive rats (207). This conclusion points to a synergism between mechanical loading and the effects of angiotensin II on smooth muscle cells.

Similarly, angiotensin II is involved with overload-induced hypertrophy of cardiac muscle cells (256). Much like smooth muscle, cardiac myocytes are affected synergistically by angiotensin II and muscle overload (258). Angiotensin II also has a proliferative effect on cardiac fibroblasts in the overloaded heart much like the effect it has in smooth muscle (185). According to Gray et al (111), angiotensin II-induced cardiac muscle cell proliferation contributes to cardiac myocyte hypertrophy via paracrine growth factor secretion. According to Quinn et al (225) skeletal muscle fibroblasts mediate skeletal myoblast proliferation through the same method, paracrine growth factor secretion, which may lend support to the local RAS having relevance in skeletal muscle.

A study by Silva et al (275) found that ACE influenced cardiac muscle mass only in the presence of pressure related overload. Specifically, they found that increasing ACE levels increased cardiac hypertrophy in response to pressure overload. However, baseline heart mass was similar in all of the mice, regardless of ACE levels. This suggests that it is the interaction of ACE and muscular overload that causes the change in hypertrophy (274). These findings were similar to those of Tian et al (318). This investigation also found no influence of ACE on initial cardiac mass. However, when the heart experienced pressure overload, there was an influence of ACE levels (317). A

study by Baker et al (14) found that ACE inhibitors were effective in completely preventing overload-induced cardiac hypertrophy in rats. This suggests that ACE activity is not only important, but possibly required for cardiac hypertrophy to occur as a result of overload (13).

These studies led Gordon et al (105) to investigate the effects of angiotensin II and ACE activity on overload-induced hypertrophy in skeletal muscle. In this study, Gordon et al overloaded the plantaris and soleus muscles in the hindlimbs of rats for 28 days. Some of the rats were given ACE inhibitors and others were given saline. It was concluded that the ACE inhibitors significantly reduced the hypertrophy in both muscles, by 57% and 96% respectively (104). This study supported the hypothesis that angiotensin II is important in promoting overload-induced muscle hypertrophy. A similar study by Westerkamp and Gordon (340) confirmed these findings. That study concluded that ACE inhibition, and thus decreased levels of angiotensin II, significantly reduced the increases in muscle wet weights seen with muscle overload. Specifically, the wet weights of the soleus and plantaris muscles were attenuated by 29 and 39% respectively. In the untreated rats, the overload procedure caused increases in muscle protein content and fiber cross-sectional area in the plantaris muscle. However, ACE inhibition also attenuated these variables by 30 and 59% respectively (339).

A study by McBride (180) investigated the effects of blocking angiotensin type 1 (AT₁) receptors on eccentric-training induced skeletal muscle hypertrophy and strength gains. AT₁ receptors are the sites where angiotensin II affects muscle cells. This study concluded that the response of skeletal muscle to eccentric loading was significantly attenuated when AT₁ receptors were blocked. Those rats who had their receptors blocked

were unable to experience muscle hypertrophy and increases in muscle contraction force (179). This finding supports the conclusions drawn by Gordon et al (110) in that decreasing angiotensin II levels significantly decreased overload-induced skeletal muscle hypertrophy.

Conflicting Arguments: There are conflicting arguments from researchers who have found that lower levels of ACE activity, achieved through external ACE inhibition, actually decrease the muscle atrophy and loss of strength and function that characterizes some disease states. A study by Onder et al (206) investigated the effects of ACE inhibitors, as a treatment for hypertension or congestive heart failure, on isometric muscle strength and walking speed over a three year period. They found that those women who took ACE inhibitors had significantly less strength deterioration than those who were on other hypertension medications or no medications at all. Similarly, they found that those subjects who were taking ACE inhibitors better maintained their normal gait speed than the other groups. Finally, these results were unchanged after adjustment for cardiovascular events (205). This finding suggests that the ACE inhibitors were the primary mediator of strength maintenance in this group of subjects. However, the findings of this study were later challenged in a commentary by Dhatariya (50). This commentary pointed out that Onder et al (204) failed to present the activity level of the subjects in their various medication groups. It is possible that those who were in the ACE inhibition group had increases in exercise tolerance, and therefore increased activity levels. This would point to the increased activity rather than ACE inhibition as the mechanism of muscle sparing.

