ABSTRACT

Title of dissertation: THE INFLUENCE OF INSULIN-LIKE GROWTH FACTOR PATHWAY GENE POLYMORPHISMS ON THE STRENGTH TRAINING RESPONSE OF MUSCLE PHENOTYPES IN OLDER ADULTS

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Strength training (ST) is considered an intervention of choice for the prevention and treatment of the adverse consequences of sarcopenia. Our group previously reported that the CA dinucleotide repeat polymorphism in the promoter region of the insulin-like growth factor 1 (*IGF1*) gene influenced the muscle strength response to ST in Caucasians. Other studies have shown that the insulin-like growth factor binding protein-3 (IGFBP-3) is a modulator of IGF-1 in circulation and is present in skeletal muscle. The -202 polymorphism in the promoter region of the *IGFBP3* gene has been shown to influence IGFBP-3 levels. In addition, there have been reports that IGF-1 and calcineurin are linked in a common pathway to induce skeletal muscle cell hypertrophy. A previous study has shown that an insertion/deletion (I/D) polymorphism in the gene encoding the regulatory subunit of calcineurin, calcineurin B, influences cardiac hypertrophy. To examine the influence of these IGF pathway gene polymorphisms on muscle mass and strength responses to ST, we studied 128 Caucasian and African American men and women before and after a 10-wk single-leg knee extension ST program. One repetition maximum strength (1 RM), muscle volume (MV), and muscle quality (MQ) were assessed at baseline and after 10 wk of ST.

There was a significant combined gene effect, including both *IGF1* main effect and *IGF1* by calcineurin B (*PPP3R1*) gene by gene interaction effect, for change in strength with ST ($P < 0.01$). There was also a significant combined gene effect for *IGF1* on change in MQ ($P < 0.05$). The gene by gene interaction of *IGF1* and *PPP3R1* by itself, approached significance for change in strength with ST ($P = 0.07$) and was right on the border of significance for change in MQ ($P = 0.05$). Moreover, *PPP3R1* II homozygotes approached significance for a greater increase in MV with ST than *PPP3R1* D-allele carriers ($P = 0.06$). There were no significant combined gene effect for *PPP3R1* (i.e., *PPP3R1* main effect combined with *PPP3R1* by *IGF1* interaction effect) for change in strength or MQ with ST. Also, there were no significant influences of the *IGFBP3* polymorphism on muscle phenotypic responses to ST. These data extend our previous findings for *IGF1* by indicating that IGF pathway gene polymorphisms may influence muscle phenotypic responses to ST in Caucasian and African American older men and women.

THE INFLUENCE OF INSULIN-LIKE GROWTH FACTOR PATHWAY GENE POLYMORPHISMS ON THE STRENGTH TRAINING RESPONSE OF MUSCLE PHENOTYPES IN OLDER ADULTS

By

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INTRODUCTION

Losses of muscle mass and strength with aging, referred to as sarcopenia, have been well-documented (141, 147) and have been associated with many adverse health consequences, including increased mortality (159). Strength training (ST) has been shown to be an effective intervention for the prevention and treatment of sarcopenia with few side effects (101, 224). Nevertheless, increases in muscle mass and strength are highly variable among individuals (107, 135), suggesting a genetic influence. Further support for a genetic influence on muscle phenotypes comes from twin studies which have shown that up to 90% of the variance in baseline muscle mass and ~ 60% of the variance in baseline muscle strength is heritable (103). Though accounting for a smaller percent of the variance, the response of these muscle phenotypes to ST also appear to be heritable (260). However, there have been few candidate genes identified as playing a role in influencing muscle responses to ST (41, 69, 107, 127, 211), and there are no reports, that we are aware of, on the influence of candidate genes that are linked in a common biological pathway.

Insulin-like growth factor-1 (IGF-1) is a potent mitogen and anabolic agent important in the growth of various body tissues, including skeletal muscle (67, 254). The decline of circulating levels of IGF-1 with advancing age is related to the loss of muscle mass and strength that occurs with age (264). ST increases skeletal muscle IGF-1 levels, even in the elderly (64, 90) and this locally produced IGF-1 can stimulate muscle hypertrophy through activation of satellite cells and increased protein synthesis rates (1, 98, 240, 289). Nevertheless, significant variability in skeletal muscle IGF-1 and muscle phenotype responses with ST have been reported (64, 91).

Some of this variability in response to ST may be accounted for by a CA dinucleotide repeat polymorphism in the promoter region of the *IGF1* gene, which encodes for the IGF-1 protein (127). Other polymorphisms within the insulin-like growth factor pathway of genes are thought to be involved in muscle hypertrophy and strength response to ST, but no studies have been reported, to our knowledge, concerning their influence on muscle phenotypic response to ST. Two examples of such genes within the insulin-like growth factor pathway, are insulin-like growth factor binding protein 3 (*IGFBP3*) and calcineurin B (*PPP3R1*) genes.

Most circulating IGF-1 is bound by IGFBP-3 (22). IGFBP-3 can potentiate or inhibit the action of IGF-1 on skeletal muscle (63). Although it is unclear whether IGFBP-3 is the primary carrier of IGF-1 in skeletal muscle, there is evidence that it does exist in skeletal muscle (70, 238, 249) and that increased secretion of IGFBP-3 in primary adult human skeletal muscle cells is stimulated by IGF-1 (70). There have been several reports that the -202 polymorphism in the promoter region of the *IGFBP3* gene can influence the levels of this protein in circulation (47, 111, 246), which may in turn modulate the activity of IGF-1. Deal et al. (47) showed that this polymorphism was directly related to promoter activity of the *IGFBP3* gene, suggesting a functional association that potentially affects protein levels of IGFBP-3.

IGF-1-induced muscle hypertrophy in skeletal muscle cells is at least partially mediated by a Ca^{2+}-dependent calcineurin signaling pathway (172, 240). Calcineurin is a Ca^{2+}/calmodulin-dependent protein phosphatase, which consists of a catalytic subunit, designated as calcineurin A, and a regulatory Ca^{2+}-binding subunit, designated as calcineurin B (281). Calcineurin plays a role in both cardiac (166, 214) and skeletal

muscle hypertrophy (54, 55, 163, 172, 240, 257). Tang et al. (258) suggested that the 5-base pair (bp) insertion/deletion (I/D) polymorphism in the promoter region of the *PPP3R1* gene was associated with the incidence of inappropriately high left ventricular mass in severe hypertensives (258). Due to the influence that this polymorphism may have on hypertrophy in cardiac muscle, and the fact that cardiac and skeletal muscle share common hypertrophic pathways (182), it is possible that this polymorphism may influence hypertrophic responses in skeletal muscle as well.

The purpose of this study was to test the hypothesis that polymorphisms in the promoter regions of the *IGF1*, *IGFBP3*, and *PPP3R1* genes, which may be linked in a common biological pathway, will significantly influence the changes in muscle volume, strength, and MQ with ST in older Caucasian and African American men and women. To test this association, the CA dinucleotide repeat polymorphism in the promoter region of the *IGF1* gene, the -202 locus polymorphism in the promoter region of the *IGFBP3* gene, and the 5-bp I/D polymorphism in the promoter region of the *PPP3R1* gene will be studied.

METHODS

Subjects. One hundred twenty-eight previously physically inactive, relatively healthy men (n = 58) and women (n = 70) between the ages of 50 and 85 years volunteered to participate in this study. A small portion of the subjects (n = 10) were from a previous study cohort in our laboratory who underwent the identical strength training (ST) intervention program (107). Another portion (n = 57) were from the same cohort, but used in a previous manuscript (127). Prior to participation, all subjects underwent a phone-screening interview, received medical clearance from their primary

care physician, and completed a detailed medical history. They were nonsmokers, free of significant cardiovascular disease and metabolic or musculoskeletal disorders that would affect their ability to safely perform heavy resistance exercise. Subjects who were already taking medications for at least three weeks prior to the start of the study were permitted into the study as long as they did not change their medications or dosages at any time throughout the study. After all methods and procedures were explained, subjects read and signed a written consent form which was approved by the Institutional Review Board of the University of Maryland, College Park. All subjects were continually reminded throughout the study not to alter physical activity levels or dietary habits for the duration of the study. Body weight was monitored weekly throughout the study to ensure compliance in maintaining a stable diet.

Body composition assessment. Body composition was estimated by dual-energy X-ray absorptiometry (DXA) using the fan-beam technology (Hologic, model QDR 4500A, version 8.21 software, Waltham, MA). A total body scan was performed at baseline and again after the ST program to assess total body and thigh fat-free mass (FFM), fat mass, and percent body fat. A standardized procedure for patient positioning, apparel, and utilization of the QDR software was used. Total body FFM was defined as lean soft tissue mass plus total body bone mineral content (BMC). The coefficients of variation (CV) for all DXA measures of body composition were calculated from repeated scans of 10 subjects who were scanned three consecutive times with repositioning. The CV was 0.6% for FFM and 1.0% for percent body fat. The scanner was calibrated daily against a spine calibration block and step phantom block supplied by the manufacturer.

In addition, a whole body phantom was scanned weekly to assess any machine drift over time.

Strength testing. One repetition maximum (1 RM) strength tests were performed before and after the ST program using an air-powered knee-extension resistance machine (Keiser A-300 Leg Extension machine). The 1 RM test was defined as the maximal resistance that could be successfully moved through the full range of motion with proper form one time. Approximately the same number of trials (6-8) and the same rest periods between the last few trials (~ 60 sec) were used to reach the 1 RM both before and after training. Before the regular ST program and the 1 RM testing were performed, subjects underwent at least three familiarization sessions in which the participants completed the training program exercise with little or no resistance and were instructed on proper warm-up, stretching and exercise technique. These low-resistance training sessions were conducted in order to familiarize the subjects with the equipment, to help control for the large 1 RM strength gains that commonly result from skill (motor learning) acquisition during the initial stages of training, and to help prevent injuries and reduce muscle soreness following the strength training protocol. The same investigator conducted strength tests for each subject both before and after training using standardized procedures with consistency of seat adjustment, body position, and level of vocal encouragement. All subjects were positioned with a pelvis strap (seat belt) to minimize the involvement of other muscle groups. The 1 RM was achieved by gradually increasing the resistance after each successful repetition from an estimated sub-maximal load until the maximal load was obtained, which resulted in failure to successfully complete a repetition when a higher load was introduced.

Training program. The training program consisted of unilateral (one-legged) training of the knee extensors of the dominant leg, three times per week, for ~ 10 weeks. Training was performed on a Keiser A-300 air powered leg extension machine, which allowed for ease of changing the resistance without interrupting the cadence of the exercise. The untrained control leg was kept in a relaxed position throughout the training program.

Following the warm-up, the training consisted of five sets of knee extension exercise for those < 75 yrs of age and four sets for those ≥ 75 yrs of age, to avoid overtraining for this age group. The protocol was designed to combine heavy resistance with high volume exercise, while eliciting near maximal effort on all repetitions. The first set was considered a warm-up set and consisted of five repetitions at 50% of the previously determined 1 RM strength value. The second set consisted of five repetitions at the current 5 RM value. The 5 RM value was increased continually throughout the training program to reflect increases in strength. The first four or five repetitions of the third set were performed at the current 5 RM value, then the resistance was lowered just enough to complete one or two more repetitions before reaching muscular fatigue. This process was repeated until a total of 10 repetitions were completed. This same procedure was used for the fourth and fifth sets, but the total number of repetitions was increased in these sets to 15 and 20, respectively. The second, third, fourth, and fifth sets were preceded by rest periods lasting 30, 90, 150, and 180 seconds, respectively. The muscle shortening phase (formerly called concentric phase) of the exercise was performed in ~ two seconds, and the lengthening phase (formerly called eccentric phase) (135) of each repetition took ~ three seconds.

Muscle volume. To quantify quadriceps muscle volume (MV), computed tomography (CT) imaging of the trained and untrained thighs was performed (GE Lightspeed Qxi, General Electric, Milwaukee) at baseline and during the last week of the 10-week unilateral ST program. Axial sections of both thighs were obtained from the most distal point of the ischial tuberosity to the most proximal part of the patella, while subjects were in a supine position. Measurements of MV in the untrained leg served as a control for seasonal, methodological, and biological variation of MV, by subtracting the changes in the control leg from the training-induced changes in the trained leg. Section thickness was set at 10 mm, with 40 mm separating each section, based on previous work in our laboratory with slight modifications (266). Quadriceps MV was estimated based on using a 4 cm interval between the center of each section. Each CT image was obtained at 120 kVp with the scanning time set of 1 s at 40 mA. A 48-cm field of view and a 512 X 512 matrix was used to obtain a pixel resolution of 0.94 mm. Using Medical Image Processing, Analysis, and Visualization (MIPAV) software (NIH, Bethesda), two technicians performed analyses of all images for each subject. Briefly, for each axial section, the cross-sectional area (CSA) of the quadriceps muscle group was manually outlined as a region of interest. The quadriceps CSA was outlined in each 10 mm axial image from the first section closest to the superior border of the patella to a point where the quadriceps muscle group is no longer reliably distinguishable from the adductor and hip flexor muscle groups. The technicians were blinded to subject identification, date of scan, and training status, for both baseline and after training analysis. Repeated measurement coefficient of variation (CV) was calculated for each investigator based on repeated measures of selected axial sections of one subject on two separate days.

Average intra-investigator CV was 1.7% and 2.3% for investigator one and two, respectively. The average inter-investigator CV was < 1%. The final MV was calculated using the truncated cone formula as we described previously (266).

In addition, data was used in this analysis from 10 subjects from a previous cohort. All methods for testing and training these subjects were the same as in the current cohort, except that MV was measured by magnetic resonance imaging (MRI). However, Mitsiopoulos et al. (164) have shown a correlation of 0.99 between CT and MRI for the measurement of skeletal MV.

Genotyping. Genomic DNA was prepared from EDTA-anticoagulated whole blood samples by standard salting-out procedures (Puregene DNS Extraction, Gentra Systems). The CA microsatellite of *IGF1* was amplified by polymerase chain reaction (PCR) of genomic DNA using fluorescence-tagged primers (222). An ABI 3100 DNA sequencer (PE Applied Biosystems) and the ABI Genescan/Genotyper 2.5 software program (PE Applied Biosystems) were used to determine the genotype of the CA repeat microsatellite in the promoter region of the *IGF1* gene. Genotype assignment was based on the method described by Rosen et al. (e.g., 19 CA repeats = 192 base pairs), in which these authors found the 192 allele to be the most common, and thus compared it with other alleles for this microsatellite (222). Therefore the genotype assignments in the present study were 192 homozygotes, 192 heterozygotes, and noncarriers of the 192 allele. Genotyping of the *IGFBP3* -202 polymorphism was performed using PCR and restriction digest of the PCR product with *Alw*21I as described by Deal et al. (47) with genotype groups designated as AA homozygotes, AC heterozygotes, and CC homozygotes. The 5-base pair (bp) insertion/deletion (I/D) polymorphism located at the -

1059 to -1063 loci relative to the transcription start site of the *PPP3R1* gene was genotyped using standard PCR and AseI restriction digest as described by Tang et al. (258) with genotype groups designated as II homozygotes, ID heterozygotes, and DD homozygotes. Direct sequencing was used to confirm the accuracy of all genotyping methods.

Statistical analyses. All statistical analyses were performed using SAS software (SAS version 9.1, SAS Institute, Cary, NC). Changes in body weight, percent body fat, and fat-free mass (FFM) with strength training (ST) within each sex, race, and genotype group were tested using paired t-tests. Fixed effect linear models were used to test differences in baseline muscle phenotypes (1 RM strength, MV, and MQ) among the categorical variables: sex, race, and genotype groups and to test for differences in the change in muscle phenotypes with ST among sex, race, and genotype groups. Initial linear models for each muscle phenotype (dependent variable) included the main effect of the following independent variables: the CA dinucleotide repeat polymorphism of *IGF1*, the -202 locus polymorphism in the promoter region of *IGFBP3*, and the 5-bp I/D polymorphism of calcineurin B (*PPP3R1*). The initial models also included their two-way interactions with each other, as well as with race (Caucasian and African American) and with sex and hormone replacement therapy status (male, female on hormone replacement therapy, or female not on hormone replacement therapy), when sufficient data existed ($n \geq 5$). The only exception was for the *PPP3R1* by *IGFBP3* gene by gene interaction, in which there were only four subjects who were both *PPP3R1* D-allele carriers and *IGFBP3* CC homozygotes, and for the *IGF1* by *IGFBP3* gene by gene interaction, in which there were only four subjects who were both *IGF1* non-carriers of

the 192 allele and *IGFBP3* AA homozygotes. It was not possible to combine both of these groups with *IGFBP3* AC heterozygotes in order to have a genotype group with $n \geq 5$. Therefore, these interactions were tested in the model with $n = 4$.

Because sample sizes for each genotype were a function of different allelic frequencies, the experiment was unbalanced. Therefore, non-independent sources of variation were removed using a backward elimination process similar to that previously described (97). The continuous variables age, height, body weight, body mass index, and baseline muscle phenotypes for models testing differences in change in muscle phenotypes were included in the models as covariates. For those final models in which interaction terms were present, the significance of the contribution for the total gene effects, including interaction and main effects, was tested by comparing the error term sums of squares for the full model (all gene effects and error term) with the error term sums of squares for the model in which the gene effects of interest were removed from the model. Results are presented as means (SD) for age, height, body weight, percent body fat and FFM, and as least squares means ± SE for muscle phenotypes.

For all analyses the initial threshold of significance was set to $P < 0.05$. Mean comparisons were made using t-tests, with P-values adjusted using a Bonferroni correction to reduce the chance of a Type I error. The P-values calculated from the linear models were multiplied by the number of comparisons for the effect of interest to determine the P-value with Bonferroni correction.

Race by genotype. To determine whether data for change in muscle phenotypes with ST for African Americans and Caucasians could be pooled, gene by race interactions were tested in each linear model for the *IGF1*, *IGFBP3*, and *PPP3R1* gene

polymorphisms. For the *IGF1* gene polymorphism there was insufficient data for the *IGF1* 192-allele homozygotic African Americans. Therefore, initially for each of the linear models *IGF1* 192-allele homozygotes and 192-allele heterozygotes were combined so that sufficient data existed to test the *IGF1* by race interaction. However, once this interaction term was no longer significant in the model, and removed from the model, the *IGF1* gene effects were tested with all *IGF1* genotype groups (192-allele homozygotes, 192-allele heterozygotes, and noncarriers of the 192-allele). In addition, to control for the potential influence of race on muscle phenotype responses to ST, race was used as a covariate in all linear models.

Percent variability explained by genotype. To estimate the percent variability for the change in strength, MV, and MQ with ST attributable to *IGF1*, *IGFBP3*, and *PPP3R1* genotypes and any relevant gene by gene interactions, the sums of squares of the gene or gene by gene interaction of interest was divided by the sums of squares of all gene effects present in the model and the sums of squares of the error. With this procedure, it was assumed that each gene involved in a gene by gene interaction contributes an equal portion to the percent variability.

Power analyses. Statistical power for the three primary comparisons was estimated for the *IGF1*, *IGFBP3*, and *PPP3R1* genotype effect on each variable using all data from the present study. Statistical power for the changes in strength was estimated to be > 0.8 with α set at 0.05, but was < 0.8 for changes in MV (Power = 0.130) and MQ (Power = 0.183).

RESULTS

Allele and genotype frequencies. Tables 1-3 show the allele and genotype frequencies for the *IGF1*, *IGFBP3*, and *PPP3R1* promoter polymorphisms. These frequencies were similar to those reported previously (47, 49, 222, 258). Data for *PPP3R1* DD genotype group was combined with the *PPP3R1* ID genotype group, as D-allele carriers, and were compared with data from *PPP3R1* II homozygotes because there was only one subject who was a *PPP3R1* carrier.

Physical characteristics. Tables 4 and 5 show that there were no significant changes in body weight, percent body fat, or fat-free mass (FFM) with ST within sex or race groups. Tables 7-9 and 11-15 of Appendix I show that there were no significant within genotype group differences for change in body weight, percent body fat, or FFM with ST, except those with MV data who were *IGF1* noncarriers of the 192 allele, who had a significant decrease in percent body fat with ST ($P < 0.001$) as shown in Table 10 of Appendix I. Table 4 shows that men had greater mean values than women for baseline 1 RM strength ($P < 0.001$), MV ($P < 0.001$), and MQ ($P < 0.01$). Table 5 shows that African Americans had greater MV than Caucasians at baseline ($P < 0.001$). However, there was a trend for a significant race by *IGFBP3* interaction for baseline strength and a significant race by *IGFBP3* interaction for baseline MQ as shown in Figures 5-6 of Appendix I. Therefore, it was difficult to interpret if there were significant racial differences in these baseline muscle phenotypes because the racial difference was inconsistent across *IGFBP3* genotype groups.

Genotype associations with muscle phenotypes at baseline. Tables 7-9 of Appendix I show that there were no significant differences in baseline muscle phenotypes

among genotype groups. The *IGFBP3* by race interaction for baseline 1 RM strength approached significance ($P = 0.06$) as shown in Figure 5 of Appendix I. Although *IGFBP3* CC homozygotic African Americans had a significantly greater baseline 1 RM strength than Caucasians who were *IGFBP3* CC homozygotes (32 ± 2.5 vs 24 ± 1.3 kg, $P = 0.04$), this difference was not consistent across *IGFBP3* genotypes (24 ± 1.8 vs 24 ± 1.2 kg, $P = 1.00$ for AA homozygotes, 26 ± 1.5 vs 23 ± 1.0 kg, $P = 1.00$ for AC heterozygotes), due to the *IGFBP3* by race interaction. There was also a significant *IGFBP3* by race interaction for baseline MQ ($P < 0.05$) as shown in Figure 6 of Appendix I. Thus, differences between *IGFBP3* genotype groups for MQ were not consistent between race groups, making it difficult to interpret the influence of *IGFBP3* on baseline MQ.

Muscle phenotype responses to ST for sex and race groups. Men had significantly greater absolute (8.9 ± 0.84 vs 5.7 ± 0.72 kg, $P < 0.01$) and relative (%) increases (38 ± 3.6 vs 27 ± 3.1%, $P < 0.05$) in knee extension 1 RM strength with ST than women. It was not possible to determine if there was a significant difference among races for absolute and relative change in knee extension 1 RM strength because of an *IGFBP3* by race interaction as shown in Figure 2 and Figure 7 of Appendix I. There was no significant difference between the absolute (140 ± 16 vs 110 ± 14 cm^3, $P = 0.10$) or relative (10 ± 1.1 vs 7.1 ± 0.99 %, $P = 0.08$) changes in MV with ST between men and women. In addition, there were no significant differences between African Americans and Caucasians for changes in absolute (130 ± 14 vs 110 ± 11 cm^3, $P = 0.31$) or relative change (8.5 ± 0.97 vs 7.6 ± 0.78%, $P = 0.39$) in MV with ST. Likewise, there was no significant difference in the absolute (3.5 ± 0.39 vs 2.8 ± 0.42 $kg/cm^3 * 10^{-3}$, $P = 0.23$) or

relative (22 ± 2.1 vs 14 ± 2.3 %, $P = 0.30$) changes in MQ for men compared to women. Also, there was a borderline significant difference in the absolute change in MQ in African Americans compared to Caucasians (3.5 ± 0.41 vs 2.6 ± 0.33 kg/cm^3 *10^{-3}, $P = 0.05$). The relative difference in MQ between African Americans and Caucasians could not be determined due to an *IGFBP3* by race interaction for this phenotype as shown in Figure 8 of Appendix I.

Race by gene interaction for change in muscle phenotypes with ST. There were no significant gene by race interactions for the changes in 1 RM strength, MV, or MQ with ST. There was a trend however, for a significant *IGFBP3* gene by race interaction for change in 1 RM strength with ST ($P = 0.09$). Because of the absence of a significant gene by race interaction, data from African Americans and Caucasians were averaged across races for all other genotype analyses.

IGF1 influence on 1 RM strength, MV and MQ responses to ST.

1 RM response: Table 10 of Appendix I shows that there was no significant influence of the *IGF1* main effect on the change in muscle strength with ST ($P = 0.51$). Figure 1 shows that the gene by gene interaction between *IGF1* and *PPP3R1* approached significance for change in strength with ST ($P = 0.07$). In this case, *IGF1* 192 homozygotes and heterozygotes responded similarly, while *IGF1* noncarriers of the 192 allele responded differently with respect to *PPP3R1* genotype groups. In fact, *PPP3R1* II homozygotes who were also 192-allele heterozygotes for *IGF1,* had significantly greater increases in strength with ST than *PPP3R1* II homozygotes, who were also noncarriers of the 192 allele for *IGF1* (8.4 ± 0.66 vs 4.7 ± 0.89 kg, $P < 0.01$). However, there were no significant differences between *PPP3R1* II homozygotes who were *IGF1* 192

homozygotes and either *PPP3R1* II homozygotes who were *IGF1* 192 heterozygotes (6.9 ± 0.81 vs 8.4 ± 0.66 kg, P > 0.05) or *PPP3R1* II homozygotes who were noncarriers of the 192 allele (6.9 ± 0.81 vs 4.7 ± 0.89 kg, P > 0.05). Also, Table 19 of Appendix I shows that for *PPP3R1* D-allele carriers there was no significant difference in change in strength with ST among *IGF1* genotype groups. The *IGF1* by *IGFBP3* and *IGF1* by race interactions for change in muscle strength with ST were not significant. Table 20 of Appendix I shows that for all relevant comparisons, there were no significant differences among genotype groups for change in strength with ST for the *IGF1* by *IGFBP3* interaction. The *IGF1* by sex and hormone replacement therapy status interaction could not be tested due to insufficient sample size. There was a significant combined gene effect, including both *IGF1* main effect and *IGF1* by *PPP3R1* gene by gene interaction effect, on change in strength with ST ($P < 0.01$). Table 6 shows that this total gene effect accounted for 3.41% of the variability in change in muscle strength with ST.

MV response: Table 13 and Figure 9 of Appendix I show that there was no significant influence of the *IGF1* main effect on the change in MV with ST ($P = 0.36$). There were no significant interactions for *IGF1* with either *IGFBP3* or *PPP3R1* for change in MV with ST. For all relevant comparisons, there were no significant differences among genotype groups change in MV (Tables 22-23 of Appendix I) with ST for these gene by gene interactions. Also there was no significant interaction between *IGF1* and race for change in MV with ST. The *IGF1* by sex and hormone replacement therapy status interaction could not be tested due to insufficient sample size. Due to the lack of at least a trend for a significant gene by gene or gene by race interaction involving

IGF1 for change in MV, a combined gene effect for *IGF1* for change in MV was not determined.

MQ response: Table 16 of Appendix I shows that there was no significant influence of the *IGF1* main effect on the change in MQ with ST ($P = 0.69$). Figure 4 shows that the gene by gene interaction between *IGF1* and *PPP3R1* was right on the borderline for being significant for the change in MQ with ST ($P = 0.05$). There was no consistent MQ response to ST of *PPP3R1* genotype groups across *IGF1* genotype groups. Those who were both *PPP3R1* II homozygotes and *IGF1* 192-allele heterozygotes had a significantly greater increase in MQ with ST than *PPP3R1* II homozygotes who were *IGF1* noncarriers of the 192 allele (3.7 ± 0.37 vs 1.8 ± 0.48 kg/cm^3 $*10^{-3}$, $P < 0.01$). *PPP3R1* II homozygotes who were 192 homozygotes had increases in MQ with ST that were not significantly different than either *PPP3R1* II homozygotes who were 192 heterozygotes (3.3 ± 0.45 vs 3.7 ± 0.37 kg/cm^3 $*10^{-3}$, $P = 1.00$) or *PPP3R1* II homozygotes who were *IGF1* noncarriers of the 192 allele (3.3 ± 0.45 vs 1.8 ± 0.48 kg/cm^3 $*10^{-3}$, $P = 0.14$). In addition, Table 19 of Appendix I shows that for *PPP3R1* D-allele carriers there were no significant differences in the change in MQ with ST among *IGF1* genotype groups. There was no significant gene by gene interaction for *IGF1* with *IGFBP3* for change in MQ with ST. For all relevant comparisons, there were no significant differences among genotype groups for change in MQ with ST (Tables 26 of Appendix I) for this interaction. Also there was no significant *IGF1* by race interaction for change in MQ with ST. The *IGF1* by sex and hormone replacement therapy status interaction could not be tested due to insufficient sample size. There was a significant combined gene effect for *IGF1*, including both *IGF1* main effect

and *IGF1* by *PPP3R1* gene by gene interaction effect, for change in MQ with ST ($P < 0.05$).

IGFBP3 influence on 1 RM strength, MV, and MQ responses to ST.

1 RM response to ST: Table 11 of Appendix I shows that there was no significant influence of the *IGFBP3* main effect on the change in muscle strength with ST ($P = 0.18$). However, Figure 2 shows a gene by race interaction that approached significance for the change in strength with ST for the -202 gene polymorphism for *IGFBP3* ($P = 0.09$). For the *IGFBP3* AA genotype group there was a larger difference in response between races than for the other *IGFBP3* genotype groups. African Americans who were AA homozygotes had a significantly greater increase in strength with ST than AA homozygotic Caucasians (10 ± 1.2 vs 5.3 ± 0.84 kg, $P < 0.01$), while there was no significant differences between races for the change in strength for the *IGFBP3* AC (7.2 ± 0.98 vs 5.9 ± 0.69 kg, $P = 1.00$) and CC genotype groups (6.6 ± 1.71 vs 4.9 ± 0.83 kg, $P = 1.00$). There were no significant gene by gene interactions for *IGFBP3* with *IGF1* or *PPP3R1* for change in strength with ST. Also for all relevant comparisons, there were no significant differences among genotype groups for change in strength (Tables 26-27 of Appendix I) with ST for these gene by gene interactions. The *IGFBP3* by sex and hormone replacement therapy status interaction could not be tested due to insufficient sample size. The combined gene effect for *IGFBP3*, which included both the *IGFBP3* main effect and the *IGFBP3* by race interaction effect, was not significant ($P > 0.05$).

MV response to ST: Table 14 and Figure 10 of Appendix I show that there was no significant influence of the *IGFBP3* gene polymorphism on the changes in MV with ST ($P = 0.91$). Moreover, there were no significant gene by gene interactions for

IGFBP3 with *IGF1* or *PPP3R1* nor was there a significant *IGFBP3* by race intearaction for change in MV with ST. Also for all relevant comparisons, there were no significant differences among genotype groups for change in MV (Tables 23-24 of Appendix I) with ST for *IGFBP3* by *IGF1* or *IGFBP3* by *PPP3R1* gene by gene interactions. The *IGFBP3* by sex and hormone replacement therapy status interaction could not be tested due to insufficient sample size. Due to the lack of at least a trend for a significant gene by gene or gene by race interaction involving *IGFBP3* for change in MV, a combined gene effect for *IGFBP3* for change in MV was not determined.

MQ response to ST: Table 17 and Figure 11 of Appendix I show that there was no significant difference among *IGFBP3* genotype groups for change in MQ with ST (P = 0.66). Similarly, there was no significant gene by gene interaction between *IGFBP3* and either *IGF1* or *PPP3R1* for change in MQ with ST. For all relevant comparisons, there were no significant differences among genotype groups for change in MQ with ST (Tables 26-27 of Appendix I). Also, there was no significant *IGFBP3* by race interaction for change in MQ with ST. The *IGFBP3* by sex and hormone replacement therapy status interaction could not be tested due to insufficient sample size. Due to the lack of at least a trend for a significant gene by gene or gene by race interaction involving *IGFBP3* for change in MQ, a combined gene effect for *IGFBP3* for change in MQ was not determined.

PPP3R1 influence on 1 RM strength, MV, and MQ responses to ST.

1 RM response: Table 12 of Appendix I shows that there was no significant influence of the *PPP3R1* main effect on the change in muscle strength with ST (P = 0.90). However, there was a trend for a significant interaction between *PPP3R1* and

IGF1 for the change in strength with ST ($P = 0.07$), as shown in Figure 1. There was no significant interaction between *PPP3R1* and *IGFBP3* nor between *PPP3R1* and race for change in strength with ST. For all relevant comparisons, there were no significant differences among genotype groups for change in strength (Tables 21 of Appendix I) with ST for the *PPP3R1* by *IGFBP3* gene by gene interaction. The *PPP3R1* by sex and hormone replacement therapy status interaction could not be tested due to insufficient sample size. The combined gene effect for *PPP3R1*, including both *PPP3R1* main effect and *PPP3R1* by *IGF1* gene by gene interaction effect, on the change in strength with ST did not reach significance ($P > 0.05$). Figure 3 shows there was a trend for II homozygotes of the I/D polymorphism in the promoter region of the *PPP3R1* gene to have a greater increase in MV with ST than D-allele carriers (130 ± 10 vs 100 ± 14 cm^3, $P = 0.06$). There were no significant gene by gene interactions between *PPP3R1* and either *IGF1* or *IGFBP3* for change in MV with ST. For all relevant comparisons, there were no significant differences among genotype groups for change in MV (Table 22 and 24 of Appendix I) with ST for these gene by gene interactions. Also there was no significant *PPP3R1* by race interaction for change in MV with ST. The *PPP3R1* by sex and hormone replacement therapy status interaction could not be tested due to insufficient sample size. Due to the lack of at least a trend for a significant gene by gene or gene by race interaction involving *PPP3R1* for change in MV, a combined gene effect for *PPP3R1* for change in MV was not determined.

MQ response: Table 18 of Appendix I shows that there was no significant difference among *PPP3R1* genotype groups for change in MQ with ST ($P = 0.70$). Figure 4 shows that the gene by gene interaction between *PPP3R1* and *IGF1* was right

on the borderline for being significant for the change in MQ with ST ($P = 0.05$). There was no consistent MQ response to ST of *PPP3R1* genotype groups across *IGF1* genotype groups. Those who were both *PPP3R1* II homozygotes and *IGF1* 192-allele heterozygotes had a significantly greater increase in MQ with ST than *PPP3R1* II homozygotes who were *IGF1* noncarriers of the 192 allele (3.7 ± 0.37 vs 1.8 ± 0.48 $kg/cm^3 *10^{-3}$, $P < 0.01$). *PPP3R1* II homozygotes who were 192 homozygotes had increases in MQ with ST that were not significantly different than either *PPP3R1* II homozygotes who were 192 heterozygotes (3.3 ± 0.45 vs 3.7 ± 0.37 $kg/cm^3 *10^{-3}$, $P = 1.00$) or *PPP3R1* II homozygotes who were *IGF1* noncarriers of the 192 allele (3.3 ± 0.45 vs 1.8 ± 0.48 $kg/cm^3 *10^{-3}$, $P = 0.14$). In addition, Table 19 of Appendix I shows that for *PPP3R1* D-allele carriers there were no significant differences in the change in MQ with ST among *IGF1* genotype groups. There was no significant gene by gene interaction for *PPP3R1* with *IGFBP3* for change in MQ with ST. For all relevant comparisons, there were no significant differences among genotype groups for change in MQ with ST (Tables 27 of Appendix I) for this interaction. Also there was no significant *PPP3R1* by race interaction for change in MQ with ST. The *PPP3R1* by sex and hormone replacement therapy status interaction could not be tested due to insufficient sample size. There was not a significant combined gene effect for *PPP3R1*, including both *PPP3R1* main effect and *IGF1* by *PPP3R1* gene by gene interaction effect, for change in MQ with ST ($P > 0.05$).

Gene polymorphism contribution to each muscle phenotype. Table 6 shows the estimated percent of variability attributable to *IGF1*, *IGFBP3*, and *PPP3R1* genotypes and to each relevant gene by gene interaction for the changes in strength, MV, and MQ

with ST. The contributions to the percent variability for the change in strength and MQ with ST for the *IGF1* and *PPP3R1* gene by gene interactions was ~4.5 and 5.9%, respectively. The single gene contributions of *IGF1*, *IGFBP3*, and *PPP3R1* to percent variability for change in strength and MQ were ~2-5% and 1-4%, respectively. For change in MV with ST the single contributions were 2-3% for *IGF1* and *PPP3R1*, while the contribution of *IGFBP3* was less than 1%.

DISCUSSION

To our knowledge, this is the first report that has investigated the influence of genes linked in a common biological pathway on muscle phenotypic responses to strength training (ST). The results offer partial support to the hypothesis that insulin-like growth factor pathway genotypes influence changes in muscle phenotypes with ST, and suggest that the *IGF1* and *PPP3R1* genes may be linked to influence muscle strength and muscle quality (MQ) responses to ST.

The major finding of this study was that there was a significant combined gene effect for *IGF1*, including both *IGF1* main effect and *IGF1* by *PPP3R1* gene by gene interaction effect, for change in strength with ST ($P < 0.01$). There was also a significant combined gene effect for *IGF1* on change in MQ ($P < 0.05$). The gene by gene interaction for *IGF1* by *PPP3R1* approached significance for both the change in strength and MQ with ST. The findings of this study complement those of a previous study from our laboratory, which used some of the same subjects that were enrolled in this investigation, and found significant *IGF1* main effects on the change in muscle strength response to ST (127). However, the present study extends these findings by showing that combined gene effects for *IGF1*, including both *IGF1* main effect and *IGF1* by *PPP3R1*

interaction effect, influence the strength and MQ responses to ST. In addition, although our results showed only a trend towards statistical significance for gene by gene interactions, they are novel in that they are the first, that we are aware of, which suggest a possible interaction between genes in a common biological pathway to influence skeletal muscle phenotypic responses to ST. Two previous studies, which investigated individual genes of this biological pathway, have shown an individual influence of the *IGF1* dinucleotide repeat polymorphism (127) and the *PPP3R1* 5-base pair (bp) insertion/deletion (I/D) polymorphism (258) on muscle phenotypes.

We had anticipated significant gene influences on muscle phenotypic responses to ST because previous studies have shown an influence of IGF-1 on calcineurin to promote skeletal muscle cell hypertrophy (172, 240). However, these studies did not test the influence of insulin-like growth factor pathway genes on responses to ST. The muscle phenotypes that we investigated are complex phenotypes and would likely be influenced by several genes in several different pathways. Thus, the contribution of two genes, even linked in a pathway, may not be enough to significantly influence a muscle phenotype. However, we found that the contribution to percent variability attributable to the *IGF1* and *PPP3R1* interaction was ~ 4.5% and 5.9%, respectively for the change in strength and MQ with ST. These contributions are larger than the contributions of single genes (~2%) reported to influence other muscle phenotypic responses to ST (41).

Another unexpected result was that there were no significant combined gene effects for *PPP3R1*, including both *PPP3R1* main effects and *PPP3R1* by *IGF1* interaction effects, on the changes in strength and MQ with ST, despite our findings suggesting a potential interaction with *IGF1* to influence these phenotypic responses to ST. Tang et

al. (258) reported that the 5-bp I/D polymorphism of the *PPP3R1* gene influenced left ventricular muscle mass in Caucasians and African Americans who were severely hypertensive (258). They reported that those possessing at least one D-allele were associated with greater risk of developing inappropriately high left ventricular mass than those possessing two copies of the I allele. The functional significance of the variant (D) allele of the *PPP3R1* polymorphism is unknown. However, these authors suggested that this variant eliminates a transcription factor binding site, and they hypothesized that this is an important binding site for a repressor or inhibitor of *PPP3R1* transcription. Our results differed from those of Tang et al. (258) in that II homozygotes tended to increase their skeletal muscle mass with overload more than D-allele carriers. These discrepancies could be due to, 1) differences in the function of calcineurin B, especially for the variant allele, in different tissues, 2) the nature of the load (ST vs hemodynamic overload) inducing hypertrophy, 3) differences in population being studied, or 4) a combination of two or more of these factors. We are unaware of any other studies that have compared variations at this locus to the response of interventions designed to change muscle mass or strength.

Contrary to our hypotheses, our results showed no significant influence of the *IGFBP3* genotype on changes in muscle phenotypes with ST, although we did observe a trend for a significant race by *IGFBP3* interaction to influence change in strength. We hypothesized a significant influence of *IGFBP3* because previous studies have shown that levels of IGFBP-3, a major carrier of IGF-1 in circulation (22), can be influenced by IGF-1 (278) and several studies have shown IGFBP-3 to be present in skeletal muscle. In addition, Foulstone et al. (70) have shown that increased secretion of IGFBP-3 in primary

adult human skeletal muscle cells is stimulated by IGF-1 (70). Moreover, previous studies have shown that the -202 polymorphism in the promoter region of the *IGFBP3* gene influences levels of the IGFBP-3 protein (47, 111, 246), although these studies have shown that several factors can interact with this polymorphism to influence protein levels, including female hormone levels, height, and BMI (47, 111, 246). In an *in vitro* study, Deal et al. (47) showed that the -202 polymorphism influenced the promoter activity of the gene, suggesting the possibility that this polymorphism could influence the levels of the protein in skeletal muscle. However, it is also possible that the isoforms of IGF-1 in skeletal muscle may be carried by a different binding protein than IGFBP-3. Therefore, even though the -202 locus of the *IGFBP3* gene may influence the levels of IGFBP-3 in skeletal muscle, this protein may not be the major potentiator of IGF-1 action in skeletal muscle.

In light of the trend for a significant *IGFBP3* by race interaction for influencing change in strength with ST, the influence of insulin-like growth factor pathway gene polymorphisms on the muscle phenotypic responses to ST should be studied more extensively in African Americans. Based on the different frequencies for the *IGF1*, *IGFBP3*, and *PPP3R1* genes between African Americans and Caucasians, it is possible that race effects may have played a greater role than genotype effects for the findings we observed. For example, African Americans had a higher frequency of the non-192 allele for the *IGF1* gene polymorphism compared with Caucasians. In contrast, Caucasians had a higher frequency of the variant (C) allele for the *IGFBP3* gene polymorphism compared with African Americans. Finally, African Americans had a higher frequency of the deletion allele for the *PPP3R1* gene polymorphism compared with Caucasians.