A study by Brink et al (30) investigated the effects of angiotensin II infusions on skeletal muscle in rats. This study found that both wet and dry muscle weights were smaller in the angiotensin II infused rats when compared to similarly fed controls. They concluded that the bulk of the difference was caused by impairment of the accumulation of muscle proteins. This was decided when considering the maintenance of the fat pad mass in the angiotensin II infused rats (29). The authors further concluded that muscle protein synthesis was not negatively affected by the increased angiotensin II, but rather the infusion increased the rate of protein degradation in the muscles. Finally, the authors found that the angiotensin II infused rats had IGF-1 levels that were decreased by 33% after 3 days and 26% after 7 days. However, when rats were infused with IGF-1 along with the angiotensin II, they were still unable to maintain muscle mass (32). This led the investigators to conclude that the angiotensin II may have triggered a defect in the insulin-like growth factor-I (IGF-1) autocrine system, which represents a potential mechanism for the increased muscle protein breakdown. It is also possible that the angiotensin II stimulated increase in muscle degradation was caused by the stimulation of ubiquitin-proteasome-mediated protein degradation pathway (27). Sanders et al (267) also concluded that the ubiquitin-proteasome proteolytic pathway was the mechanism through which angiotensin II causes muscle atrophy. This study of cancer related cachexia found that angiotensin II up regulated this pathway resulting in increased protein breakdown. The investigation also found that infusion of IGF-I attenuated the increased protein degradation induced by angiotensin II. These results confirm Brink et al's (28) finding that IGF-I may down regulate the ubiquitin-proteasome proteolytic pathway. Sanders et al (266) also found that muscle atrophy was attenuated with ACE

inhibitors. This led the authors to conclude that protein catabolism caused by angiotensin II was mediated by angiotensin I (265). Finally, a study by Song et al (279) demonstrated that actin cleavage due to increased caspase-3 activation in skeletal muscle is the mechanism for angiotensin II-related atrophy. The authors concluded that angiotensin II induced muscle wasting by reducing the action of IGF-I, which in turn stimulated that ubiquitin-proteasome proteolytic pathway. The stimulation of this pathway activated caspase-3 which is responsible for actin cleavage (278).

In summary, angiotensin II seems to be involved with overload-related muscle hypertrophy. It has been established that those with high levels of angiotensin II are more likely to undergo pressure-induced cardiac hypertrophy (12, 191, 200, 259, 277, 316). Also, skeletal muscle hypertrophy has been shown in animal models to be correlated with angiotensin II in the presence of overload (103, 338). Furthermore, investigators have found that angiotensin II mediated skeletal muscle hypertrophy specifically through the AT₁ receptors (184). The studies that found low levels of angiotensin II to be more effective at sparing muscle mass were frequently in diseased states. Furthermore, they did not investigate the interaction between angiotensin II levels and muscle overload (i.e., physical activity). This may account for the conflicted findings.

ACE Polymorphism: The ACE gene is located on chromosome 17. Within this gene, a 287 base pair insertion/deletion (I/D) polymorphism occurs in the 16th intron (251). In Caucasians, the allele frequency for this insertion/deletion polymorphism is approximately 25%, 50%, and 25% for II, ID, and DD genotypes respectively. However, there is some evidence of a different distribution in other racial groups. In a study by

Barley et al (19), Caucasians had a breakdown of 22%, 52% and 26% for II, ID, and DD genotypes respectively, or a 48% I allele frequency and a 52% D allele frequency for the entire white portion of the cohort. However, the Afro-Caribbean group demonstrated 16% II, 44% ID, and 40% DD, or a 38% I allele frequency and a 62% D allele frequency (18). An earlier study by Barley et al (16) found similar differences between racial groups. Specifically, this study found the distribution among Caucasians to be 24.7% II, 48.4% ID, and 26.9% DD, and Black Nigerians to be 16.2% II, 48.8% ID, and 35% DD. This study also included Samoans (distribution: 82.8% II, 15.5% ID, and 1.7% DD) and Yanomami Indians (distribution: 71.4% II, 26.5% ID, and 2.0% DD) (15). A third study, once again showed variability in ACE genotype with Caucasians having 31% II, 40% ID and 29% DD, while African Americans were 11% II, 60% ID, and 29% DD. Specifically for the frequency of the deletion allele, the breakdown between the groups was 59% for African Americans and 49% for Caucasians (171).

Given the evidence that ACE is important for muscle growth during overload, several studies have examined whether the ACE I/D polymorphism is an important moderator of cardiac muscle hypertrophy that is caused by overload. One study by Montgomery et al (192) found that the response of cardiac mass to exercise training was associated with ACE genotype. The training resulted in left ventricular mass increasing 2.0, 38.5 and 42.3 g in subjects with the II, ID and DD genotypes respectively (189). These findings were supported in a study of army recruits by Myerson et al (199). This study found no genetic effect on left ventricular mass at baseline. However, after training, there was a highly significant difference between genotype groups. Furthermore, the left ventricular growth was in excess of increases in lean body mass in

DD homozygotes but when accounting for lean body mass, left ventricular hypertrophy in II homozygotes became insignificant (198).

ACE Levels: ACE genotype is a strong marker of angiotensin-converting enzyme activity in the body. ACE levels are very stable within people, however plasma levels can vary up to 5.7 times among individuals (3). This association was shown in a study by Cambien et al (39) who showed a familial similarity in plasma ACE levels that is likely due to genetic factors. The authors concluded that the associated ACE levels were due to genetic factors rather than shared environmental influences because the association was limited to parent/offspring relationships and was not present between spouses (38). A study by Alhenc-Gelas et al (2) took the opposite approach to explaining ACE levels: testing potential environmental and hormonal factors. This study failed to identify any environmental or hormonal factors that had a significant relationship with plasma ACE levels (1). This study reinforces the conclusion that ACE levels are largely under genetic control rather than being dictated by environmental or hormonal variables. Another family study by Tiret et al (320) found that adults who were ID heterozygotes had higher ACE activity than those who were II homozygotes. Similarly, those who were DD homozygotes had higher levels of ACE activity than the ID heterozygotes. Furthermore, these relationships were maintained when investigating the association between ACE genotype and angiotensin-converting enzyme activity in the offspring of the adult subjects (319). A study by Rigat et al (250) was able to quantify the effect of ACE genotype on serum ACE levels to be 47%. Once again, the subjects in this study who were carriers of the deletion allele had higher ACE levels than those who were II

homozygotes (249). Finally, a study by Williams et al (351) concluded that circulating ACE activity was significantly associated with ACE genotype. Specifically, the DD homozygotes had the highest levels of ACE activity and II homozygotes had the lowest levels of ACE activity (350). How the I/D polymorphism, located in an intron, functionally influences ACE enzyme levels is unclear. The polymorphism may affect a regulatory element in the gene, affecting either transcription or mRNA degradation, or may simply act as a marker for a functional polymorphism in another region of the gene. Despite the exact mechanism remaining a mystery, most of the studies performed have indicated that candidate polymorphisms located in more active regions of the gene are in tight linkage disequilibrium with the I/D polymorphism. Therefore, regardless of the mechanism through which the I/D polymorphism affects enzyme levels, the evidence favors the hypothesis that the I/D polymorphism serves as a marker of ACE genotype involvement in many pathological conditions (271).

ACE Genotype & Cardiovascular Phenotypes: In addition to the strong correlation between ACE genotype and ACE enzyme levels, ACE genotype has also been shown to be correlated with multiple cardiovascular phenotypes. Murphey et al (194) showed a significant correlation between ACE genotype and bradykinin degradation. This study concluded that DD homozygotes had the greatest rate of bradykinin metabolism and that ACE II homozygotes had the least (195). Studies have also shown that inhibition of ACE is an appropriate method of controlling blood pressure. Fagard et al (58) showed that inhibiting the conversion of angiotensin I to angiotensin II, is effective at decreasing blood pressure during physical activity. The pharmacological use

of ACE inhibitors essentially simulates a person having the II genotype. Therefore, those who are II homozygotes may have a less drastic blood pressure effect to physical activity.

ACE genotype has also been linked to cardiovascular disease and incidence of myocardial infarction. Cambien et al (40) observed an increased prevalence of DD homozygotes in patients with a myocardial infarction on their medical history. Another paper by Cambien et al (36) also concluded that men with the DD genotype were more likely to experience myocardial infarction. This study found that being a DD homozygote for the ACE gene is an independent risk factor for myocardial infarction. This conclusion was made because ACE DD genotype was highly correlated with myocardial infarction in a subpopulation who were otherwise considered low risk (37). Mattu et al (175) found an increased likelihood of coronary artery disease in men who were DD homozygotes for the ACE gene. This increase in frequency was maintained regardless of these subjects being low risk for other known risk factors for coronary artery disease (174). Raynolds et al (238) found a higher frequency of the DD genotype in people in the end stages of ischemic cardiomyopathy than in controls. Finally, Evans et al (57) found a significant overrepresentation of DD homozygotes among 213 cases of fatal myocardial infarctions.