Similar differences between African Americans and Caucasians in allele frequencies for the *IGF1* and *PPP3R1* gene polymorphisms have been observed in previous studies (49, 110, 120, 258). There are no reports that we are aware of on the frequency difference between races for the *IGFBP3* polymorphism. To determine if there was a difference in response among races we tested for all possible genotype by race interactions and our results suggested there was no difference, except for the *IGFBP3* gene polymorphism for change in strength with ST.

There are several limitations of the present study, but the major limitation is the low statistical power for MV and MQ assessments. The lower statistical power for detecting differences among genotype groups for changes in MV and MQ with ST was, in part, due to smaller effect sizes projected for these phenotypes compared with changes in muscle strength. Additionally, the use of an untrained control leg in the design of the present study may have reduced the effect size needed for MV. However, the use of a control leg allowed for a better assurance that the results represent the independent effects of ST by controlling for variation due to methodological, biological, or seasonal factors. Thus, future studies should consider changes in MV and MQ with larger sample sizes to test for gene by gene interactions, as well as to investigate other genes in this biological pathway. Another possible limitation was that race by environment effects may have influenced our results. Nevertheless, we covaried for race in all analyses and tried to control for all possible race by environment interactions that could have potentially contributed a race effect to our results. One final limitation was that we assumed that each gene involved in a gene by gene interaction contributed equally to muscle phenotype variability. This

assumption was made because it was not possible to calculate the contributions of each gene involved in the interaction.

Future studies should be performed using larger sample sizes to better determine the influence of *IGF1*, *IGFBP3*, and *PPP3R1*, especially for gene by gene interactions, on muscle phenotypic responses and to investigate if other polymorphisms in the insulin-like growth factor pathway play a larger role in influencing muscle phenotypes. For example, it is possible that other polymorphisms in the *PPP3R1* gene, or a polymorphism in the catalytic subunit of calcineurin may be more responsible for influencing muscle phenotypic responses to ST. Secondly, there is a need to investigate other IGF-1-dependent mechanical signaling pathways that influence muscle phenotypic responses to ST. For example, it is conceivable that the IGF1-PI3K/Akt/mTOR pathway (186) may compensate for some of the effects of a potentially detrimental allele for the *PPP3R1* gene polymorphism. Finally, measurements should be made on transcription and protein levels of the insulin-like growth factor pathway gene polymorphisms investigated in the current study to better understand how they may influence muscle phenotype responses to ST.

In conclusion, this is the first study to examine the effects of insulin-like growth factor pathway gene polymorphisms on muscle phenotypic responses to ST in older adults. The results suggest that combined *IGF1* effects, i.e., the main effect for *IGF1* combined with the interaction effect with *PPP3R1*, will significantly influence muscle phenotypic responses. Although the results from *IGF1* by *PPP3R1* interactions should be interpreted with caution due to limited sample size for some of the combined genotype groups, they do provide support for the generation of new hypotheses involving *IGF1* by

PPP3R1 interactions that should be tested in future studies. Such studies will provide a better understanding of the role of gene polymorphisms on the responses to ST.

Table 1. ***IGF1*** **CA promoter allele and genotype frequency for all subjects**

Allele	**Total (%)**	**Caucasians**	**African Americans**
192	141 (55)	115 (61)	26 (39)
Non-192	115 (45)	75 (39)	40 (61)
Genotype			
192/192	39 (30)	34 (36)	5 (15)
192/-	63 (49)	47 (49)	16 (48)
Noncarriers of the 192 allele	26 (20)	14 (15)	12 (36)

CA = cytosine adenine
192 allele is equivalent to 19 CA repeats

Table 2. ***IGFBP3 A-202C*** **promoter allele and genotype frequency for all subjects**

Allele	Total (%)	Caucasians	African Americans
A	128 (50)	90 (47)	38 (58)
C	128 (50)	100 (53)	28 (42)
Genotype			
A/A	33 (26)	22 (23)	11 (33)
A/C	62 (48)	46 (48)	16 (48)
C/C	33 (26)	27 (28)	6 (18)

Table 3. *PPP3R1* 5-base pair I/D promoter allele and genotype frequency for all subjects

Allele	Total (%)	Caucasians	African Americans
I	227 (89)	177 (93)	50 (76)
D	29 (11)	13 (7)	16 (24)
Genotype			
I/I	100 (78)	82 (86)	18 (55)
I/D	27 (21)	13 (14)	14 (42)
D/D	1 (1)	0 (0)	1 (3)

I = insertion
D = deletion

Table 4. Physical characteristics for all men (n = 58) and women (n = 70) at baseline

	Men (n = 53-58)[1]		Women (n = 61-70)[1]	
	Baseline	**After ST**	**Baseline**	**After ST**
Age	65 (8)	--	63 (9)	--
Height (cm)	174 (7)	--	162 (7)	--
Weight (kg)	85.8 (13.5)	86.0 (13.4)	72.1 (12.6)	72.3 (13.2)
Body Fat (%)	28.0 (4.9)	27.6 (4.6)	38.6 (5.7)	38.1 (5.7)
FFM (kg)	61.2 (8.1)	61.7 (7.9)	43.8 (5.7)	44.2 (5.9)
1 RM (kg)	32 ± 1.0†		22 ± 1.0	
MV (cm^3)	1740 ± 32†		1340 ± 35	
MQ (kg/cm^3)*10^{-3}	18.8 ± 0.56*		16.1 ± 0.61	

Values are means (SD)
Values for 1 RM, MV, and MQ are least square means ± SE
† Significantly greater than women, $P < 0.001$
*Significantly greater than women, $P < 0.01$
FFM = Fat Free Mass
1 RM = Knee extension one repetition maximum
MV = Muscle Volume
MQ = Muscle Quality
[1]Sample size variability was due to missing data for muscle phenotypes

Table 5. Physical characteristics for all Caucasians (n = 95) and African Americans (n = 33) at baseline

	Caucasians (n = 85-95)[1]		African Americans (n = 29-33)[1]	
	Baseline	**After ST**	**Baseline**	**After ST**
Age	65 (8)	--	62 (8)	--
Height (cm)	168 (9)	--	166 (7)	--
Weight (kg)	78.2 (15.3)	78.4 (15.6)	78.5 (12.7)	78.9 (12.8)
Body Fat (%)	34.1 (7.6)	33.7 (7.5)	33.0 (7.3)	32.5 (7.2)
FFM (kg)	51.4 (11.3)	51.8 (11.3)	52.6 (10.5)	53.3 (10.6)
1 RM (kg)	24 ± 0.9		27 ± 1.2	
MV (cm^3)	1380 ± 28		1560 ± 35†	
MQ (kg/cm^3)*10^{-3}	17.0 ± 0.48		17.1 ± 0.65	

Values are means (SD)
Values for 1 RM, MV, and MQ are least square means ± SE
† Significantly greater than Caucasians, $P < 0.001$
FFM = Fat Free Mass
1 RM = Knee extension one repetition maximum
MV = Muscle Volume
MQ = Muscle Quality
[1]Sample size variability was due to missing data for muscle phenotypes

Table 6. Percent Variability for Muscle Phenotypes Attributable to *IGF1*, *IGFBP3*, and *PPP3R1*

Percent Variability for Genotypes for Change in Muscle Strength with Strength Training			
Genotype	**Individual Sources**	**Total Genotype**	**P-Value**
IGF1	1.14	3.41 = 1.14 + ½ (4.54)	< 0.01
IGFBP3	2.93	4.97 = 2.93 + ½ (4.07)	> 0.05
PPP3R1	0.01	2.28 = 0.01 + ½ (4.54)	> 0.05
*IGF1*PPP3R1*	4.54		0.07
*IGFBP3*Race	4.07		0.09
Percent Variability for Genotypes for Change in Muscle Volume with Strength Training			
Genotype	**Individual Sources**	**Total Genotype**	**P-Value**
IGF1	1.86	1.86	0.36
IGFBP3	0.16	0.16	0.91
PPP3R1	3.21	3.21	0.06
Percent Variability for Genotypes for Change in Muscle Quality with Strength Training			
Genotype	**Individual Sources**	**Total Genotype**	**P-Value**
IGF1	0.70	3.63 = 0.70 + ½ (5.86)	< 0.05
IGFBP3	0.79	0.79	0.66
PPP3R1	0.14	3.07 = 0.14 + ½ (5.86)	> 0.05
*IGF1*PPP3R1*	5.86		0.05

Note: The "Total Gene" effect was computed as the main effect plus one-half of any gene by gene interaction or gene by race interaction. For example for *IGF1*, "Total Gene" effect is the *IGF1* main effect (1.14) plus one half of the *IGF1* by *PPP3R1* gene by gene interaction (1/2 (4.54)). The other half of the gene by gene interaction is credited to *PPP3R1*.

FIGURE LEGENDS

Figure 1. Influence of calcineurin B (*PPP3R1*) by insulin-like growth factor 1 (*IGF1*) genotype groups on change in one repetition maximum (1 RM) strength with strength training (ST). There was a trend for a significant gene by gene interaction between *IGF1* and *PPP3R1* ($P = 0.072$). *PPP3R1* II homozygotes who were also *IGF1* 192-allele heterozygotes had significantly greater increases in 1 RM strength with ST than *PPP3R1* II homozygotes who were also *IGF1* noncarriers of the 192 allele (* $P = 0.004$). Values are covaried for age, hormone replacement therapy status and sex, race, height, body weight, body mass index, and baseline 1 RM strength. Values are means ± SE.

Figure 2. Influence of insulin-like growth factor binding protein 3 (*IGFBP3*) genotype by race groups on change in 1 RM strength with strength training (ST). There was a trend for a significant *IGFBP3* gene by race interaction ($P = 0.094$). African American *IGFBP3* AA homozygotes had significantly greater increases in 1 RM strength with ST than Caucasian *IGFBP3* AA homozygotes (* $P = 0.005$). Values are covaried for age, hormone replacement therapy status and sex, race, height, body weight, body mass index, and baseline 1 RM strength. Values are means ± SE.

Figure 3. Influence of calcineurin B (*PPP3R1*) genotype groups on change in muscle volume (MV) with strength training (ST). There was a trend for *PPP3R1* II homozygotes to have greater increases in MV with ST than the *PPP3R1* D-allele carriers ($P = 0.061$). Values are covaried for age, hormone replacement therapy status and sex, race, height, body weight, body mass index, and baseline MV. Values are means ± SE.

Figure 4. Influence of calcineurin B (*PPP3R1*) by insulin-like growth factor 1 (*IGF1*) genotype groups on change in muscle quality (MQ) with strength training (ST). There was a borderline significant gene by gene interaction between *IGF1* and *PPP3R1* (P = 0.051). *PPP3R1* II homozygotes who were also *IGF1* 192-allele heterozygotes had significantly greater increases in 1 RM strength with ST than *PPP3R1* II homozygotes who were also *IGF1* noncarriers of the 192 allele (* P = 0.005). Values are covaried for age, hormone replacement therapy status and sex, race, height, body weight, body mass index, and baseline MQ. Values are means ± SE.

Figure 1 Change in Muscle Strength with Strength Training for Calcineurin B (*PPP3R1*) and Insulin-like Growth Factor 1 (*IGF1*) Genotype Groups

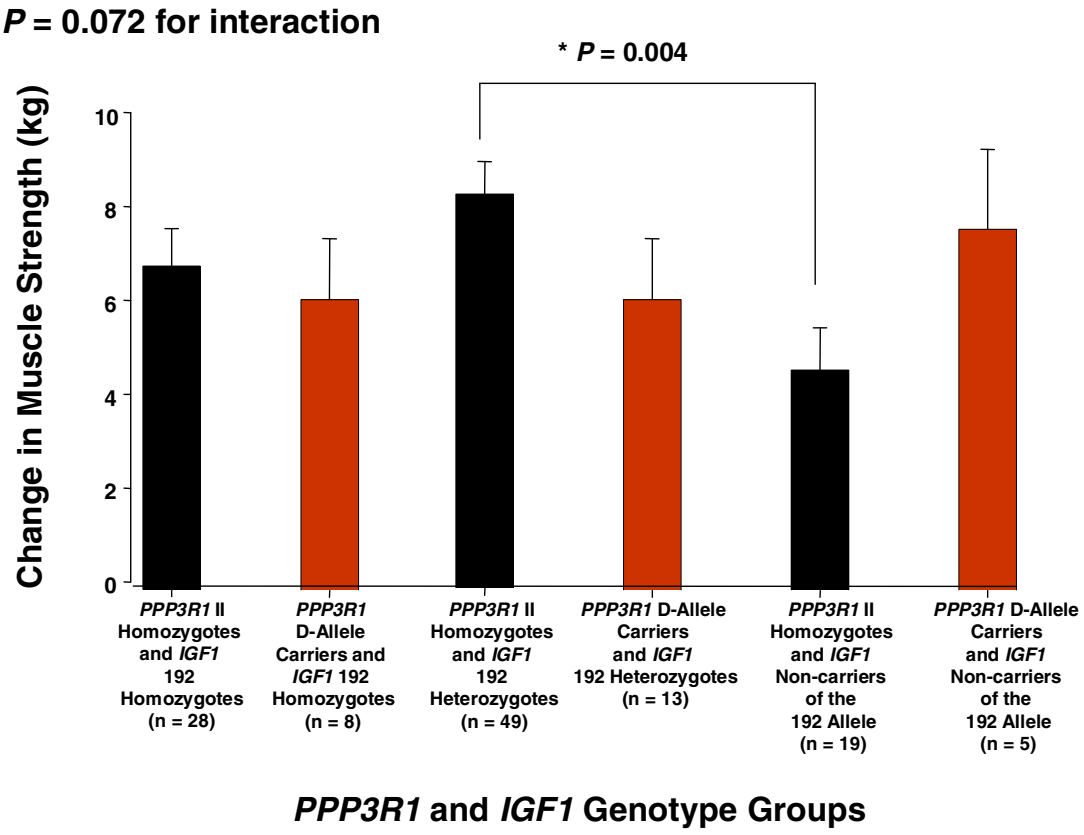


Figure 2 Change in Muscle Strength with Strength Training for Race and Insulin-like Growth Factor Binding Protein 3 (*IGFBP3*) Genotype Group

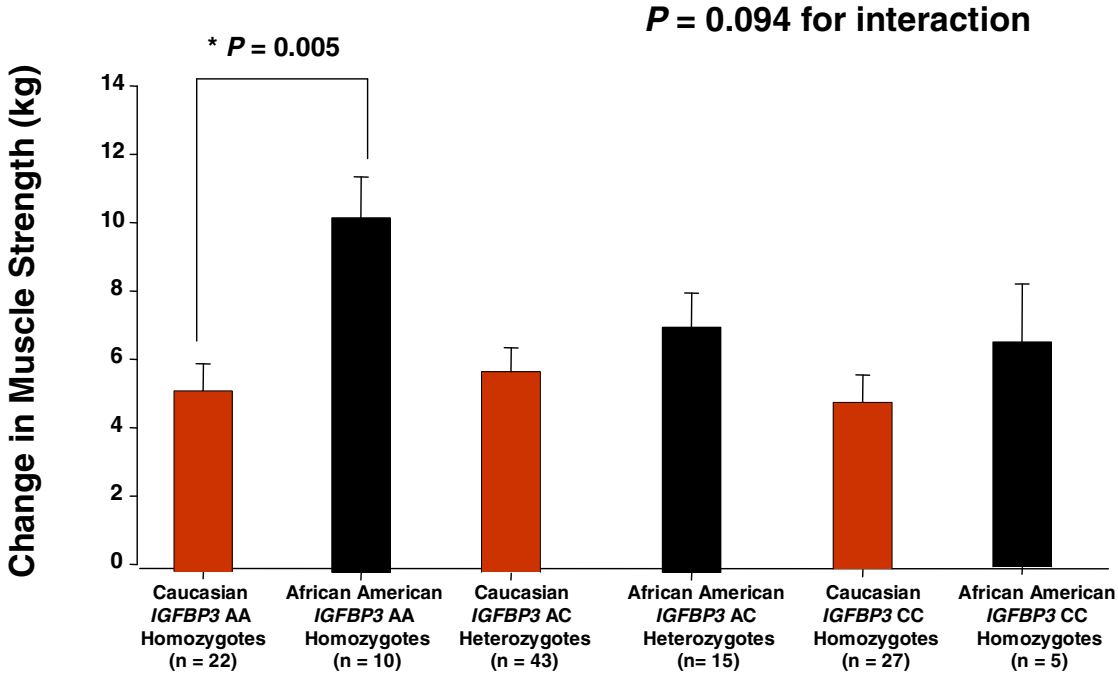


Figure 3 Change in Muscle Volume with Strength Training for Calcineurin B (*PPP3R1*) Genotype Groups

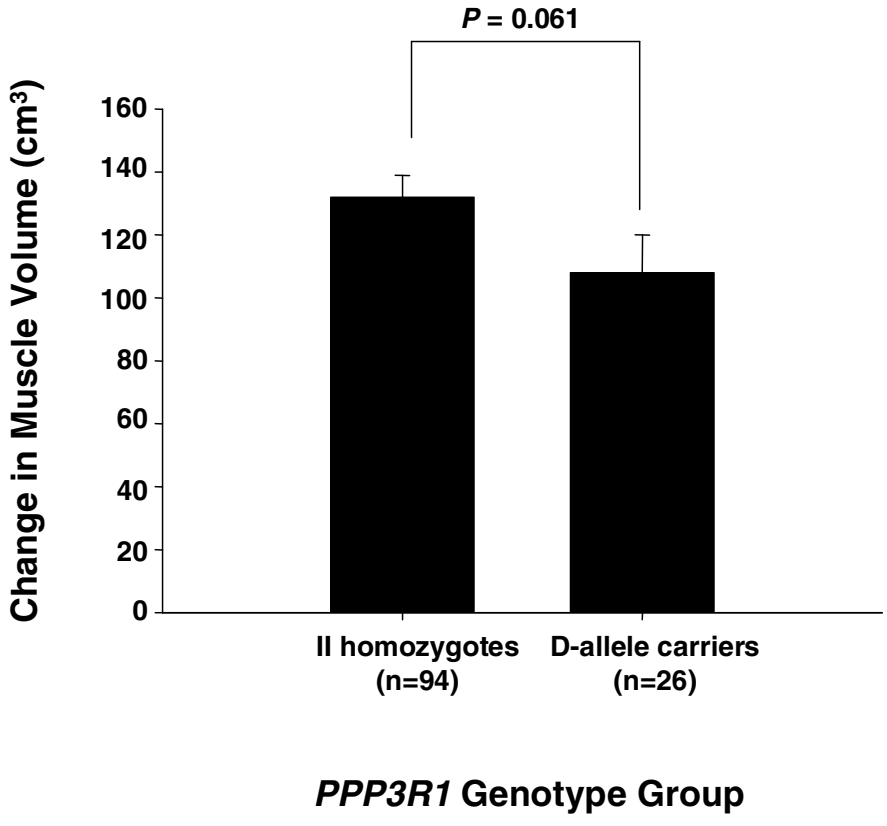
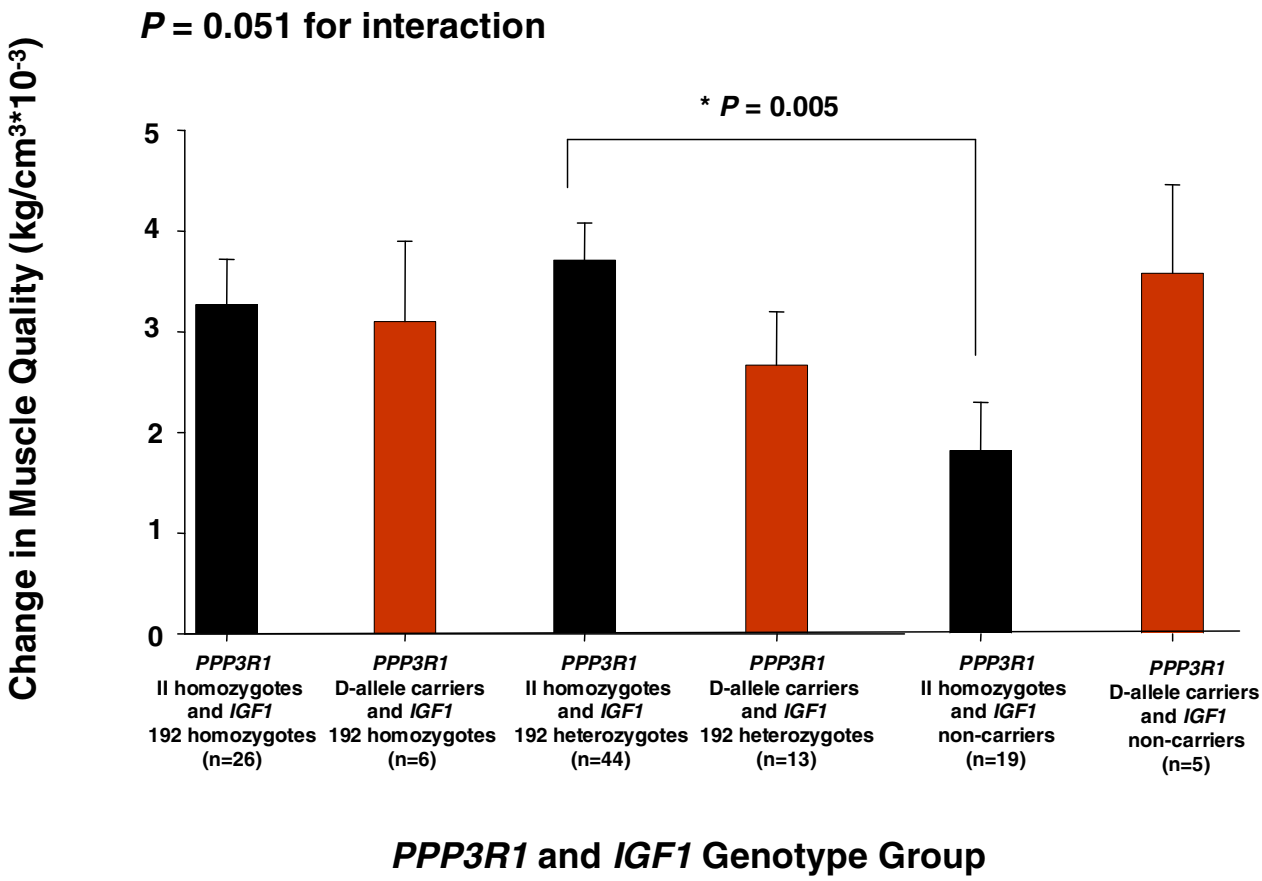


Figure 4 Change in Muscle Quality with Strength Training for Calcineurin B (*PPP3R1*) and Insulin-like Growth Factor 1 (*IGF1*) Genotype Groups



APPENDIX A

Research Hypotheses

Delimitations

Limitations

Operational Definitions

APPENDIX A

Research Hypotheses, Delimitations, Limitations, and Operational Definitions

Research Hypotheses

1. Carriers of the 192 allele of the CA dinucleotide repeat polymorphism in the promoter region of the insulin-like growth factor 1 (*IGF1*) gene will have greater increases in muscle strength and muscle volume with strength training than noncarriers of the 192 allele.
2. AA homozygotes at the -202 locus in the promoter region of the insulin-like growth factor binding protein 3 (*IGFBP3*) gene will have greater increases in muscle strength and muscle volume with strength training than C-allele carriers.
3. D-allele carriers of the 5-base pair (bp) insertion deletion polymorphism of the calcineurin B (*PPP3R1*) gene will have greater increases in muscle strength and muscle volume with strength training than II homozygotes.