These studies all point to the D allele as being correlated with increased risk for various cardiovascular maladies. However, there are also studies that refute these conclusions. Bohn et al (25) investigated the allele frequencies of a group of myocardial infarction survivors. The investigators found that among the 234 survivors there was a lower frequency of DD genotype (24). This conclusion was supported by other studies

by Miettinen et al (188) and Samani et al (261). A large prospective study by Lindpaintner et al (159) also concluded that ACE genotype is not associated with risk of myocardial infarction. This study also found that that ACE genotype is not useful in predicting risk of ischemic heart disease (158). Studies have also found there to be no association between ACE genotype and coronary artery disease. Friedl et al (86) showed that there was no correlation between ACE genotype and patience with confirmed coronary artery disease. Katsuya et al (138) found there to be no elevation in risk for coronary artery disease in carriers of the DD genotype. Finally a study by Winkelmann et al (366) found that ACE genotype was not useful as a predictor of either coronary artery disease or myocardial infarction. This conclusion was drawn because the investigators found no evidence that the DD genotype increases the risk of either disease (365).

If the ACE I/D polymorphism is in fact related to cardiac diseases, with carriers of the DD genotype being at increased risk, then this suggests that the insertion allele may be beneficial due to its lower levels of ACE activity. These beneficial effects of the I allele on the cardiovascular system led investigators to hypothesize that those with the I allele may be at an advantage when performing endurance activities.

ACE Genotype & Endurance Performance: The importance of ACE genotype to cardiovascular regulation led to the first studies of ACE genotype in the context of exercise, which were performed with endurance athletes. Many of these investigations concluded that the ACE I/D polymorphism is related to performance in aerobic endeavors. A study by Gayagay et al (99) examined the association between ACE genotype and endurance performance in a group of Olympic level Australian rowers.

This study concluded that these athletes had a significantly higher number of I alleles and II genotypes than D alleles or DD genotypes (98). These findings were similar to those of a study of the ACE genotype by Alvarez et al (5). This study investigated the association between ACE genotype and endurance performance in elite athletes who competed in cycling, long-distance running and handball. They found an excess in the II/ID genotypes among the athletes when compared to a group of healthy controls. Additionally, among the elite cyclists, those who were judged to be the most accomplished were almost entirely II homozygotes or ID heterozygotes. In fact, this group of the most elite cyclists only included one athlete who was a DD homozygote (4). In 2001, this association was further studied, this time in high altitude mountain climbers. This study, performed by Woods et al (370), also found an excess of the II genotype in climbers compared to controls. Finally, these conclusions were further mirrored by a 2004 study by Tsianos et al (328) that studied elite long-distance swimmers. This study found that the I allele was much more frequent in those athletes who competed over long distances when compared to swimmers who competed over shorter distances. Specifically, Tsianos et al found that the I allele frequencies were 0.59 for long-distance swimmers as opposed to only 0.29 for those who competed in shorter events. In this cohort, only 1 of the 15 swimmers in the long-distance group was of DD genotype (327).

ACE Genotype & Sprint Performance: Research on the ACE gene and its association with performance led to the finding of an association of the D allele with improved performance in power-related sports. Myerson et al (197) used a cohort of runners to study the correlation between event distance and ACE genotype. There were linear trends of I allele frequency increasing with distance and D allele frequency

increasing with decreased distance (196). There have also been two studies that have found similar results in swimmers. The first, by Woods et al (368), found that there was a significantly higher frequency of the D allele in the elite swimmers who competed in events of less than 400 meters. However, this association only occurred when investigating a cohort of truly elite swimmers. When this cohort was combined with another group of competitive, but not elite, swimmers, the association failed to be significant (367). The second study that investigated a cohort of swimmers was performed by Tsianos et al (326). This study defined short-distance swimmers as those competing in races that lasted 5 or 10 kilometers. In this cohort only one of the individuals out of the 19 in the short-distance group had the II genotype (329). Finally, a study by Nazarov et al (202) investigated the ACE genotype in groups of swimmers, track and field athletes, skiers and triathletes. Once again, ACE genotype was associated with event duration, with the athletes competing in shorter events having an excess of the D allele. This association was observed in both the swimmers and the track and field athletes; however, there was no association in the skiers or triathletes (201).

VO₂Max: The high level of endurance performance that is correlated with the I allele may not be the result of an advantage in aerobic capacity. One paper that did show a correlation between ACE genotype and VO_{2max} was by Hagberg et al (113). This study found that, after accounting for physical activity level, VO_{2max} was correlated with ACE genotype, with II homozygotes testing the highest and DD homozygotes testing the lowest. Specifically, it was concluded that ACE genotype accounted for 12% of the inter-individual variation in VO_{2max} (112). Conversely, other studies have shown that there is no association. A study by Day et al (48) investigated the association between

ACE genotype, circulating ACE activity, and VO_{2max} in sedentary females. This study showed no correlation between either ACE genotype or ACE activity and VO_{2max} when exercising on a cycle ergometer (47). A study by Rankinen et al (229) investigated the effects of ACE genotype on various aspects of aerobic fitness, including VO_{2max} . This study found that there was no correlation between ACE genotype and VO_{2max} at baseline. It also found that the DD homozygotes, rather than the II homozygotes as expected, underwent greater improvements in VO_{2max} with aerobic training. However, this finding was only true in Caucasian offspring and all other groups showed no correlation with training effect. Thus, it was concluded that ACE genotype was not a major contributor of VO_{2max} at either baseline or as a result of training (228). Another study by Rankinen et al (231) further investigated the association between ACE genotype and VO_{2max} , this time in aerobically trained athletes. Once again they found no correlation between the II genotype, or the I allele, and high levels of cardiorespiratory fitness as measured by VO_{2max} (230). Finally, Woods et al (372) found that there was no significant difference in baseline VO_{2max} between II and DD homozygotes. Similarly, they showed no gene*training interaction effect on VO_{2max} in these same groups (371).

Muscle Efficiency: If ACE genotype doesn't affect endurance performance through improved aerobic capacity, then the mechanism of advantage may be involved with muscular efficiency. A study by Williams et al (363) investigated the association between ACE genotype and the mechanical efficiency (energy used per unit power output) of skeletal muscle. They found that the insertion allele enhances mechanical efficiency in trained muscle. The authors suggested two potential mechanisms from this improved efficiency, both directly effecting skeletal muscle tissue. The first possible

mechanism was the increased number of slow-twitch muscle fibers (362). Muscle fibers of this type are known to be more efficient in slow contractions (45). The second mechanism suggested by the authors is that II homozygotes may have higher levels of nitric oxide concentrations, which would in turn raise mitochondrial efficiency and thus contractile function in skeletal muscle (361). A study by Zhang et al (377) seemed to support the first potential mechanism. This study investigated the possible association between ACE genotype and percentage of slow-twitch, type I muscle fibers. They concluded that there was a positive trend connecting ACE genotype with number of type I fibers. Specifically, ACE II homozygotes had the highest number of type I slow-twitch fibers, followed by ID heterozygotes and DD homozygotes. Furthermore, the ID heterozygotes had significantly more type I fibers than DD homozygotes (376). These studies suggest that the effect of ACE genotype on endurance performance may exist at the muscular level rather than at the level of the cardiovascular system. This sentiment is shared by Jones et al (132) who concluded in their review of ACE genotype and human performance that the enhanced endurance that is associated with the I allele stems from a local increase in muscle efficiency rather than a central cardiorespiratory effect.

ACE Genotype & Muscle Adaptation to Strength Training: The association between sprint type events and the D allele gave forth to investigations into a potential connection between ACE genotype and strength training-related muscle phenotypes. The idea of studying ACE genotype in conjunction with strength training was also indirectly supported by studies showing its relationship with muscle hypertrophy, discussed above. The first such investigation came in 2000 when Folland et al (83) studied the effect of ACE genotype on the skeletal muscle response to resistance training. In this study, the

subjects were all 18-30 year old males and the training stimulus was single-leg, knee extension strength training. In this protocol, one leg was trained entirely isometrically, while the opposing leg was trained in a more typical, dynamic manner. This study showed a gene*environment interaction between ACE and resistance training. More specifically, Folland et al (71) concluded that there was no association between ACE and strength in the untrained state, a small association with the dynamic training protocol, and a significant association with isometric strength training. Finally, it was concluded that those subjects with the D allele of the ACE gene had greater increases in all of the strength measurements taken compared to those who were homogeneous for the I allele (70). This study showed not only that there is a gene-environment interaction involving ACE genotype, but also that the magnitude of that interaction may be based on the mode of the training stimulus.