Delimitations

1. The scope of this study will be delimited to ~130 men and women between the ages of 50 and 85 who volunteer as participants and complete the study protocol.
2. Participation in the study will be limited to healthy participants free of musculoskeletal or cardiovascular disease.
3. Based on previous research, subjects will be divided into three groups for the *IGF1* and *IGFBP3* genes and into two groups for the *PPP3R1* gene in determining the effect of these genotypes. The groups will be based on homo-

and heterozygosity for the 192 allele for the CA dinucleotide repeat polymorphism for the *IGF1* gene and for the promoter region polymorphism at the -202 locus in the IGFBP3 gene. For the *PPP3R1* gene grouping will be based on the presence or absence of at least one deletion allele for the 5 bp insertion/deletion polymorphism.

Limitations

1. The participants will be volunteers and not randomly selected from the general population. Therefore, the results of this study cannot be generalized to individuals who do not possess characteristics such as age, body size, physical activity, etc. similar to those of subjects in the study.
2. Subjects will self-report many factors related to health and lifestyle such as physical activity habits, dietary habits, medication regimens, and medical conditions and they will be asked to keep such lifestyle components constant during the training program. The accuracy of these components will not be verified, therefore it is possible that inaccurate self-reports may occur, which could adversely affect the results of this study.
3. Genotypes other than the *IGF1* promoter, *IGFBP3* promoter, and *PPP3R1* 5 bp insertion/deletion sites will not be considered in the proposed study. It is possible that the effects of these polymorphisms are present only in the presence of a specific, but unknown, genetic background (epistasis). Also these polymorphisms may be in linkage disequilibrium with the polymorphism that actually affects the phenotype of interest.

Operational Definitions:

5-RM: Refers to the maximal amount of resistance an individual can move through a complete range of motion only five times.

192 polymorphism (*IGF1* gene): This polymorphism is identified by the length of a CA dinucleotide repeat found in the promoter region of the *IGF1* gene. It can be 16 to 22 dinucleotides in length (99% of the population) and is located at nucleotide position 1087-1127 in the human *IGF1* DNA sequence in the original human *IGF1* DNA sequence Genbank accession number AY260957.

RS# 10665874

-202 polymorphism (*IGFBP3* gene): This polymorphism is identified by an A or C nucleotide base at the -202 locus or at position 1704 in the promoter region of the *IGFBP3* gene. The Genbank position number is M35878.

Calcineurin B (*PPP3R1*) gene (protein phosphatase 3, regulatory subunit B, alpha isoform 1): A gene spanning approximately 12 kb located on chromosome 2p16-p15 containing 4 introns of lengths >4.6, 1.1, 0.6, and 1.4 kb (282).

Calcineurin B protein: A 19 kDa Ca (2+)-binding regulatory subunit making up calcineurin (calmodulin-regulated protein phosphatase), which plays a critical role in transcriptional regulation and growth control in T lymphocytes by a mechanism believed to involve dephosphorylation of the nuclear factor NF-AT, which is essential for transcription of the interleukin-2 gene.

Combined gene effect: Gene effect which includes both the main effect for that gene and either a gene by race interaction with that gene, or a gene by gene interaction, including that gene and another gene.

Computed tomography (CT): A technique for assessing regional muscle size based on the examination of axial scans of the thigh. Visual images are created from the measurement of the intensity of x-rays and analyzed to measure cross-sectional area. The images are based on the attenuation of x-rays as they pass through the body. Attenuation scores are measured in Hounsfield units, which depend upon the level of absorption of emitted x-ray beams, -1000 in air to +1000 in bone. Skeletal muscle is typically 0 to 100 Hounsfield units while adipose tissue is usually -190 to -30 Hounsfield units.

Dual-energy x-ray absorptiometry (DXA): A technique for assessing whole and regional body composition that considers the body to be composed of three compartments: bone mineral mass, soft tissue, and lean tissue. Tissue amounts are based on the attenuation of x-rays as they pass through the body.

***IGF1* gene:** A gene of at least 45 kb containing six exons and five introns (247). The location of the human *IGF1* gene is 12q22-q23 (28, 271).

IGF-1 protein: A polypeptide similar in structure to insulin with autocrine/paracrine effects on muscle during growth and differentiation and in adult life.

***IGFBP3* gene:** A gene spanning 8.9 kb containing 4 exons with a 5^{th} exon containing the 3'-untranslated region. The location of the human *IGFBP3* gene is on human chromosome 7p14-p12 (58).

IGFBP-3 protein: A polypeptide which functions as the major carrier of IGF-1 in the circulation, as a modulator of IGF-1 bioactivity, and as a direct growth

inhibitor in the extravascular tissue compartment, where it is expressed in a highly regulated manner.

Insertion/deletion polymorphism (*PPP3R1* gene): This polymorphism is identified by the insertion or deletion of a 5-base pair (bp) sequence located at the -1063 to -1059 position. The Genbank accession number is NT022184-12. RS# 3039851

Muscle quality: Also known as specific tension or specific force, it is the strength of a muscle divided by muscle volume (the amount of force production per unit area of muscle tissue).

Muscle volume: Muscle volume will be determined by the MIPAV software and equations used by Tracy et al. (266). Briefly, this involves an equation that utilizes the 8-10 axial thigh slices that are obtained from the CT scan.

Sarcopenia: A condition characterized by the loss of muscle size, quality, and function that occurs with aging. This typically leads to or exacerbates ailments such as osteoporosis and loss of functional independence.

APPENDIX B

Consent for Research Participation

Detailed Telephone Interview

Medical Clearance

Medical History

DXA Record

CT Appointment Request

1 RM Data Collection

DXA Result Example

Training Log

APPENDIX B: FORMS

CONSENT TO PARTICIPATE IN A RESEARCH PROJECT

Project Title: Effects of Gene Variations on Age- and Strength Training-Induced Changes in Muscular Strength, Body Composition, Blood Pressure, Glucose Metabolism, and Lipoprotein-lipid Profiles

I state that I am over 18 years of age, in good physical health, and have elected to participate in a program of research being conducted by Dr. Ben Hurley in the Department of Kinesiology at the University of Maryland, College Park, MD 20742.

I understand that the primary purpose of this study is to assess the role that genetics may play in causing losses of muscular strength and muscle mass with age and gains in strength and muscle mass as a result of strength training. I understand that another purpose of the study will be to assess the influence of genes on changes in body composition, blood pressure, blood sugar metabolism, blood fats muscle power, and performance of common physical tasks with age and strength training.

I understand that the procedures involve three phases. During the first phase, I will undergo testing, which will include a blood draw to analyze my DNA (genetic material), blood sugar and fats, and other blood proteins. My blood pressure, body composition, bone mineral density, leg muscle volume, muscle strength, muscle power, and ability to complete selected tasks similar to common activities of daily living will also be assessed during this first phase. The second phase of the study involves my participation in a strength training program three times a week for approximately six months. The third and final phase will be a repeat of all previously taken measures, except analysis of my DNA, which will not need to be repeated. Some of the tests will be repeated both after ~ 10 weeks of training and again after the entire training program. These repeat tests will include blood pressure, strength, power, muscle volume and body composition. Other tests will be repeated only after the entire training program.

I understand that the blood draw will require providing about 2 to 3 tablespoons of blood. I understand that there is a risk of bruising, pain and, in rare cases, infection or fainting as a result of blood sampling. However, these risks to me will be minimized by allowing only qualified people to draw my blood. A portion of this blood sample will be sent to the University of Pittsburgh to analyze my DNA. I understand that the remainder will be stored at the University of Maryland for later analysis of my blood sugar, the hormone that regulates my blood sugar (insulin), blood fats, and other blood proteins. I understand that a portion of this sample may also be used for potential future studies, but only as such studies examine strength, body composition (i.e., fat, muscle & bone), metabolism of blood sugar, and blood pressure. I understand that I may contact the principal investigator at any future point in time to request that any stored blood sample be destroyed immediately.

I understand that while I am lying on a padded table, my leg muscle and fat mass will be measured by computed tomography (CT). The CT scan will be performed at Washington Adventist Hospital. My percent body fat and bone mineral density measurements will be performed at the United States Department of Agriculture in Beltsville, Maryland by dual-energy x-ray absorptiometry (DXA). This will require my lying still on a padded exam table wearing metal-free clothing for about 10 minutes at a time, totaling less than 30 total minutes for the entire procedure.

I understand that there will be a total radiation dose of no more than 1 Rem to the whole body (effective dose equivalent) from each CT scan. This amount is well below the maximal annual radiation dose (5 Rems) allowed for exposure in the workplace. The body composition and bone density testing completed by DXA involves a small radiation exposure. The radiation exposure I will receive from DXA is equal t to an exposure of less than 50 millirems to the whole body. Naturally occurring radiation (cosmic radiation, radon, etc.) produces whole body radiation of about 300 millirems per year. Therefore, the total dose of radiation exposure due to the DXA measurement is minimal and the combined dose of DXA and CT is considered low.

I understand that strength and power assessment*s* will be performed on machines that measure how much force and how fast I can exert force through a typical range of knee extension motion. Strength testing will also be performed on the same exercise machines used for training by measuring the maximal amount of force that I can move through the full range of an exercise. During each strength training session I will be asked to exercise on machines which offer resistance against extending and flexing my arms, legs, and trunk region for approximately 40 minutes or less a day, three times a week for up to six months. I understand that I may experience some temporary muscle soreness as a result of the testing sessions. There is also a risk of muscle or skeletal injury from strength and power testing, as well as from strength training. The investigators of this study will use procedures designed to minimize this risk.

I understand that I will be asked to complete some tasks to measure my ability to carry out normal daily activities. These tasks include rising from a chair, short brisk walks and climbing a flight of stairs. Any risk of injury during the completion of these tasks will be minimized by having all sessions supervised by an exercise physiologist qualified to direct this type of testing and wearing a safety harness during the short brisk walks and climbing a flight of stairs.

I understand that it is also possible that heart or blood vessel problems could arise during my participation in the testing or training involved in this study. Although unusual, it is possible that these problems could lead to a heart attack or even death. Therefore, prior evaluation and permission from my physician at my expense will be required to participate in this study. I also understand that it is possible that these risks will not be eliminated completely, even with a medical evaluation prior to participation in the study.

I understand that this study is not designed to help me personally, but may help the investigators better understand who is likely to be most and least susceptible to losing strength, power, and muscle mass with advanced age and who is most and least likely to benefit from strength training.

I understand that my decision of whether or not to participate in this study is voluntary. I understand that I am free to ask questions about this study before I decide whether or not to participate in the study. I understand that if I consent to participate in the study I am free to withdraw from participation at any time without penalty or coercion, or without any requirement that I provide an explanation to anyone of my decision to withdraw. In addition, I understand that refusal to participate will not involve a penalty or loss of benefit to which a volunteer would ordinarily be entitled to at that time. If I am on hormone replacement therapy (HRT) prior to the study, I must remain on them and if I am not on HRT prior to the study, I must remain off them throughout the

study to qualify for continued participation. If I am taking other medications prior to the study, I will be permitted to participate as long as I had been on these mediations for at least 4 weeks prior to the study and do not stop taking them prior to the end of the study. I understand that all information collected in this study is confidential. For my participation in the study I will receive information after the study is completed about my blood pressure, blood test results, bone mineral density, body composition, and functional ability upon request, free of charge. However, I understand that I will not receive any financial compensation in exchange for my participation in this study.

In the event of physical injury resulting from participation in this study, upon my consent, emergency treatment will be available at the medical center of Washington Adventist Hospital with the understanding that any injury that requires medical attention becomes my financial responsibility. I understand that the University of Maryland at College Park will not provide any medical or hospitalization insurance coverage for participants in this research study, nor will they provide compensation for any injury sustained as a result of this research study, except as required by law.

I understand that I can discuss this research study at any time with the principal investigator, Dr. Ben Hurley at (301) 405-2457 or with the study coordinator of this project at (301) 405-2569.

I have read and understand the above information and have been given an adequate opportunity to ask the investigators any questions I have about the study. My questions, if any, have been answered by the investigators to my satisfaction. By my signature I am indicating my decision to consent to participate voluntarily in this study.

Principal investigator: Ben Hurley, Ph.D., Dept of Kinesiology, HLHP Building, University of Maryland, College Park, MD 20742-2611, Ph: (301) 405-2486.

Printed Name of Subject_____

Signature of Subject_____ Date_____

Contact information of Institutional Review Board: If you have questions about your rights as a research subject or wish to report a research-related injury, please contact:
Institutional Review Board Office, University of Maryland, College Park, MD 20742;
e-mail, irb@deans.umd.edu; telephone, 301-405-4212.

Name of Interviewer:_____ Eligible to Participate: ___Yes ___No
Date of Interview: _____ _____Need More Information or Review

University of Maryland at College Park
Department of Kinesiology

THE GUSTO STUDY
Data Sheet for Detailed Subject Telephone Interview

AGE: _____

50 – 64 years _____
65 or older _____

o **Brief Explanation of Study**
o **Permission to Conduct Interview?** _____Yes _____No

Comment:_____

o **Contact Information**

Name: Mr. Mrs._____
Address:_____
_____
Phone #:(W)_____(H)_____
E-Mail:_____
Best Way and Time to Contact:_____

- **Time Commitment** – Available
  ____Yes ____No Wants to be contacted after _____(Date) Comment:_____
  _____

- **Proximity to UMD Campus**
  Length of commute: _____ miles or _____ minutes
  Within reasonable commute_____ Willing to make unreasonable commute_____
  Too far to commute_____

- **Age**
  Age: _____ yrsDate of Birth: _____/_____/_____
  MM DD YY
  Approximate Height: _____Approximate Weight: _____

- **Racial Identification:**
  ___ American Indian or Alaskan Native
  ___ Asian or Pacific Islander
  ___ Black, not of Hispanic origin
  ___ Hispanic
  ___ White, not of Hispanic origin
  ___ Other/Unknown

- **Smoking**
  Always Non-Smoker_____ Non-Smoker for _____ Smoker_____

- **Communication Log**
  _____
  _____
  _____
  _____
  _____

Name: _____

- **Physical Activity**

1. Do you do any walking/jogging? _____

Hours per week? _____

Times per week?_____

Speed/Pace?_____

Hills? _____

Do you perspire? _____

2. What household jobs do you do? Gardening, housework, yardwork etc. _____

_____

_____

Hours per week? _____

Times per week?_____

Do you perspire? _____

3. Do you do any recreational activities? Sports, fishing, golfing, yoga, pilates, exercise classes etc.

_____

Hours per week? _____

Times per week?_____

Do you perspire? _____

4. What is your profession? _____

Please describe a typical day at work. _____

_____

_____

How much time each day do you spend walking around?_____

5. Do you lift any heavy objects regularly?_____

6. Is there any aspect of your physical activity that is very inconsistent or sporadic?_____

_____

Relatively Sedentary?

_____Yes _____No

Cardiovascular/Respiratory Conditions

____No ____Yes (Record on Medical History/Treatment Form)

Comments:_____

_____

- **Heart Problems**:

  Did your doctor ever tell you that you had a heart problem? ___Yes ___No

  If yes, what was the date of onset? _____

  What did the doctor call it? (Angina, Heart Failure, Heart attack, Rhythm disturbances, heart murmurs, enlarged heart, diseases of heart valves, others).

  _____

  _____

- **Osteoarthritis/Degenerative Arthritis**

  ___No ___Yes

  If yes, how long and what was the severity_____

  _____

- **High Blood Pressure**

No_____

Yes_____ Controlled (Record High BP and Treatment on Medical History/Treatment Form)

Yes_____ Uncontrolled

Comments:_____

_____

- **Lower Back Pain**

  ___No ___Yes

  If yes, how severe?_____

- **Frailty**

  No Incidents_____

  Fracture as Adult?_____ Describe:_____

  _____

  > 2 Falls in One Year?_____ Describe:_____

  _____

  Comments:_____

  _____

- **Diabetes**

_____No

_____Yes – Type II (Non-Insulin Dependent)

(Record Type II Diabetes and Treatment on Medical History/Treatment Form)

_____Yes – Type I – (Insulin Dependent – not qualified for the GUSTO study)

Comments:_____

_____

- **Orthopedic Conditions**

_____No

_____Yes (Record on Medical History/Treatment Form)

Comments:_____

_____

- **Stroke/Paralytic conditions**

_____Yes ____No. (If yes ask subject if there is any residual weakness of any extremity)

- **Surgical History**

___No ___Yes
If yes, what type (surgeries of the joints, heart surgeries, angioplasty, bypass surgery, Pacemakers)_____
When_____

- **Other Medical Conditions**

_____No
_____Yes (Record on Medical History/Treatment Form)
Comments:_____
_____

- **Information on where to send Physician Consent Form**

Name of Physician: _____
Specialty of Physician:_____
Have you seen your physician within the past 12 months? ____Yes ____No
Phone Number:_____
Fax Number: _____
Address (if phone and fax unknown):_____
_____
_____
(Please explain to the subject that he/she is unlikely to get med clearance if they have not seen their doc within the past 12 months and request them to go to the physician. If willing, request them to let us know after they meet their doctor and fax the med clearance form to physician AFTER they go to their doctor)

- **Summary**

Interviewer Signature: _____

Questions/ Comments:_____
_____
_____

Reviewer Initials: _____

_____Qualifies _____Need More Information
_____Needs Dr. Hurley's Review _____ Disqualified

Questions/ Comments:_____
_____

Medical Clearance to Participate in Research Project

It is my understanding that _____ (name of the volunteer), a patient under my care, has volunteered to participate in the study entitled, ***"Do Genes Influence Responses to Strength Training?"*** The volunteer must have the approval of her or his physician to participate in this study.