A second study that used a leg training protocol to investigate ACE was done by Williams et al (349). This group aimed to investigate the relationship between ACE activity and strength response to training. The subject pool in this cohort was made up of white males with the average age of 22 years. They performed 4 sets of 10 repetitions at their 10 rep max for 24 training sessions (348). This study also found an association between ACE genotype and muscle strength, however the association was different from that reported by Folland et al. Williams et al stated that pretraining strength was in fact correlated with circulating ACE activity, which in turn was correlated with ACE genotype, with those carrying at least one D allele having elevated ACE activity. More specifically, those subjects with higher circulating ACE levels also had higher isometric

strength in the untrained state. Conversely, the training related changes in muscle strength were found to be independent of ACE genotype (347).

There have also been two studies that have used upper arm resistance training protocols to study the association of ACE genotype with strength phenotypes. One example of these studies is by Pescatello et al (220). They used a progressive, unilateral training program consisting of 3 sets of 12 repetitions of five biceps and triceps exercises. This protocol was used in a cohort of 367 men and 264 women with a mean age of 24.2 years, 79.5% of whom were Caucasian, out of the FAMuSS study (221). The findings in this study were counter to those in the previous investigations in that those subjects with the I allele had greater gains in maximum voluntary contraction in both the trained and untrained arms; however, those with the D allele had greater increases in 1RM and muscle mass in the untrained arm. Finally, ACE genotype was not related to baseline measures of strength or size (218). The second study that used an upper arm training protocol was published in 2004 by Thomis et al (311), and investigated the effects of 10 weeks of biceps training on male twins. They concluded that ACE genotype had no effect on 1RM strength or torque (310).

Table D2: Summary of ACE genotype & strength training literature

	Baseline Strength	Strength Adaptation	Baseline Muscle Size	Muscle Size Adaptation
Folland et al (2000)	No	Yes	-	-
Williams et al (2005)	Yes	No	-	-
Pescatello et al (2006)	No	Yes	No	No

Thomis et al (2004)	No	No	No	No
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No: no significant association of ACE genotype with phenotype. Yes: significant association of ACE genotype with phenotype. “-“: not studied.

In summary, the findings that ACE genotype is correlated with sprint/power performance and that ACE genotype may affect skeletal muscle in the periphery through its relationship with muscle efficiency promote the possibility of the gene’s association with strength training. Furthermore, the role of angiotensin II in muscle hypertrophy provides a possible mechanism, which increases the likelihood of the ACE gene’s involvement in muscle strength and mass. As shown in Table D1, only four studies to date have investigated this potential relationship, with inconsistent results. Specifically, two studies have found a gene*environment interaction, albeit conflicting interactions (67, 219), one study found a correlation between ACE genotype and baseline strength (346), and one study found no relationship at all (309). However, there are some important inconsistencies and limitations in these studies. For the most part, these studies investigated small sample sizes. Three of the studies had samples under 100 people (81, 33, and 50 respectively) (69, 308, 345). The two studies that investigated leg training protocols (Folland et al and Williams et al) also had inconsistency between their testing protocols and their training protocols (68, 359). Both of these studies involved strength interventions using dynamic training. However, Williams et al used isometric and isokinetic tests of strength. Similarly, Folland et al used only isometric tests to evaluate strength after subjects performed dynamic strength training with one leg and isometric training with the other. Clearly, these testing methods ignore the principle of specificity and may underreport strength gains.

ACE Genotyping Methods: Genotyping of the ACE I/D polymorphism is performed using a polymerase chain reaction (PCR)-based DNA amplification using flanking primers. The sense primer sequence is 5' CTGGAGACCACTCCCATCCTTTTCT 3' and the antisense primer is 5' GATGTGGCCATCACATTCGTCAGAT 3'. The PCR product is a 190 base pair fragment for the deletion (D) genotype and a 490 base pair fragment for the insertion (I) genotype (248, 325). Therefore, a single band of either 190 or 490 base pairs denoted a homozygote for either the insertion or deletion genotype, respectively, and two bands stemming from the same sample confirmed an ID heterozygote. Genotyping is performed by separating the PCR amplicon on a 2% agarose gel with ethidium bromide staining with UV transillumination (325).

Summary:

Skeletal muscle is important in determining many performance and functional capabilities. This is particularly true as people age and everyday tasks become more difficult to complete. Older individuals who lack muscle strength are far more likely to experience limited mobility, reduced independence and decreased quality of life. This lack of strength among the elderly tends to be correlated with the loss of muscle mass with age, known as sarcopenia.

Strength training interventions work to increase muscle strength and mass in both young and old populations. In fact, many studies have concluded that strength training interventions can have similar relative effects independent of age. Strength training interventions are able to improve functional abilities in addition to increasing muscle strength and mass. In older adults, strength training results in improved performance on

functional tests including gait speed, chair rise and stair climb tests. This suggests that strength training is an appropriate intervention in the attempt to combat the functional losses involved with sarcopenia. However, within these training studies, investigators have found large amounts of variability among individual subjects despite applying consistent training stimuli. This suggests a genetic influence that is involved in muscle strength and mass responses to training. Accordingly, family and twin studies have shown heritability of muscle strength and mass both at baseline and after strength training. There have also been studies that have shown a gene*training interaction that may affect an individual's ability to respond to strength training.

Investigation of the ACE gene's I/D polymorphism began with researching its involvement in the cardiovascular system and its relationship with various cardiovascular phenotypes including blood pressure and left ventricular hypertrophy. These studies showed that lower levels of ACE activity, associated with the I allele, promote cardiovascular health. This conclusion led to the investigation of ACE genotype in relation to endurance performance. These studies concluded that the I allele was correlated with high levels of endurance performance; however, an unexpected correlation between sprint/power performance and the D allele was also discovered. One potential explanation for this is that carriers of the I allele may have a higher aerobic capacity. However, VO_2 max does not consistently vary with ACE genotype. On the other hand, muscle efficiency does seem to be associated with ACE genotype, suggesting that ACE genotype may directly affect the skeletal muscles rather than having only central effects. ACE and angiotensin II have been shown to be involved in both cardiac and skeletal muscle hypertrophy. The peripheral effects of ACE along with the

correlation of the D allele and sprint/power performance suggest that ACE genotype may have an effect on strength training adaptation. Unfortunately, the studies that have investigated this relationship have been inconsistent with their methods and results and therefore more research is needed to fully understand this potential association. Therefore, the purpose of the proposed study was to investigate the possible association between ACE genotype and skeletal muscle strength and mass, and their adaptation to strength training in older adults.

Appendix E – IRB Approval



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INSTITUTIONAL REVIEW BOARD

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March 22, 2007

MEMORANDUM

Addendum Approval Notification

To: Dr. Ben Hurley
Mr. David Charbonneau
Department of Kinesiology

From: Roslyn Edson, M.S., CIP, *Rae*
IRB Manager
University of Maryland, College Park

Re: **IRB Application Number: 00830**
Project Title: "Effects of Gene Variations on Age- and Strength Training-Induced Changes in Muscular Strength, Body Composition, Glucose Metabolism, Lipoprotein-lipid Profiles"

Approval Date Of Addendum: March 16, 2007

Expiration Date of IRB Project Approval: January 18, 2008

Application Type: *Addendum/Modification: Approval of request, submitted to the IRB Office on 13 March 2007, to add Mr. David Charbonneau to the research team as a student investigator.*

Type of Review of Addendum: Expedited

Type of Research: Non-exempt

The University of Maryland, College Park Institutional Review Board (IRB) Office approved your IRB application. The research was approved in accordance with the University's IRB policies and procedures and 45 CFR 46, the Federal Policy for the Protection of Human Subjects. Please reference the above-cited IRB application number in any future communications with our office regarding this research.

Recruitment/Consent: For research requiring written informed consent, the IRB-approved and stamped informed consent document is enclosed. The IRB approval expiration date has been stamped on the informed consent document. Please keep copies of the consent forms used for this research for three years after the completion of the research.

Continuing Review: If you want to continue to collect data from human subjects or to analyze private, identifiable data collected from human subjects, after the expiration date for this approval (indicated above), you must submit a renewal application to the IRB Office at least 30 days before the approval expiration date.

(continued)

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