Exclusionary criteria for eligibility are listed below. If you believe that your patient named above has any of the medical conditions indicated below, please place a check in front of the condition(s) indicated:

____ Severe cardiovascular disease, such as ____unstable angina, ____uncontrollable hypertension, ____uncontrolled dysrhythmias, ____severe stenotic or regurgitant valvular disease, ____hypertrophic cardiomyopathy, and ____symptomatic peripheral arterial disease
____ Severe COPD or other signs of significant pulmonary dysfunction
____ Intracranial aneurysm
____ Musculoskeletal diseases that cause severe joint pain at rest or upon exertion
____ Diseases that promote muscle protein breakdown
____ Joint, vascular, abdominal or thoracic surgery in the past year
____ History of bone fragility fractures
____ Having any condition that is likely to be aggravated by muscular exertion
____ Being unable to engage safely in mild to moderate exercise, such as independently walking up at least one flight of stairs or walking two blocks on level ground

Although we are unaware of any cardiac complications that have resulted from strength testing or strength training, there is only a limited amount of data available in people over the age of 75. There is one report of non-fatal subarachnoid hemorrhage associated with strength training in three patients who had pre-existing intracranial aneurysms. For this reason, any patient who has known or suspected intracranial aneurysms or who is at high risk for having an intracranial aneurysm, should not participate in this study.

Please check one of the following:
____ Clearance granted
____ Clearance not granted
____ Please send me the following information about the study:

Volunteers in this study will participate in resistance exercise under the supervision of exercise specialists trained specifically for this study under the direction of the Principal Investigator, Ben Hurley Ph.D., Professor, Department of Kinesiology, College of Health and Human Performance, University of Maryland, College Park, Maryland 20742 (email: bh24@umail.umd.edu; tele: 301-405-2486; fax: 301-405-5578).

Physician's signature:_____ Date:_____

Name:_____ **Sex**____ **Initials:** __ __

Name of Interviewer: _____ **Date:** _____

Emergency contact name, address, phone_____

_____

Have you ever been a patient at Washington Adventist Hospital? ____Yes ____No ____not sure

MEDICAL HISTORY FOR GUSTO STUDY

DIRECTIONS:

Read the following questions out loud to each prospective volunteer and check "yes" or "no". Any answers that require qualification should be written in the space below the question or on the back of the sheet.

YES NO

SECTION *A*

Musculoskeletal system:

Have you ever been told by your doctor that you have any of the following?

a. Osteoarthritis or degenerative arthritis ____ ____

b. Rheumatoid arthritis ____ ____

c. Unknown or other type of arthritis (eg: Ankylosing Spondylitis) _____ ____

d. Osteoporosis ____ ____

e. Any other disease of joint or muscle: _____ ____

Comments:_____

_____

SECTION *B*

Cardiovascular system:

1. Has any family member had a heart attack prior to the age of 55? ____ ____

   If so, please describe the relationship:

	YES	NO
2. Have you ever had frequent cramping in your legs?	____	____
If yes, is it a current problem?	____	____
3. Have you ever had pain or cramping in your legs while walking?	____	____
If yes, is it a current problem?	____	____
If yes, is this pain relieved by rest or by discontinuing your walk?	____	____
4. Have you ever been told that you have high blood pressure?	____	____

If yes,

a. What was the date of diagnosis? _____

b. Were you given any medications? ____ ____

(Please list the medications with dose on the last page)

c. How long have you been on the medications? _____ ____ ____

d. Has there been a recent change in the medications and if so, when? _____

5. Did a doctor ever tell you that you had a heart problem? ____ ____

If yes,

a. What was the date of onset?

b. What did the doctor call it? (eg: Angina, Heart Failure, Heart Attack, Rhythm disturbances, heart murmurs, enlarged heart, diseases of heart valves, others). *Please circle relevant one(s). If others, please ask subject to expl*

c. Were you given any medications? *(Please list the medications with dose on the last page)*

d. Was Echocardiography ever done? ____ ____

6. Have you ever had any chest pain or discomfort other than breast pain (in women)? or pain and discomfort due to a respiratory or digestive problem? ____ ____

If yes,

a. What was the month and year of the first occurrence? _____

b. What was the month and year of the most recent occurrence? _____

c. What was the frequency of occurrence? (eg: once a month, once a week, once a year etc.)

_____

d. How would you describe the pain or discomfort? (Eg: Pressure, Burning,

Squeezing, Piercing, Stabbing, Shooting or Sticking) *Circle appropriate one or if different, please describe*_____

How many minutes did it last?_____

e. Does the pain or discomfort move? If yes, to where?

f. Does the pain or discomfort tend to occur:

After meals- ____ ____

At night- ____ ____

When Exercising- ____ ____

When walking in cold windy weather- ____ ____

When upset, excited or nervous- ____ ____

Other-

g. Is this pain relieved by

A change in posture- ____ ____

Rest- ____ ____

Physical activity- ____ ____

Bicarbonate of soda, Tums or antacids- ____ ____

Prescribed medications- ____ ____

Other-

h. Did you ever consult a doctor for this pain or discomfort? ____ ____

If yes,

Do you know the diagnosis?_____

Were you given any medications and if so was there a recent change in the medication (within past one month)? (*Please list on last page, if yes*) ____ ____

7. Do you have any history of high cholesterol in your blood as evident by previous blood lipid tests? ____ ____

Comments:_____

_____

SECTION *C* **YES NO**

Respiratory System:

1. Have you ever had persistent cough with sputum production for almost all days for 3 months for two consecutive years? ____ ____

   If yes,

   a. How long did it last?

   b. Did your doctor prescribe any medications and has there been any recent change in the medication:

(*Please list on last page, if any*)

2. Have you ever had attacks of wheezing? ____ ____

   If yes,

   a. Was it seasonal/ periodic? ____ ____

   b. Have you ever-required hospitalization to abort an acute attack? ____ ____

Comments:_____

_____

SECTION *D*

Endocrine system:

Has your doctor ever told you that you have any of the following?

a. Thyroid problems? ____ ____

b. Adrenal problems? ____ ____

c. Diabetes mellitus? ____ ____

If yes, which type?

Date of onset-_____

Were you on any medication, diet control ____ ____

SECTION *E* **YES NO**

Reproductive system:

Menstrual History

a. Have you attained menopause? ____ ____

If so,

Are you on Hormone Replacement Therapy? ____ ____

If yes, how long have you been on hormone replacement therapy?_____

Comments:_____
_____

SECTION *F* **YES NO**

Neurological system:

1. Do you have any problems with your memory? If yes,
   a. When answering the telephone, do you recall
      what you were doing before it rang? ____ ____
   b. If someone calls you, can you give the directions to your house? ____ ____
   c. Can you keep appointments without a reminder? ____ ____
   d. Can you remember what clothes you wore yesterday? ____ ____

   If the subject answers "no" to any of the above questions

   Do a Mini Mental Status Examination of the subject.
2. Any problems with vision other than corrective lens changes? ____ ____

   If yes, which of the following conditions- Blindness, Temporary loss of vision, Double vision, Glaucoma, Cataract, Macular degeneration or others.

	YES	NO
3. Ringing in your ears?	____	____
4. Vertigo (a feeling of spinning, or unsteadiness)	____	____
5. Fainting Spells (black outs)?	____	____
6. Seizure or convulsions?	____	____
7. Migraine or severe headaches?	____	____
8. Paralysis of arm or leg?	____	____
9. A head injury with loss of consciousness?	____	____
10. Pain, numbness or tingling in your arm or hand?	____	____
11. Pain in your lower back?	_____	____
12. Kidney stones?	_____	____
13. Ruptured vertebral disc in neck or back?	_____	____
14. Have you had pain in any part of body (including headache) while exercising?	_____	____
15. Numbness or pain in your legs?	____	____
16. Have you been told that you have a peripheral neuropathy?	____	____
17. Tremors?	____	____
18. Problems with walking?	____	____
a. Do you fall frequently?	____	____
b. Is your walking problem related to pain, weakness or loss of balance?	____	____
19. Stroke?	____	____
20. Epilepsy?	____	____
21. Operations on skull or brain?	____	____
22. Multiple sclerosis?	____	____
23. Meningitis or Brain fever?	____	____
24. Parkinson's disease	____	____

25. Any history of neurological consultation? ____ ____

Comments:_____

_____

SECTION *H* **YES** **NO**

Hematology/Immunology/Oncology :

1. Have you ever been told by your physician that you had a problem with anemia or any disease of the red blood cells or the white blood cells? ____ ____
2. Any family history of this problem? ____ ____
3. Do you have any history of bleeding disorders? ____ ____
4. Have you ever been diagnosed as having cancer? ____ ____

   If yes, which organ, date of onset? _____
5. Were you given any medications, radiation or undergone any surgery? ____ ____

Comments:_____

_____

SECTION *I*

Surgical History:

Have you undergone any surgeries? (Please include abdominal surgery) ____ ____

If yes,

a. Where and for what purpose? _____
b. Date of Surgery? _____
c. Length of stay in hospital _____
d. Any complications of Surgery? _____

Comments:_____

_____

Has a doctor ever told that you have been suffering from

a) Cystic medial degeneration ____ ____

b) Any Connective tissue disorder? ____ ____

Has any of your family member had an intracranial aneurysm or bleeding? ____ ____

Have you ever been diagnosed with an abdominal aneurysm? ____ ____

History of severe pain in the abdomen? ____ ____

If yes, Please specify_____

Any history of severe headache? ____ ____

If Yes,

What was the date of onset?_____

Was it associated with neurological signs like blurred vision, nausea/vomiting, seizures, drowsiness,memory impairment,sensory or motor loss(weakness)? _____ ____

Was it a new or different type of headache other than tension, migraine etc? _____ ____

Was it the worst ever experienced? _____ ____

Did it occur after exertion, coughing or straining? _____ ____

SECTION *J*

Do you have any other health problems not covered in this questionnaire? ____ ____

If yes, please do specify.

Comments:_____
_____

DEXA Body Scan – USDA / University of Maryland
Conway/Hurley/Kostek

Date:_____ Time:_____am/pm

Name:_____ Gender: M / F

Date of Birth:_____

Height:_____ inches _____ cm

Weight:_____ lbs. _____ kg

Subject number:_____

Dominant leg: R / L

Time and composition of last meal (or snack):

_____

_____

_____

_____

Comments:_____

_____

Initials of examiner and DXA technician:_____

The GUSTO Study

"**G**enes **U**nderlying **S**trength **T**raining adaptations in **O**lder adults"

UNIVERSITY OF MARYLAND

College Park

To: Washington Adventist Hospital, Centralized Records & Admitting

Fax #: (301) 891-6149

From: Ben Hurley, Ph.D., Professor, Department of Kinesiology

Fax #: (301) 405-5578 Phone #: (301) 405-2569

RE: Scheduling of patients for CT muscle mass study

Patient Name _____

Previously a patient at Washington Adventist Hospital: ___Yes ___No

Date/Time for CT scan _____ DOB: _____ Age _____ Sex ___

CT scanner: ___ Old scanner ____ Newer scanner ___ Either

Address _____ Phone # _____

_____

_____

Diabetes: __Yes __No If yes, type 1 or type 2? _____ Meds: _____

Scan type: Extremity (bilateral thigh) Contrast: **NO**

Emergency Contact (relationship) _____ Phone # _____

University of Maryland / National Institute on Aging
GUSTO

Symptom-limited Baseline Knee Extension 1-RM

Arms across chest	____
Seat Belt	____
Remember to breathe	____
CHECK EACH LINE BEFORE TEST	

Examiners Name_____
Name_____ Date_____
Time _____ Location_____
Body weight_____ Age_____ Predicted 1-RM_____

Seat_____ Leg_____ Blood Pressure_____ ***Right leg / Left leg***

	Resistance	**P/D scale**	**RPE scale**
Rest	_____	_____	_____
Set 1	0	_____	_____
Set 2	_____	_____	_____
Set 3	_____	_____	_____
Set 4	_____	_____	_____
Set 5	_____	_____	_____
Set 6	_____	_____	_____
Set 7	_____	_____	_____
Set 8	_____	_____	_____
Set 9	_____	_____	_____
Set 10	_____	_____	_____
Set 11	_____	_____	_____
Set 12	_____	_____	_____

Most severe P/D: _____ Subject's initials: _____

Post BP_____ 3 min. post BP_____ **Valid** **Invalid**

If invalid, please explain: _____
_____
Notes: _____
_____
_____

Data entry #1:_____initials _____date	
Data entry #2:_____initials _____date	

University of Maryland / National Institute on Aging
GUSTO

Symptom-limited Post Unilateral Training Knee Extension 1-RM

Arms across chest	____
Seat Belt	____
Remember to breathe	____
CHECK EACH LINE BEFORE TEST	

Examiners Name_____
Name_____ Date_____
Time _____ Location_____
Body weight_____ Age_____ Predicted 1-RM_____

Seat_____ Leg_____ Blood Pressure_____ ***Right leg / Left leg***

Participant's initials indicating that the P/D and RPE scale is understood and that he/she has the right to stop the test at anytime _____

	Resistance	**P/D scale**	**RPE scale**
Rest	_____	_____	_____
Set 1	0	_____	_____
Set 2	_____	_____	_____
Set 3	_____	_____	_____
Set 4	_____	_____	_____
Set 5	_____	_____	_____
Set 6	_____	_____	_____
Set 7	_____	_____	_____
Set 8	_____	_____	_____
Set 9	_____	_____	_____
Set 10	_____	_____	_____
Set 11	_____	_____	_____
Set 12	_____	_____	_____

Most severe P/D: _____ Subject's initials: _____

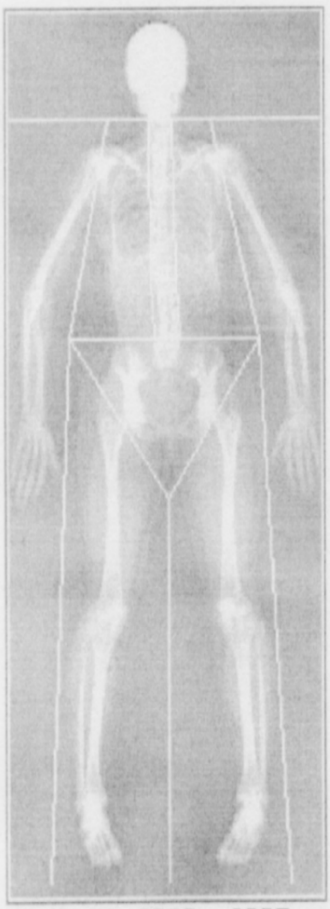
Post BP_____ 3 min. post BP_____ **Valid** **Invalid**

If invalid, please explain: _____
_____
Notes: _____
_____
_____

Data entry #1:_____initials _____date	
Data entry #2:_____initials _____date	

DXA Result Example

HOLOGIC



oMay 1 10:50 2003 [327 x 150]
Hologic QDR-4500A (S/N 45816)
Whole Body Fan Beam V8.26a:3*

A11220209 Fri Nov 22 11:34 2002
Name:
Comment: GUSTO post unilateral
I.D.: GUSTO Sex: F
S.S.#: - - Ethnic: W
ZIP Code: Height:5'10"
Operator: MJD Weight: 133
BirthDate: Age: 61
Physician: GUSTO
Image not for diagnostic use

TBAR1790 - 1
F.S. 68.00% 0(10.00)%
Head assumes 17.0% brain fat
LBM 73.2% water

Region	Fat (grams)	Lean+BMC (grams)	% Fat (%)
L Arm	1082.4	2034.7	34.7
R Arm	1104.2	2059.6	34.9
Trunk	6946.6	21128.9	24.7
L Leg	4457.0	6865.2	39.4
R Leg	4287.2	6747.0	38.9
SubTot	17877.4	38835.4	31.5
Head	808.2	3267.2	19.8
TOTAL	18685.6	42102.6	30.7

HOLOGIC

Unilateral Strength Training

BP Questions:
1) Ever been told high Blood Pressure?
   -If yes, taken medication today and yesterday?
2) Heavy meal in past 90 minutes?
3) Had coffee/tea in past 30 minutes?
4) Smoked in past 30 minutes?
5) Any type of exercise in past 30 minutes?

Subject's Name: _____ Seat position _____ 1 RM value ____ Leg ____

Training Session #	FAM I	FAM II	1	2	3	4	5	6			
Date											
Pre-Ex .BP (mm Hg)											
5 RM*Resistance (lbs)											
Peak Ex.BP (mm Hg)											
Post Ex.BP (mm Hg)											
Weight (lbs)											

*= Weight adjusted as needed to maintain 5 RM

Training Session #	10	11	12	13	14	15	16	17	18	19	20
Date											
Pre-Ex .BP (mm Hg)											
5 RM*Resistance (lbs)											
Peak Ex.BP (mm Hg)											
Post Ex.BP (mm Hg)											
Weight (lbs)											

*= Weight adjusted as needed to maintain 5 RM

Training Session #	21	22	23	24	25	26	27	28	29	30	31
Date											
Pre-Ex .BP (mm Hg)											
5 RM*Resistance (lbs)											
Peak Ex.BP (mm Hg)											
Post Ex.BP (mm Hg)											
Weight (lbs)											

*= Weight adjusted as needed to maintain 5 RM

Training

- 5 reps @ 50% of 1 RM resistance- 30 sec rest
- 5 reps @ 5 RM resistance- 1.5 min rest

1) P/D: ___, ___, ___	2) P/D: ___, ___, ___	3) P/D: ___, ___, ___	4) P/D: ___, ___, ___	5) P/D: ___, ___, ___	6) P/D: ___, ___, ___
7) P/D: ___, ___, ___	8) P/D: ___, ___, ___	9) P/D: ___, ___, ___	10) P/D: ___, ___, ___	11) P/D: ___, ___, ___	12) P/D: ___, ___, ___
13) P/D: ___, ___, ___	14) P/D: ___, ___, ___	15) P/D: ___, ___, ___	16) P/D: ___, ___, ___	17) P/D: ___, ___, ___	18) P/D: ___, ___, ___
19) P/D: ___, ___, ___	20) P/D: ___, ___, ___	21) P/D: ___, ___, ___	22) P/D: ___, ___, ___	23) P/D: ___, ___, ___	24) P/D: ___, ___, ___
25) P/D: ___, ___, ___	26) P/D: ___, ___, ___	27) P/D: ___, ___, ___	28) P/D: ___, ___, ___	29) P/D: ___, ___, ___	30) P/D: ___, ___, ___

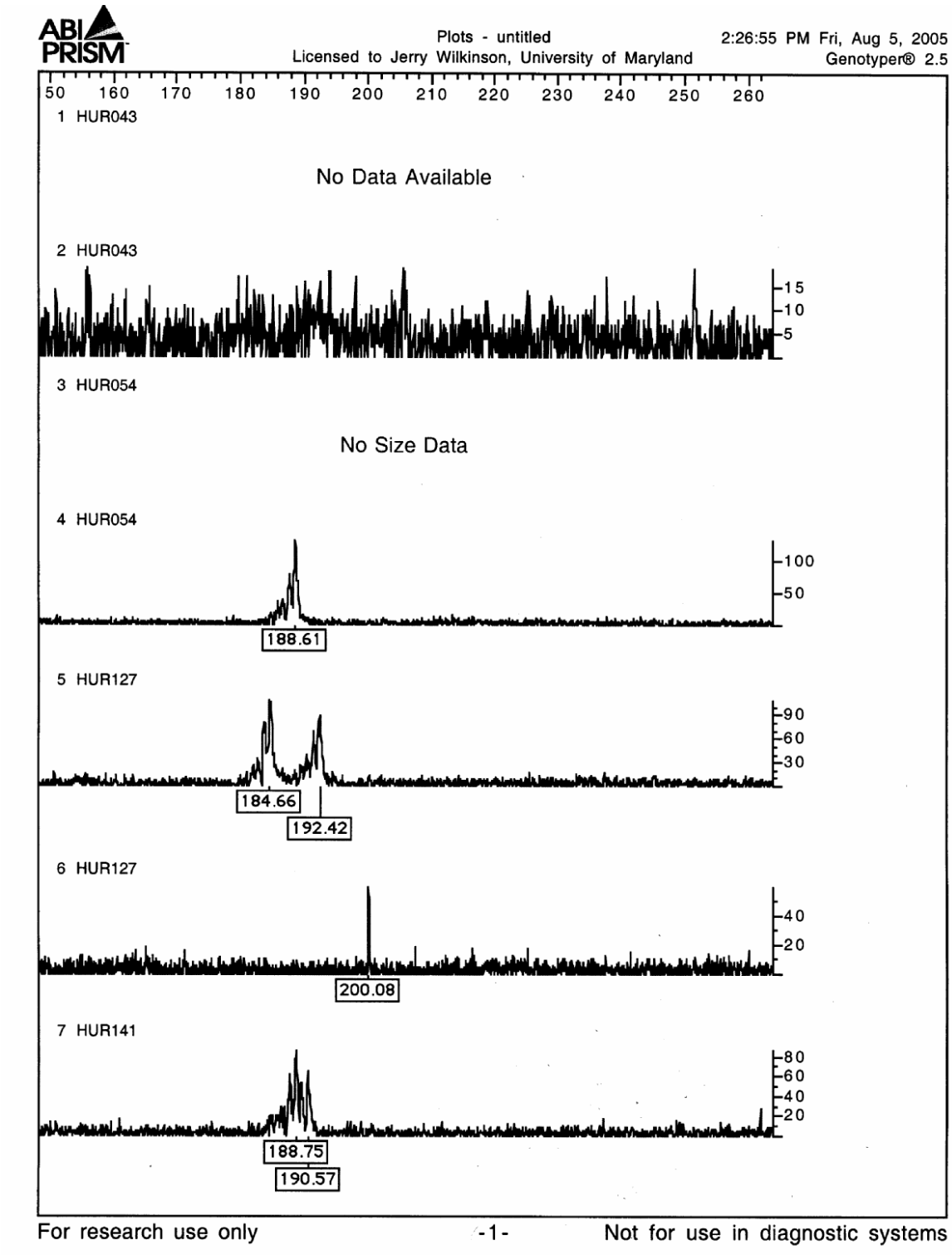
Comments/Notes:

*P/D (Pain/Discomfort Scale) taken before training, after Set 2 of training, and immediately after training.

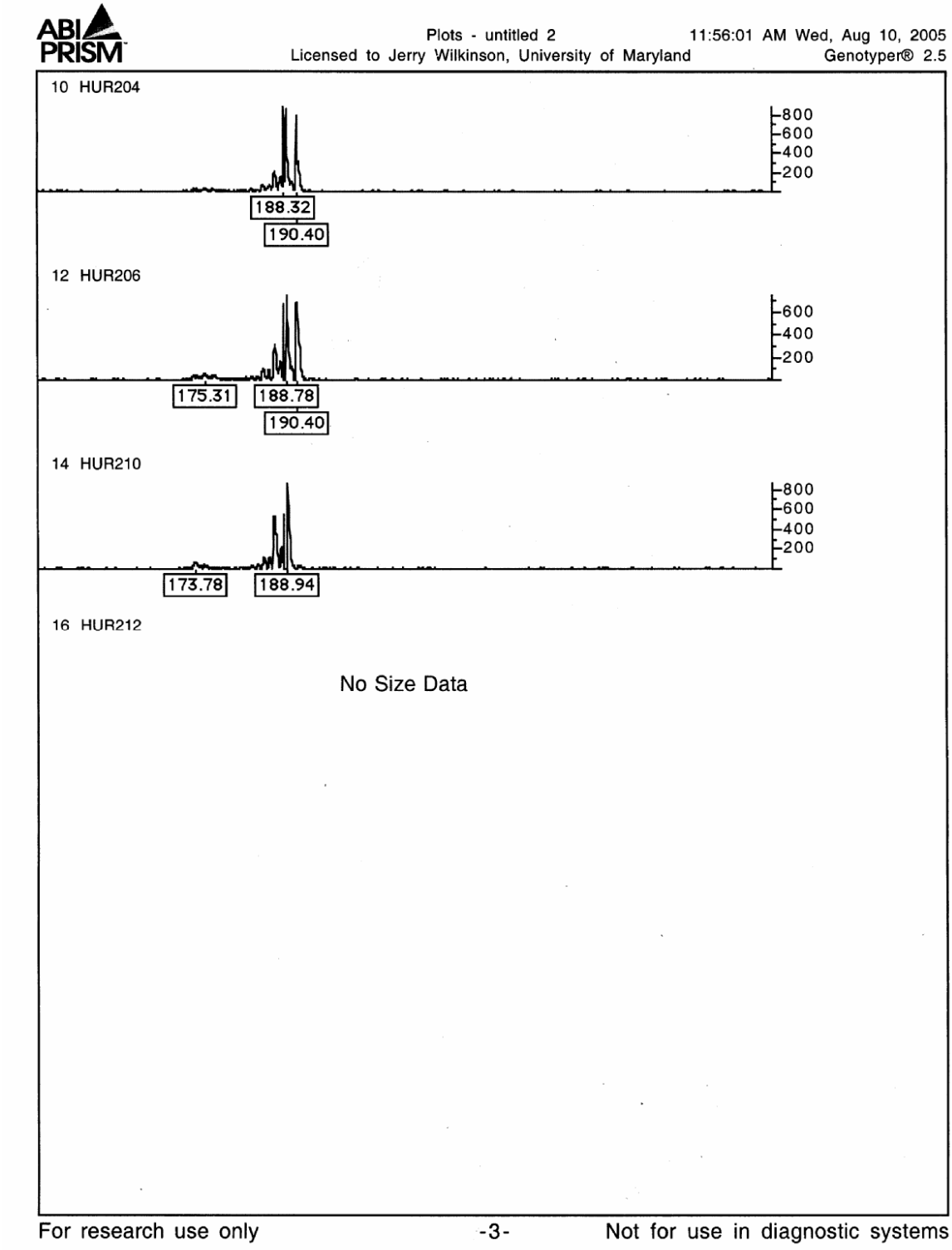
APPENDIX C

IGF1 Genotyping

APPENDIX C: *IGF1* GENOTYPING



HUR127 genotype confirmed by direct sequencing as 188/196 (add 4 base pairs to peaks above due to primer)



HUR210 genotype confirmed by direct sequencing as 192/192 (add 4 base pairs to peaks above due to primer)

APPENDIX D

Raw Data Table

APPENDIX D: RAW DATA TABLE

ID Number	Sex	IGF1 Genotype	IGFBP3 Genotype	CalbB Genotype	Race	Age	Height	Pre Training Weight	Post Training Weight	Pre Training BMI	Post Training BMI	Pre Training FFM
						yrs	cm	kg	kg	kg/m²	kg/m²	g
Con 002	M	192 HET	CC	II	C	71	170.0	62.58	63.60	21.65	22.01	47402.0
Con 003	M	192 HET	AC	II	C	66	173.0	79.02	79.33	26.40	26.50	54879.0
Con 004	M	192 HET	CC	II	C	69	178.0	87.37	86.23	27.58	27.21	54721.0
Con 005	M	192 HET	CC	II	C	71	180.0	75.87	75.19	23.42	23.21	53851.0
Con 006	M	192 HOM	CC	II	C	72	178.0	70.92	73.25	22.38	23.12	49951.0
Con 007	M	192 HET	AC	II	C	68	168.0	68.80	68.67	24.38	24.33	52031.0
Con 014	F	192 HET	CC	ID	C	67	165.0	72.55	73.21	26.65	26.89	40005.0
Con 016	F	192 HOM	AC	II	C	64	152.0	67.05	72.65	29.02	31.45	36779.0
Con 017	F	192 HET	AA	ID	AA	64	165.0	59.55	60.91	21.87	22.37	39635.0
Con 022	F	NON-192	CC	II	C	70	150.0	59.92	60.10	26.63	26.71	35040.0
HUR 011	M	192 HET	AC	II	AA	71	180.0	89.94	89.89	27.76	27.74	67505.0
HUR 012	F	NON-192	CC	II	AA	66	168.2	70.32	69.94	24.86	24.72	44029.4
HUR 015	F	192 HET	AC	II	C	78	168.5	87.64	86.92	30.87	30.61	45664.3
HUR 016	F	192 HOM	AA	ID	AA	52	156.0	70.97	69.64	29.16	28.61	48768.6
HUR 017	M	192 HET	AA	II	C	80	160.5	66.39	64.88	25.77	25.19	51831.3
HUR 018	M	192 HET	AC	ID	C	77	168.6	78.70	79.61	27.68	28.01	56365.1
HUR 021	F	192 HET	AC	II	AA	57	161.0	88.85	90.02	34.28	34.73	51076.6
HUR 023	F	192 HOM	AC	II	C	61	165.1	62.56	63.46	22.95	23.28	40395.7
HUR 024	M	192 HET	AA	ID	AA	53	161.5	77.24	78.80	29.61	30.21	53393.7
HUR 025	F	192 HET	AC	II	C	57	169.6	90.55	93.21	31.48	32.41	52940.7
HUR 026	F	192 HET	AC	ID	AA	59	172.3	66.66	66.56	22.45	22.42	47934.0
HUR 028	F	192 HOM	AA	II	C	64	160.0	63.71	65.95	24.88	25.76	38212.7
HUR 030	F	192 HET	AC	II	C	57	162.6	60.36	59.94	22.84	22.68	41604.8
HUR 031	F	192 HOM	AC	II	C	60	165.0	88.24	89.79	32.41	32.98	48257.0

ID Number	Post Training FFM	Pre Training Body Fat %	Post Training Body Fat %	Pre Training 1RM Untrained (UT) Leg	Post Training 1RM UT Leg	Pre Training 1RM Trained (T) Leg	Post Training 1RM T Leg	Pre Training MV UT Leg	Post Training MV UT Leg	Pre Training MV T Leg
	g			kg	kg	kg	kg	cm^3	cm^3	cm^3
Con 002	49831.0	23.20	20.70	.	.	29	37	1504.33	1564.94	1527.98
Con 003	54682.0	29.40	29.90	.	.	37	44	1785.40	1798.63	1815.40
Con 004	56031.0	32.65	30.21	.	.	30	40	1803.30	1894.00	1769.80
Con 005	53599.0	28.00	27.70	.	.	28	34	1796.30	1890.00	1718.60
Con 006	51092.0	28.40	29.10	.	.	32	42	1818.00	1834.00	1708.00
Con 007	54038.0	23.40	20.50	.	.	27	38	1683.02	1794.10	1614.96
Con 014	40375.0	43.30	43.40	.	.	17	23	1118.42	1136.21	1217.20
Con 016	39644.0	44.00	44.30	.	.	14	16	1131.00	1189.30	1090.20
Con 017	42527.0	32.10	29.00	.	.	17	28	1517.00	1562.50	1439.00
Con 022	35943.0	44.80	40.40	.	.	15	16	1089.60	1127.39	935.70
HUR 011	67229.3	24.94	25.21	37	43	36	56	1963.09	1909.87	1985.40
HUR 012	44012.8	37.39	37.07	20	20	25	33	1088.37	1047.77	1226.64
HUR 015	46447.1	47.90	46.56	16	17	18	26	1097.24	1100.21	1188.24
HUR 016	44794.9	31.28	35.67	24	23	26	30	1358.21	1365.46	1380.09
HUR 017	49790.2	21.93	23.26	10	17	21	28	1300.02	1223.33	1321.77
HUR 018	57662.4	28.38	27.57	27	31	31	37	1585.25	1578.20	1531.46
HUR 021	53923.1	42.51	40.10	24	26	18	26	1393.67	1410.85	1278.04
HUR 023	40976.7	35.43	35.43	19	19	19	23	1092.76	1161.69	1081.50
HUR 024	55113.1	30.88	30.06	38	37	38	42	1627.78	1578.47	1580.82
HUR 025	51198.5	41.54	45.07	19	24	13	24	1183.84	1208.92	979.83
HUR 026	47394.8	28.09	28.80	25	30	29	38	1487.63	1482.96	1570.26
HUR 028	43174.6	40.02	34.53	10	10	15	22	699.95	782.06	758.44
HUR 030	42425.3	31.07	29.22	16	16	18	24	1095.26	1094.93	1265.30
HUR 031	48078.8	45.31	46.45	11	15	16	23	1024.82	1010.66	1203.36

ID Number	Post Training MV T Leg cm^3	Pre Training MQ UT Leg kg/cm^3	Post Training MQ UT Leg kg/cm^3	Pre Training MQ T Leg kg/cm^3	Post Training MQ T Leg kg/cm^3	HRT status
Con 002	1691.55	.	.	0.019	0.022	.
Con 003	2000.33	.	.	0.020	0.022	.
Con 004	2055.00	.	.	0.017	0.020	.
Con 005	2045.60	.	.	0.016	0.017	.
Con 006	1948.10	.	.	0.019	0.022	.
Con 007	1858.90	.	.	0.017	0.021	.
Con 014	1272.21	.	.	0.014	0.018	N
Con 016	1252.50	.	.	0.013	0.013	N
Con 017	1770.80	.	.	0.012	0.016	N
Con 022	1132.32	.	.	0.016	0.014	N
HUR 011	2148.56	0.019	0.022	0.018	0.026	.
HUR 012	1335.18	0.018	0.019	0.021	0.025	N
HUR 015	1281.61	0.015	0.015	0.015	0.020	N
HUR 016	1407.24	0.018	0.017	0.019	0.021	Y
HUR 017	1432.60	0.007	0.014	0.016	0.020	.
HUR 018	1640.99	0.017	0.020	0.020	0.023	.
HUR 021	1471.64	0.017	0.018	0.014	0.018	N
HUR 023	1183.62	0.017	0.017	0.017	0.019	N
HUR 024	1755.46	0.023	0.024	0.024	0.024	.
HUR 025	1139.65	0.016	0.020	0.013	0.021	Y
HUR 026	1648.52	0.017	0.021	0.018	0.023	N
HUR 028	928.14	0.015	0.012	0.020	0.024	Y
HUR 030	1303.08	0.014	0.015	0.014	0.018	N
HUR 031	1296.60	0.011	0.015	0.013	0.017	N

ID Number	Sex	IGF1 Genotype	IGFBP3 Genotype	CalbB Genotype	Race	Age	Height	Pre Training Weight	Post Training Weight	Pre Training BMI	Post Training BMI	Pre Training FFM
						yrs	cm	kg	kg	kg/m^2	kg/m^2	g
HUR 032	M	NON-192	AA	II	C	54	168.6	95.69	95.68	33.66	33.66	61266.3
HUR 034	F	192 HOM	CC	II	C	65	172.7	91.01	88.72	30.52	29.75	53634.5
HUR 035	F	192 HET	AC	ID	AA	76	167.7	79.19	80.89	28.16	28.76	47153.7
HUR 036	M	192 HET	CC	II	C	75	169.0	87.44	87.65	30.61	30.69	65136.1
HUR 037	F	192 HET	AA	II	AA	71	163.1	62.57	60.58	23.52	22.77	45863.2
HUR 038	M	192 HET	AC	II	C	61	164.9	63.64	64.12	23.41	23.58	50103.2
HUR 039	M	NON-192	AC	II	C	77	179.5	96.94	99.40	30.09	30.85	64732.6
HUR 041	M	192 HOM	CC	II	C	63	163.7	71.62	70.37	26.73	26.26	48925.3
HUR 043	F	NON-192	AA	II	AA	68	157.5	82.34	82.34	33.20	33.20	48241.0
HUR 046	M	192 HET	AC	II	AA	59	161.8	82.99	81.54	31.70	31.15	63562.7
HUR 047	M	192 HET	CC	II	C	54	179.6	93.26	95.52	28.91	29.61	63989.0
HUR 048	F	192 HOM	CC	II	C	53	168.3	75.57	75.71	26.68	26.73	44628.3
HUR 049	F	192 HET	AC	ID	C	77	162.6	87.45	89.36	33.09	33.82	43836.3
HUR 051	F	NON-192	AC	ID	AA	64	165.0	67.49	66.32	24.79	24.36	44879.5
HUR 053	F	192 HET	AA	II	C	67	162.0	94.42	94.77	35.98	36.11	52069.0
HUR 054	M	192 HOM	AC	ID	AA	70	184.9	89.51	91.04	26.18	26.63	64234.1
HUR 055	F	192 HET	CC	ID	C	61	164.7	66.39	65.61	24.48	24.19	40047.6
HUR 056	F	192 HET	AC	II	AA	66	162.6	59.87	57.86	22.64	21.89	39289.9
HUR 059	F	192 HET	CC	II	C	78	145.4	53.40	51.62	25.26	24.41	33904.5
HUR 060	F	192 HET	CC	II	C	76	159.8	67.96	69.39	26.61	27.17	44671.1
HUR 061	F	192 HOM	AA	ID	C	66	161.5	101.07	105.24	38.75	40.35	58914.3
HUR 062	M	192 HET	CC	II	C	69	172.7	80.04	79.82	26.84	26.76	55830.3
HUR 063	M	192 HET	AA	II	C	66	171.2	74.82	75.01	25.53	25.59	51426.4
HUR 064	M	NON-192	CC	II	AA	64	173.2	81.06	82.76	27.02	27.59	64804.9

ID Number	Post Training FFM g	Pre Training Body Fat %	Post Training Body Fat %	Pre Training 1RM UT Leg kg	Post Training 1RM UT Leg kg	Pre Training 1RM T Leg kg	Post Training 1RM T Leg kg	Pre Training MV UT Leg cm^3	Post Training MV UT Leg cm^3	Pre Training MV T Leg cm^3
HUR 032	62716.4	35.97	34.45	32	37	35	41	1788.61	1781.29	1839.69
HUR 034	53730.4	41.07	39.44	22	24	23	29	1556.40	1548.20	1566.18
HUR 035	48789.4	40.45	39.68	17	18	14	18	1255.02	1250.00	1289.29
HUR 036	64311.5	25.51	26.63	20	22	22	28	.	.	.
HUR 037	44916.1	26.70	25.86	12	18	14	24	1150.73	1142.46	1251.14
HUR 038	50077.1	21.27	21.90	23	35	21	37	1427.99	1417.28	1347.38
HUR 039	67135.8	33.22	32.46	27	28	30	33	1887.32	1882.06	1976.79
HUR 041	48522.5	31.69	31.04	17	19	20	28	1369.61	1381.55	1425.93
HUR 043	49283.4	41.42	40.15	18	23	19	22	1375.91	1395.78	1382.60
HUR 046	63432.3	23.41	22.21	26	17	22	29	1808.37	.	1815.33
HUR 047	64174.0	31.38	32.82	37	46	42	53	2047.54	2095.16	2349.34
HUR 048	45767.2	40.95	39.55	19	20	18	27	986.24	963.08	1026.55
HUR 049	46081.4	49.87	48.43	15	15	16	16	1016.64	1036.54	1125.47
HUR 051	44329.6	33.50	33.16	27	25	27	33	1233.88	1195.26	1459.37
HUR 053	52818.1	44.85	44.27	24	29	22	25	1490.47	1546.51	1525.53
HUR 054	67124.8	28.23	26.27	38	.	40	.	2150.56	2104.06	2245.18
HUR 055	42024.7	39.68	35.95	20	16	23	31	1139.21	1091.69	1286.09
HUR 056	39287.5	34.37	32.10	17	18	18	21	989.16	1007.18	1004.03
HUR 059	32431.9	36.51	37.17	9	7	10	10	.	.	.
HUR 060	44117.1	34.27	36.42	4	3	16	22	.	.	963.42
HUR 061	58521.8	41.71	44.39	10	14	11	17	1218.60	1292.68	1352.01
HUR 062	57064.7	30.25	28.51	38	41	34	42	1650.70	1678.13	1731.26
HUR 063	53300.6	31.26	28.94	26	26	25	31	1365.89	1435.83	1403.88
HUR 064	66863.8	20.06	19.21	38	48	38	48	2105.89	2182.44	1996.72

ID Number	Post Training MV T Leg cm^3	Pre Training MQ UT Leg kg/cm^3	Post Training MQ UT Leg kg/cm^3	Pre Training MQ T Leg kg/cm^3	Post Training MQ T Leg kg/cm^3	HRT status
HUR 032	1997.04	0.018	0.021	0.019	0.021	.
HUR 034	1705.31	0.014	0.015	0.014	0.017	Y
HUR 035	1304.66	0.013	0.015	0.011	0.014	N
HUR 036	.	.	.	.	.	.
HUR 037	1310.54	0.011	0.016	0.011	0.018	N
HUR 038	1469.19	0.016	0.025	0.016	0.025	.
HUR 039	2053.46	0.014	0.015	0.015	0.016	.
HUR 041	1480.35	0.013	0.014	0.014	0.019	.
HUR 043	1460.63	0.013	0.016	0.014	0.015	N
HUR 046	.	0.014	.	0.012	.	.
HUR 047	2605.08	0.018	0.022	0.018	0.020	.
HUR 048	1110.92	0.020	0.021	0.018	0.024	N
HUR 049	1147.96	0.015	0.015	0.015	0.014	N
HUR 051	1498.30	0.022	0.021	0.018	0.022	N
HUR 053	1659.37	0.016	0.019	0.015	0.015	N
HUR 054	2372.10	0.017	.	0.018	.	.
HUR 055	1379.69	0.017	0.015	0.018	0.022	N
HUR 056	1130.03	0.018	0.018	0.018	0.018	N
HUR 059	.	.	.	.	.	N
HUR 060	1122.08	.	.	0.016	0.019	N
HUR 061	1499.12	0.009	0.011	0.008	0.012	N
HUR 062	1986.45	0.023	0.025	0.020	0.021	.
HUR 063	1571.37	0.019	0.018	0.018	0.020	.
HUR 064	2309.68	0.018	0.022	0.019	0.021	.

ID Number	Sex	IGF1 Genotype	IGFBP3 Genotype	CalbB Genotype	Race	Age	Height	Pre Training Weight	Post Training Weight	Pre Training BMI	Post Training BMI	Pre Training FFM
						yrs	cm	kg	kg	kg/m^2	kg/cm^3	g
HUR 065	M	192 HOM	CC	II	C	65	178.0	97.44	97.94	30.75	30.91	67683.4
HUR 066	F	192 HET	AC	II	C	71	160.0	67.11	67.59	26.21	26.40	38384.5
HUR 067	M	192 HET	AC	II	AA	71	162.0	74.56	75.50	28.41	28.77	50320.6
HUR 068	M	NON-192	CC	II	C	66	178.2	79.05	79.01	24.89	24.88	57791.8
HUR 070	F	192 HET	CC	II	AA	64	156.2	84.81	86.97	34.76	35.65	47774.9
HUR 071	M	192 HOM	AC	ID	C	75	172.3	86.89	87.91	29.27	29.61	57768.8
HUR 074	F	192 HOM	AA	II	C	65	158.5	63.28	59.04	25.19	23.50	37969.9
HUR 075	M	192 HET	CC	II	C	71	172.1	88.63	85.65	29.93	28.92	63335.0
HUR 076	F	192 HET	AA	II	C	58	160.6	61.08	60.44	23.68	23.43	39591.4
HUR 077	F	192 HOM	AC	II	C	70	156.4	69.38	66.21	28.36	27.07	42959.2
HUR 078	M	192 HOM	CC	ID	C	71	168.9	75.22	73.94	26.37	25.92	57583.8
HUR 079	M	192 HET	CC	II	C	71	176.5	93.76	99.23	30.10	31.85	64636.0
HUR 080	M	NON-192	AC	II	C	81	171.0	61.16	59.96	20.92	20.50	47245.3
HUR 081	F	192 HET	AA	II	C	83	143.7	57.82	59.79	28.00	28.95	38602.9
HUR 082	M	192 HOM	AC	II	AA	68	171.5	84.05	84.40	28.58	28.70	63012.1
HUR 083	F	NON-192	AC	ID	AA	71	159.5	72.88	72.29	28.65	28.41	41545.1
HUR 084	F	NON-192	AC	II	C	80	151.4	55.56	54.71	24.24	23.87	37503.9
HUR 085	M	192 HOM	AA	II	C	71	190.4	114.89	114.92	31.69	31.70	81388.7
HUR 087	M	192 HET	AC	II	C	62	170.8	85.00	89.26	29.14	30.60	65519.6
HUR 090	F	192 HET	AA	II	AA	69	160.4	78.53	80.62	30.52	31.34	46972.5
HUR 091	F	192 HOM	AC	II	C	60	154.9	64.98	65.44	27.07	27.26	37890.4
HUR 092	M	192 HET	AC	II	C	65	178.7	77.25	78.77	24.19	24.67	59311.2

ID Number	Post Training FFM g	Pre Training Body Fat %	Post Training Body Fat %	Pre Training 1RM UT Leg kg	Post Training 1RM UT Leg kg	Pre Training 1RM T Leg kg	Post Training 1RM T Leg kg	Pre Training MV UT Leg cm^3	Post Training MV UT Leg cm^3	Pre Training MV T Leg cm^3
HUR 065	68258.8	30.54	30.30	28	28	31	35	.	.	.
HUR 066	39580.3	42.80	41.44	11	5	13	17	.	.	754.57
HUR 067	53147.1	32.51	29.61	32	35	30	39	1410.03	1465.69	1572.30
HUR 068	58585.8	26.89	25.85	19	25	28	34	1523.69	1476.85	1630.64
HUR 070	49035.4	43.67	43.62	17	22	24	28	1067.06	1042.98	1215.26
HUR 071	59496.3	33.52	32.32	24	25	32	35	1602.07	1565.27	1652.87
HUR 074	37458.7	39.99	36.56	21	22	22	25	1156.38	1134.82	1211.67
HUR 075	61812.5	28.54	27.83	18	28	18	31	1461.55	1422.52	1432.84
HUR 076	38563.2	35.18	36.19	16	13	17	19	967.07	919.38	790.02
HUR 077	41577.8	38.08	37.21	11	14	14	19	975.61	965.93	1085.48
HUR 078	57897.8	23.45	21.70	27	32	32	40	1599.31	1560.93	1638.03
HUR 079	64948.7	31.06	34.55	37	38	37	45	1894.34	2035.03	1885.21
HUR 080	46919.4	22.75	21.74	14	16	14	20	1142.33	1087.42	1185.80
HUR 081	39290.1	33.23	34.29	8	8	10	11	903.83	906.17	789.50
HUR 082	63076.4	25.03	25.26	29	37	26	36	1943.91	1917.18	1651.74
HUR 083	41930.0	42.99	41.99	11	13	13	19	935.25	925.40	996.07
HUR 084	36669.3	32.50	32.98	4	.	12	15	736.80	723.36	754.03
HUR 085	80452.7	29.16	29.99	35	39	32	38	2007.84	2069.05	1968.10
HUR 087	66980.9	22.92	24.96	41	47	46	55	2011.20	1981.38	1813.64
HUR 090	46421.4	40.18	42.42	19	24	21	30	1425.25	1442.95	1472.33
HUR 091	38210.3	41.69	41.61	11	14	14	17	907.93	894.34	900.88
HUR 092	59198.5	23.22	24.84	22	24	25	34	1644.50	1591.36	1625.35

ID Number	Post Training MV T Leg cm^3	Pre Training MQ UT Leg kg/cm^3	Post Training MQ UT Leg kg/cm^3	Pre Training MQ T Leg kg/cm^3	Post Training MQ T Leg kg/cm^3	HRT status
HUR 065	.	.	.	.	.	.
HUR 066	805.09	.	.	0.018	0.021	N
HUR 067	1765.51	0.023	0.024	0.019	0.022	.
HUR 068	1692.03	0.013	0.017	0.017	0.020	.
HUR 070	1288.53	0.016	0.021	0.019	0.022	N
HUR 071	1801.06	0.015	0.016	0.019	0.019	.
HUR 074	1270.27	0.018	0.019	0.018	0.020	N
HUR 075	1550.88	0.013	0.020	0.013	0.020	.
HUR 076	915.99	0.017	0.015	0.022	0.021	N
HUR 077	1138.09	0.012	0.015	0.013	0.017	N
HUR 078	1670.90	0.017	0.020	0.019	0.024	.
HUR 079	2036.85	0.020	0.019	0.020	0.022	.
HUR 080	1174.80	0.012	0.014	0.012	0.017	.
HUR 081	854.65	0.009	0.009	0.012	0.013	Y
HUR 082	1846.59	0.015	0.019	0.016	0.020	.
HUR 083	1086.87	0.012	0.014	0.013	0.018	N
HUR 084	867.74	0.005	.	0.016	0.018	N
HUR 085	2158.39	0.018	0.019	0.016	0.018	.
HUR 087	2103.57	0.021	0.024	0.026	0.026	.
HUR 090	1621.71	0.014	0.017	0.014	0.018	N
HUR 091	982.01	0.012	0.016	0.015	0.017	N
HUR 092	1742.22	0.013	0.015	0.016	0.020	.

ID Number	Sex	IGF1 Genotype	IGFBP3 Genotype	CalbB Genotype	Race	Age	Height	Pre Training Weight	Post Training Weight	Pre Training BMI	Post Training BMI	Pre Training FFM
						yrs	cm	kg	kg	kg/m^2	kg/m^2	g
HUR 093	F	192 HOM	AC	II	C	65	162.1	78.74	79.68	29.96	30.32	43864.9
HUR 094	F	192 HET	AA	ID	C	65	154.7	73.19	72.94	30.58	30.48	40979.0
HUR 097	F	192 HET	AA	II	C	85	155.6	66.99	68.71	27.67	28.38	42539.2
HUR 098	M	192 HET	CC	II	C	71	174.1	87.64	87.18	28.92	28.76	60127.3
HUR 105	F	192 HOM	AC	II	C	65	170.2	61.11	61.21	21.10	21.14	35587.1
HUR 108	M	NON-192	CC	II	C	59	182.2	91.13	93.82	27.45	28.26	55218.2
HUR 110	F	192 HET	AC	II	C	70	158.5	74.32	72.83	29.58	28.99	41586.3
HUR 114	F	192 HET	AC	II	C	70	157.5	65.00	64.52	26.21	26.02	40458.5
HUR 115	M	192 HOM	AC	II	C	60	175.3	78.67	77.28	25.61	25.16	62648.2
HUR 117	M	192 HOM	AA	ID	C	65	166.6	63.39	65.44	22.83	23.56	52397.3
HUR 118	F	192 HOM	AC	II	C	60	170.2	73.20	74.14	25.27	25.59	44219.0
HUR 119	F	NON-192	CC	DD	AA	57	162.6	75.75	75.83	28.67	28.70	47913.2
HUR 122	M	192 HET	AC	ID	C	56	182.9	81.67	81.74	24.42	24.44	56552.4
HUR 124	F	NON-192	AC	II	C	66	165.1	65.32	62.29	23.96	22.85	43282.8
HUR 126	F	192 HET	AA	II	C	76	156.2	70.45	70.47	28.87	28.88	39120.2
HUR 127	M	NON-192	CC	II	AA	55	175.3	125.34	122.27	40.81	39.81	81832.1
HUR 128	F	192 HET	CC	II	C	52	157.5	50.48	48.69	20.35	19.63	38277.7
HUR 129	F	192 HET	AA	II	C	52	160.0	82.32	81.81	32.15	31.95	48938.8
HUR 130	F	192 HET	AA	ID	AA	50	170.2	66.32	65.62	22.90	22.66	37156.9
HUR 131	F	192 HOM	AC	II	C	64	160.0	61.82	61.18	24.14	23.89	40591.3
HUR 133	F	NON-192	AC	ID	AA	51	162.6	81.35	81.18	30.78	30.72	49953.1
HUR 135	M	192 HOM	AC	II	C	64	177.8	76.63	77.00	24.24	24.36	52392.1
HUR 137	F	NON-192	AA	II	AA	50	167.6	81.64	82.07	29.05	29.20	48037.8

ID Number	Post Training FFM g	Pre Training Body Fat %	Post Training Body Fat %	Pre Training 1RM UT Leg kg	Post Training 1RM UT Leg kg	Pre Training 1RM T Leg kg	Post Training 1RM T Leg kg	Pre Training MV UT Leg cm^3	Post Training MV UT Leg cm^3	Pre Training MV T Leg cm^3
HUR 093	42358.7	44.29	46.84	17	19	16	23	965.05	957.53	974.09
HUR 094	39387.9	44.01	46.00	19	18	20	21	1080.98	1037.13	1067.88
HUR 097	42014.6	36.50	38.85	17	16	16	19	958.75	998.50	959.31
HUR 098	57247.9	31.40	34.33	28	29	28	35	1623.93	1601.09	1650.67
HUR 105	37492.1	41.76	38.75	7	10	12	19	795.42	866.93	903.23
HUR 108	59089.3	39.41	37.02	32	34	40	43	1466.45	1484.18	1604.73
HUR 110	42972.1	44.04	40.99	11	16	11	17	1092.50	1123.80	1109.80
HUR 114	41045.6	37.76	36.38	12	12	13	20	819.66	854.46	900.33
HUR 115	59658.9	20.36	22.80	27	30	28	36	1664.80	1647.67	1673.82
HUR 117	53477.9	17.34	18.28	20	18	26	31	1121.04	1113.20	1290.43
HUR 118	44432.4	39.59	40.07	11	19	12	23	1147.21	1149.15	1125.61
HUR 119	47470.4	36.75	37.40	35	33	35	38	1571.37	1554.78	1568.87
HUR 122	56004.5	30.76	31.49	34	35	33	42	1576.48	1640.25	1664.85
HUR 124	42626.6	33.74	31.56	24	24	23	25	1254.24	1242.56	1244.93
HUR 126	39275.8	44.47	44.27	13	15	11	13	926.25	985.08	884.06
HUR 127	80205.3	34.71	34.40	43	43	52	56	2408.23	2326.44	2689.28
HUR 128	36847.7	24.17	24.32	.	15	17	19	985.89	988.24	1083.79
HUR 129	49084.6	41.00	40.00	20	22	20	28	.	.	.
HUR 130	37196.0	43.98	43.31	5	7	11	16	606.56	639.37	878.86
HUR 131	39973.8	34.34	34.66	.	13	.	19	809.83	816.88	808.59
HUR 133	50236.5	38.59	38.12	30	31	28	34	1513.92	1559.13	1504.74
HUR 135	53894.9	31.63	30.00	30	35	30	38	1435.20	1394.07	1352.60
HUR 137	49471.1	41.16	39.72	24	26	20	27	1660.00	1628.90	1519.08

ID Number	Post Training MV T Leg cm^3	Pre Training MQ UT Leg kg/cm^3	Post Training MQ UT Leg kg/cm^3	Pre Training MQ T Leg kg/cm^3	Post Training MQ T Leg kg/cm^3	HRT status
HUR 093	1050.20	0.018	0.020	0.017	0.021	Y
HUR 094	1170.87	0.018	0.018	0.019	0.018	Y
HUR 097	1042.61	0.018	0.016	0.017	0.018	Y
HUR 098	1762.66	0.017	0.018	0.017	0.020	.
HUR 105	1023.50	0.009	0.012	0.013	0.018	N
HUR 108	1754.57	0.022	0.023	0.025	0.024	.
HUR 110	1180.10	0.010	0.014	0.009	0.015	N
HUR 114	1063.76	0.014	0.014	0.014	0.019	N
HUR 115	1862.97	0.016	0.018	0.017	0.019	.
HUR 117	1356.08	0.018	0.017	0.020	0.023	.
HUR 118	1226.72	0.010	0.017	0.011	0.018	Y
HUR 119	1644.94	0.022	0.021	0.023	0.023	N
HUR 122	1858.25	0.022	0.022	0.020	0.023	.
HUR 124	1353.92	0.019	0.020	0.018	0.019	N
HUR 126	1001.47	0.014	0.016	0.013	0.013	N
HUR 127	2706.01	0.018	0.019	0.019	0.021	.
HUR 128	1149.96	.	0.015	0.016	0.016	N
HUR 129	.	.	.	.	.	N
HUR 130	911.37	0.009	0.011	0.013	0.018	N
HUR 131	959.69	.	0.015	.	0.020	N
HUR 133	1626.63	0.020	0.020	0.019	0.021	N
HUR 135	1452.53	0.021	0.025	0.022	0.026	.
HUR 137	1588.65	0.015	0.016	0.013	0.017	N

ID Number	Sex	IGF1 Genotype	IGFBP3 Genotype	CalbB Genotype	Race	Age	Height	Pre Training Weight	Post Training Weight	Pre Training BMI	Post Training BMI	Pre Training FFM
						yrs	cm	kg	kg	kg/m^2	kg/m^2	g
HUR 139	M	192 HOM	AA	II	C	51	180.3	91.41	91.21	28.11	28.04	71832.5
HUR 141	F	192 HET	AA	ID	AA	57	167.6	65.31	67.06	23.24	23.86	43665.6
HUR 145	M	192 HET	AA	ID	AA	56	170.2	99.70	100.24	34.42	34.61	70143.7
HUR 149	F	NON-192	CC	ID	AA	56	162.6	69.10	68.97	26.15	26.10	44689.3
HUR 150	M	192 HET	AA	II	AA	56	167.6	88.59	89.53	31.52	31.86	68093.1
HUR 151	F	192 HOM	AC	II	C	50	162.6	61.65	61.48	23.33	23.27	38584.8
HUR 155	F	NON-192	AC	II	C	65	172.3	94.17	94.21	31.73	31.75	58614.3
HUR 156	M	192 HET	AA	II	C	61	177.8	111.03	111.54	35.12	35.28	73329.1
HUR 160	M	192 HOM	AC	II	AA	61	172.7	76.46	74.95	25.63	25.12	56222.1
HUR 161	M	192 HOM	AC	ID	C	58	175.3	88.32	87.63	28.75	28.53	62380.5
HUR 169	F	192 HOM	AC	II	C	64	157.5	56.52	54.45	22.79	21.96	35652.4
HUR 171	M	NON-192	AC	II	AA	74	182.8	78.92	80.35	23.62	24.04	64058.7
HUR 172	M	NON-192	AC	II	C	56	172.7	82.61	81.95	27.69	27.47	60955.4
HUR 174	M	NON-192	AA	II	C	74	183.7	84.64	84.69	25.08	25.10	65591.9
HUR 175	M	192 HET	AA	II	C	51	170.2	101.84	102.73	35.15	35.46	65444.5
HUR 177	F	192 HOM	AA	ID	C	51	170.2	67.43	66.74	23.28	23.04	43658.6
HUR 179	M	192 HOM	AA	II	C	59	181.0	94.02	93.27	28.70	28.47	62401.5
HUR 180	F	192 HOM	CC	II	C	53	176.7	66.05	65.51	21.15	20.98	43759.1
HUR 181	F	192 HOM	AC	ID	AA	52	175.3	70.75	75.56	23.02	24.59	52480.9
HUR 187	F	192 HET	AC	II	C	60	158.3	98.15	96.92	39.17	38.68	53518.6
HUR 188	M	192 HET	AC	II	C	51	175.7	119.20	119.35	38.61	38.66	78859.4
HUR 198	M	192 HOM	AC	II	C	59	177.8	104.56	100.16	33.08	31.68	73627.3
HUR 201	F	NON-192	AC	II	AA	61	165.3	87.40	90.24	31.99	33.03	51533.7
HUR 203	F	192 HET	AC	II	C	53	168.5	55.54	55.87	19.56	19.68	39446.7

ID Number	Post Training FFM g	Pre Training Body Fat %	Post Training Body Fat %	Pre Training 1RM UT Leg kg	Post Training 1RM UT Leg kg	Pre Training 1RM T Leg kg	Post Training 1RM T Leg kg	Pre Training MV UT Leg cm^3	Post Training MV UT Leg cm^3	Pre Training MV T Leg cm^3
HUR 139	71387.4	21.42	21.73	41	38	46	54	2154.39	2133.82	2165.35
HUR 141	44567.5	33.14	33.54	28	32	26	32	1494.26	1539.43	1494.20
HUR 145	72482.7	29.64	27.69	36	55	40	65	2449.62	2576.84	2535.79
HUR 149	45856.7	35.33	33.51	17	30	18	.	1394.81	1397.98	1370.24
HUR 150	70156.0	23.14	21.64	40	49	38	60	2154.32	2250.78	2151.01
HUR 151	38638.2	37.41	37.16	16	15	18	21	1107.41	1032.30	1073.13
HUR 155	60691.6	37.76	35.58	27	27	16	18	.	.	.
HUR 156	73812.4	33.96	33.83	37	59	45	64	2377.61	2392.46	2366.45
HUR 160	55588.8	26.47	25.83	30	37	27	38	1860.18	1817.94	1877.26
HUR 161	62267.1	29.37	28.94	39	38	37	45	1883.44	1939.03	1904.49
HUR 169	33981.7	36.93	37.59	10	12	11	15	862.25	871.01	924.92
HUR 171	63515.7	18.84	20.95	34	36	34	40	1756.19	1746.91	1754.24
HUR 172	60651.6	26.21	25.99	29	34	35	42	1837.19	1841.92	1928.83
HUR 174	66169.2	22.50	21.87	35	41	35	46	1874.68	1883.24	1744.85
HUR 175	67957.9	35.74	33.85	26	28	31	40	1796.95	1803.03	1862.48
HUR 177	44068.5	35.26	33.97	22	27	21	28	.	.	.
HUR 179	64051.8	33.63	31.33	33	37	40	45	.	.	.
HUR 180	44961.6	33.74	31.00	19	19	22	23	.	.	.
HUR 181	53940.4	25.82	28.61	40	.	37	48	.	.	.
HUR 187	55044.1	45.47	43.20	48	53	23	25	1275.79	1309.10	1389.78
HUR 188	79181.3	33.84	33.66	10	12	51	.	2161.44	2189.29	2224.28
HUR 198	70027.5	29.58	30.08	30	34	33	37	2051.98	2038.10	2036.36
HUR 201	54279.7	41.00	39.90	21	22	28	30	1667.35	1475.34	1614.92
HUR 203	40021.8	28.98	28.37	15	18	15	25	.	.	.

ID Number	Post Training MV T Leg cm^3	Pre Training MQ UT Leg kg/cm^3	Post Training MQ UT Leg kg/cm^3	Pre Training MQ T Leg kg/cm^3	Post Training MQ T Leg kg/cm^3	HRT status
HUR 139	2263.00	0.019	0.018	0.021	0.024	.
HUR 141	1632.11	0.019	0.021	0.017	0.020	Y
HUR 145	2997.12	0.015	0.021	0.016	0.022	.
HUR 149	1500.69	0.012	0.021	0.013	.	N
HUR 150	2477.50	0.019	0.022	0.018	0.024	.
HUR 151	1048.02	0.015	0.015	0.016	0.020	N
HUR 155	.	.	.	.	.	N
HUR 156	2634.74	0.015	0.025	0.019	0.024	.
HUR 160	1922.20	0.016	0.020	0.014	0.020	.
HUR 161	2012.14	0.021	0.020	0.019	0.023	.
HUR 169	943.95	0.012	0.014	0.012	0.016	N
HUR 171	1983.36	0.019	0.021	0.019	0.020	.
HUR 172	2078.37	0.016	0.018	0.018	0.020	.
HUR 174	1934.50	0.019	0.022	0.020	0.024	.
HUR 175	2128.00	0.014	0.016	0.017	0.019	.
HUR 177	.	.	.	.	.	N
HUR 179	.	.	.	.	.	.
HUR 180	.	.	.	.	.	Y
HUR 181	.	.	.	.	.	N
HUR 187	1512.27	0.037	0.040	0.016	0.016	N
HUR 188	2478.82	0.005	0.006	0.023	.	.
HUR 198	2188.71	0.015	0.017	0.016	0.017	.
HUR 201	1798.38	0.012	0.015	0.017	0.016	N
HUR 203	.	.	.	.	.	Y

ID Number	Sex	IGF1 Genotype	IGFBP3 Genotype	CalbB Genotype	Race	Age	Height	Pre Training Weight	Post Training Weight	Pre Training BMI	Post Training BMI	Pre Training FFM
						yrs	cm	kg	kg	kg/m²	kg/m²	g
HUR 204	F	192 HET	AC	II	C	50	155.9	107.94	107.86	44.41	44.38	52259.3
HUR 206	M	192 HET	AC	II	C	61	179.2	86.89	86.51	27.06	26.94	66760.7
HUR 208	M	NON-192	AC	II	C	54	185.1	92.99	93.45	27.14	27.27	68730.6
HUR 209	M	192 HET	CC	II	C	68	182.2	103.27	100.96	31.11	30.41	69769.5
HUR 210	F	192 HOM	AC	II	C	66	160.1	92.76	95.95	36.19	37.43	48503.4
HUR 212	M	192 HOM	CC	II	C	56	168.7	84.39	84.43	29.65	29.67	61194.8
HUR 213	F	192 HET	AC	II	C	75	159.9	63.20	60.77	24.72	23.77	39594.0
HUR 215	F	192 HET	CC	II	C	58	165.6	69.83	70.82	25.46	25.83	42929.1
HUR 216	M	NON-192	AC	ID	C	66	170.9	89.45	90.41	30.63	30.95	60017.1
HUR 220	F	NON-192	AA	II	C	58	161.2	61.69	61.98	23.74	23.85	36879.3
Mean						64	168	78.3	78.5	27.90	27.86	51720
SD						8	9	14.6	14.9	4.52	4.64	11086
SEM							1	1.3	1.3	0.40	0.41	980

ID Number	Post Training FFM g	Pre Training Body Fat %	Post Training Body Fat %	Pre Training 1RM UT Leg kg	Post Training 1RM UT Leg kg	Pre Training 1RM T Leg kg	Post Training 1RM T Leg kg	Pre Training MV UT Leg cm^3	Post Training MV UT Leg cm^3	Pre Training MV T Leg cm^3
HUR 204	51058.2	51.59	52.66	21	24	22	30	1228.95	1245.01	1244.56
HUR 206	65943.9	23.17	23.78	37	35	43	52	1811.37	1802.95	2069.87
HUR 208	69911.4	26.09	25.19	59	.	53	59	2556.46	2485.65	2208.23
HUR 209	69024.0	32.44	31.63	41	45	35	42	2153.00	2059.61	2076.84
HUR 210	50560.2	47.71	47.31	17	20	14	18	1151.57	1193.79	1105.77
HUR 212	62504.3	27.49	25.97	39	40	37	50	1795.76	1765.31	1914.51
HUR 213	39026.3	37.35	35.78	16	18	15	23	1019.77	1004.67	1095.38
HUR 215	43900.2	38.52	38.01	23	23	23	27	1156.52	1164.64	1216.86
HUR 216	61451.6	32.90	32.03	28	35	26	40	1812.26	1802.16	1851.78
HUR 220	37363.2	40.22	40.00	16	15	16	18	971.59	977.08	983.44
Mean	52140	33.8	33.4	24	26	24	31	1448	1452	1468
SD	11109	7.5	7.4	10	12	10	12	427	428	420
SEM	982	0.7	0.7	1	1	1	1	39	39	38

ID Number	Post Training MV T Leg cm^3	Pre Training MQ UT Leg kg/cm^3	Post Training MQ UT Leg kg/cm^3	Pre Training MQ T Leg kg/cm^3	Post Training MQ T Leg kg/cm^3	HRT status
HUR 204	1389.37	0.017	0.019	0.017	0.021	N
HUR 206	2152.22	0.020	0.019	0.021	0.024	.
HUR 208	2415.24	0.023	.	0.024	0.024	.
HUR 209	2129.36	0.019	0.022	0.017	0.020	.
HUR 210	1214.56	0.015	0.016	0.012	0.015	N
HUR 212	2159.93	0.022	0.023	0.019	0.023	.
HUR 213	1165.86	0.015	0.018	0.013	0.019	N
HUR 215	1290.08	0.020	0.019	0.019	0.021	N
HUR 216	2006.70	0.016	0.019	0.014	0.020	.
HUR 220	1085.12	0.017	0.016	0.017	0.017	N
Mean	1600	0.0164	0.0183	0.0167	0.0197	
SD	463	0.0043	0.0041	0.0033	0.0032	
SEM	42	0.0004	0.0004	0.0003	0.0003	

APPENDIX E

Final Statistical Models and Results for Baseline Muscle Phenotypes

APPENDIX E: FINAL STATISTICAL MODELS AND RESULTS FOR BASELINE MUSCLE PHENOTYPES

Model for comparison in muscle strength baseline among sex, race, and genotype groups:

IGF1 is the *IGF1* genotype, 1 is 192 homozygote, 2 is 192 heterozygotes, 3 is non-carriers of the 192 allele

IGFBP3 is the *IGFBP3* genotype, 11 is AA homozygotes, 12 is AC heterozygotes, 11 is CC homozygotes

Calbb is the calcineurin B genotype, 11 is the II homozygotes, 12 is the D-allele carriers

Race: 1 is Caucasians or 2 is African American

Age is subject's age

hrt_sex is hormone replacement status variable: MN is male, FN is females not on hormone replacement therapy, FY is females on hormone replacement therapy

Height is subject's height

bwpre is subject's baseline body weight

bmipre is subject's baseline body mass index

RMTLPREKG is subject's baseline muscle strength for training leg

```
proc mixed data=one covtest;
class hrt_sex igf1 igfbp3 calbb race;
model rmtlprekg=
                        race
                        height
                        igf1
                        igfbp3
                        calbb
                        age
                        bwpre
                        hrt_sex
                        bmipre
                        igfbp3*race
                        / outp=resides ddfm=kr htype=3 solution;

                              *hrt_sex       FN      FY      MN;
estimate 'females vs males'     hrt_sex      0.5     0.5     -1/E;
estimate 'mean for females' height 167.62 age 64.11 bwpre 78.21
        bmipre 27.79 intercept 1     hrt_sex     0.5 0.5 0/E;
lsmeans race hrt_sex igf1 igfbp3 calbb igfbp3*race/pdiff;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;
```

Results:

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Race	1	107	6.79	0.0105
Height	1	107	0.67	0.4150
IGF1	2	107	1.50	0.2276
IGFBP3	2	107	3.19	0.0452
Calbb	1	107	3.38	0.0689
Age	1	107	24.00	<.0001
bwpre	1	107	3.02	0.0850
hrt_sex	2	107	29.96	<.0001
bmipre	1	107	2.20	0.1411
IGFBP3*Race	2	107	2.88	0.0605

Least Squares Means

Label	Estimate	Standard Error	DF	t Value	Pr > |t|
females vs males	-10.3709	1.4450	107	-7.18	<.0001
mean for females	22.0469	1.0456	107	21.09	<.0001

Least Squares Means

Effect	hrt_sex	IGF1	IGFBP3	Calbb	Race	Estimate	Standard Error	DF	t Value	Pr > |t|
Race					1	23.7579	0.8504	107	27.94	<.0001
Race					2	27.2388	1.1900	107	22.89	<.0001
hrt_sex	FN					21.8164	0.9539	107	22.87	<.0001
hrt_sex	FY					22.2663	1.6658	107	13.37	<.0001
hrt_sex	MN					32.4123	1.0371	107	31.25	<.0001
IGF1		1				24.1648	1.1152	107	21.67	<.0001
IGF1		2				25.7870	0.9475	107	27.22	<.0001
IGF1		3				26.5432	1.2481	107	21.27	<.0001
IGFBP3			11			24.1906	1.1234	107	21.53	<.0001
IGFBP3			12			24.3286	0.9840	107	24.72	<.0001
IGFBP3			22			27.9758	1.4250	107	19.63	<.0001
Calbb				11		24.3518	0.8206	107	29.67	<.0001
Calbb				12		26.6449	1.1627	107	22.92	<.0001
IGFBP3*Race			11		1	24.2424	1.2484	107	19.42	<.0001
IGFBP3*Race			11		2	24.1388	1.8066	107	13.36	<.0001
IGFBP3*Race			12		1	23.1419	1.0309	107	22.45	<.0001
IGFBP3*Race			12		2	25.5154	1.4793	107	17.25	<.0001
IGFBP3*Race			22		1	23.8894	1.2604	107	18.95	<.0001
IGFBP3*Race			22		2	32.0622	2.5121	107	12.76	<.0001

Differences of Least Squares Means

Effect	hrt_sex	IGF1	IGFBP3	Calb b	Race	_ hrt_sex	_ IGF1	_ IGFBP3	_ Calbb	_ Race	Estimate	Standard Error	P[1]
Race					1					2	-3.4809	1.3362	0.0105
hrt_sex	FN					FY					-0.4499	1.7313	1.0000
hrt_sex	FN					MN					-10.5959	1.4066	<.0001
hrt_sex	FY					MN					-10.1459	1.9225	<.0001
IGF1		1					2				-1.6223	1.1701	0.5055
IGF1		1					3				-2.3785	1.4972	0.3453
IGF1		2					3				-0.7562	1.3706	1.0000
IGFBP3			11					12			-0.1380	1.3648	1.0000
IGFBP3			11					22			-3.7852	1.7155	0.0885
IGFBP3			12					22			-3.6472	1.5387	0.0558
Calbb				11					12		-2.2932	1.2481	0.0689
IGFBP3*Race			11		1			11		2	0.1036	2.1440	1.0000
IGFBP3*Race			11		1			12		1	1.1006	1.4061	1.0000
IGFBP3*Race			11		1			22		1	0.3530	1.5504	1.0000
IGFBP3*Race			11		2			12		2	-1.3765	2.2629	1.0000
IGFBP3*Race			11		2			22		2	-7.9233	3.0819	0.1035
IGFBP3*Race			12		1			12		2	-2.3735	1.6216	1.0000
IGFBP3*Race			12		1			22		1	-0.7476	1.3193	1.0000
IGFBP3*Race			12		2			22		2	-6.5468	2.8153	0.1971
IGFBP3*Race			22		1			22		2	-8.1728	2.7706	0.0351

[1] With 107 df

Model for comparison in muscle volume baseline among sex, race, and genotype groups:

IGF1 is the IGF1 genotype, 1 is 192 homozygote, 2 is 192 heterozygotes, 3 is non-carriers of the 192 allele

IGFBP3 is the IGFBP3 genotype, 11 is AA homozygotes, 12 is AC heterozygotes, 11 is CC homozygotes

Calbb is the calcineurin B genotype, 11 is the II homozygotes, 12 is the D-allele carriers

Race: 1 is Caucasian or 2 is African American

Age is subject's age

hrt_sex is hormone replacement status variable: MN is male, FN is females not on hormone replacement therapy, FY is females on hormone replacement therapy

Height is subject's height

bwpre is subject's baseline body weight

bmipre is subject's baseline body mass index

MVTB is subject's baseline muscle volume for training (exercising) leg

```
proc mixed data=one;
class race hrt_sex igf1 igfbp3 calbb;
model  mvtb=
                    igf1
                    igfbp3
                    calbb
                    age
                    race
                    hrt_sex
                    bmipre
                    height
                    bwpre
                    /outp=resids ddfm=kr htype=3;

                          *hrt_sex      FN     FY     MN;
estimate 'females vs males'   hrt_sex      0.5    0.5    -1;
estimate 'mean for females' height 167.57 age 64.14 bwpre 78.62 bmipre 27.89
intercept 1        hrt_sex     0.5     0.5     0;
lsmeans race hrt_sex igf1 igfbp3 calbb/pdiff;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;
```

Results:

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
IGF1	2	107	0.98	0.3804
IGFBP3	2	107	0.88	0.4187
CalbB	1	107	0.58	0.4492
Age	1	107	12.49	0.0006
Race	1	107	21.20	<.0001
hrt_sex	2	107	41.42	<.0001
bmipre	1	107	11.18	0.0011
Height	1	107	3.83	0.0530
bwpre	1	107	23.25	<.0001

Least Squares Means

Label	Estimate	Standard Error	DF	t Value	Pr > |t|
females vs males	-400.36	48.0958	107	-8.32	<.0001
mean for females	1338.08	34.9550	107	38.28	<.0001

Least Squares Means

Effect	hrt_sex	Race	IGF1	IGFBP3	CalbB	Estimate	Standard Error	DF	t Value	Pr > |t|
Race		1				1381.24	28.0867	107	49.18	<.0001
Race		2				1561.39	35.3901	107	44.12	<.0001
hrt_sex	FN					1335.54	30.3115	107	44.06	<.0001
hrt_sex	FY					1340.19	57.1854	107	23.44	<.0001
hrt_sex	MN					1738.23	31.8235	107	54.62	<.0001
IGF1			1			1437.40	36.2803	107	39.62	<.0001
IGF1			2			1484.62	28.7487	107	51.64	<.0001
IGF1			3			1491.93	38.8077	107	38.44	<.0001
IGFBP3				11		1466.79	34.9485	107	41.97	<.0001
IGFBP3				12		1448.23	29.7480	107	48.68	<.0001
IGFBP3				22		1498.94	38.5739	107	38.86	<.0001
CalbB					11	1456.35	26.9719	107	53.99	<.0001
CalbB					12	1486.29	36.4080	107	40.82	<.0001

Differences of Least Squares Means

Effect	hrt_sex	Race	IGF1	IGFBP3	CalbB	_hrt_sex	_Race	_IGF1	_IGFBP3	_CalbB	Estimate	Standard Error	P[1]
Race		1					2				-180.15	39.1243	<.0001
hrt_sex	FN					FY					-4.6484	59.0864	1.0000
hrt_sex	FN					MN					-402.69	45.3823	<.0001
hrt_sex	FY					MN					-398.04	65.6694	<.0001
IGF1			1					2			-47.2179	37.2314	0.6225
IGF1			1					3			-54.5280	46.3371	0.7257
IGF1			2					3			-7.3102	40.8802	1.0000
IGFBP3				11					12		18.5626	38.6627	1.0000
IGFBP3				11					22		-32.1474	45.5530	1.0000
IGFBP3				12					22		-50.7101	38.3552	0.5667
CalbB					11					12	-29.9402	39.4222	0.4492

[1] With 107 df.

Model for comparison in muscle quality baseline among sex, race, and genotype groups:

IGF1 is the IGF1 genotype, 1 is 192 homozygote, 2 is 192 heterozygotes, 3 is non-carriers of the 192 allele

IGFBP3 is the IGFBP3 genotype, 11 is AA homozygotes, 12 is AC heterozygotes, 11 is CC homozygotes

Calbb is the calcineurin B genotype, 11 is the II homozygotes, 12 is the D-allele carriers

Race: 1 is Caucasian or 2 is African American

Age is subject's age

hrt_sex is hormone replacement status variable: MN is male, FN is females not on hormone replacement therapy, FY is females on hormone replacement therapy

Height is subject's height

bwpre is subjects' baseline body weight

bmipre is subject's baseline body mass index

mqb is subject's baseline muscle quality (strength per muscle volume) for training leg

```
proc mixed data=one covtest scoring=10 convh=1E-5 covtest;
class race hrt_sex igf1 igfbp3 calbb;
model mqb=
                    age
                    race
                    height
                    bwpre
                    igf1
                    igfbp3
                    calbb
                    hrt_sex
                    bmipre
                  igfbp3*race
                /outp=resids ddfm=kr htype=3 solution;
                              *hrt_sex        FN      FY      MN;
estimate 'females vs males'    hrt_sex 0.5 0.5 -1/E;
estimate 'mean for females' height 167.62 age 64.51 bwpre 78.59 bmipre 27.92 intercept
1              hrt_sex     0.5      0.5      0/E;
lsmeans race hrt_sex igf1 igfbp3 calbb igfbp3*race/pdiff;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;
```

Results:

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Age	1	98	16.44	0.0001
Race	1	98	0.02	0.8862
Height	1	98	0.36	0.5473
bwpre	1	98	0.49	0.4877
IGF1	2	98	1.77	0.1753
IGFBP3	2	98	3.89	0.0237
CalbB	1	98	1.45	0.2308
hrt_sex	2	98	7.98	0.0006
bmipre	1	98	0.20	0.6522
Race*IGFBP3	2	98	5.73	0.0044

Least Squares Means

Label	Estimate	Standard Error	DF	t Value	Pr > |t|
females vs males	-2.6907	0.8309	98	-3.24	0.0016
mean for females	16.1215	0.6070	98	26.56	<.0001

Least Squares Means

Effect	hrt_sex	Race	IGF1	IGFBP3	CalbB	Estimate	Standard Error	DF	t Value	Pr > |t|
Race		1				16.9665	0.4823	98	35.18	<.0001
Race		2				17.0694	0.6455	98	26.44	<.0001
hrt_sex	FN					15.7085	0.5322	98	29.52	<.0001
hrt_sex	FY					16.5337	0.9901	98	16.70	<.0001
hrt_sex	MN					18.8117	0.5579	98	33.72	<.0001
IGF1			1			16.2361	0.6291	98	25.81	<.0001
IGF1			2			17.3004	0.5214	98	33.18	<.0001
IGF1			3			17.5174	0.6674	98	26.25	<.0001
IGFBP3				11		16.0605	0.6139	98	26.16	<.0001
IGFBP3				12		16.5198	0.5510	98	29.98	<.0001
IGFBP3				22		18.4736	0.7734	98	23.89	<.0001
CalbB					11	16.6106	0.4656	98	35.67	<.0001
CalbB					12	17.4254	0.6353	98	27.43	<.0001
Race*IGFBP3		1		11		17.5893	0.7232	98	24.32	<.0001
Race*IGFBP3		1		12		16.4017	0.5612	98	29.22	<.0001
Race*IGFBP3		1		22		16.9086	0.7025	98	24.07	<.0001
Race*IGFBP3		2		11		14.5318	0.9593	98	15.15	<.0001
Race*IGFBP3		2		12		16.6379	0.8354	98	19.92	<.0001
Race*IGFBP3		2		22		20.0386	1.3320	98	15.04	<.0001

Differences of Least Squares Means

Effect	hrt_sex	Race	IGF1	IGFBP3	CalbB	_hrt_sex	_Race	_IGF1	_IGFBP3	_CalbB	Estimate	Standard Error	P[1]
Race		1					2				-0.1029	0.7172	0.8862
hrt_sex	FN					FY					-0.8252	1.0261	1.0000
hrt_sex	FN					MN					-3.1032	0.7768	0.0003
hrt_sex	FY					MN					-2.2781	1.1418	0.1464
IGF1			1					2			-1.0643	0.6377	0.2949
IGF1			1					3			-1.2812	0.8006	0.3381
IGF1			2					3			-0.2170	0.7263	1.0000
IGFBP3				11					12		-0.4593	0.7466	1.0000
IGFBP3				11					22		-2.4130	0.9141	0.0291
IGFBP3				12					22		-1.9537	0.8239	0.0197
CalbB					11					12	-0.8148	0.6758	1.0000
Race*IGFBP3		1		11			1		12		1.1875	0.7836	1.0000
Race*IGFBP3		1		11			1		22		0.6807	0.8750	1.0000
Race*IGFBP3		1		11			2		11		3.0575	1.1743	0.1773
Race*IGFBP3		1		12			1		22		-0.5068	0.7225	1.0000
Race*IGFBP3		1		12			2		12		-0.2362	0.9008	1.0000
Race*IGFBP3		1		22			2		22		-3.1300	1.4638	0.3150
Race*IGFBP3		2		11			2		12		-2.1061	1.2379	0.8280
Race*IGFBP3		2		11			2		22		-5.5068	1.6278	0.0090
Race*IGFBP3		2		12			2		22		-3.4007	1.4982	0.2286

[1] With 98 df.

APPENDIX F

Final Statistical Models and Results for Muscle Phenotype Changes with Strength Training

APPENDIX F: FINAL STATISTICAL MODELS AND RESULTS FOR MUSCLE PHENOTYPE CHANGES WITH STRENGTH TRAINING

Model for change in muscle strength with strength training:

IGF1 is the IGF1 genotype, 1 is 192 homozygote, 2 is 192 heterozygotes, 3 is non-carriers of the 192 allele

IGFBP3 is the IGFBP3 genotype, 11 is AA homozygotes, 12 is AC heterozygotes, 11 is CC homozygotes

Calbb is the calcineurin B genotype, 11 is the II homozygotes, 12 is the D-allele carriers

Race: 1 is Caucasian or 2 is African American

Age is subject's age

sex: 1 male or 2 female

hrt_sex is hormone replacement therapy status variable: MN is male, FN is females not on hormone replacement therapy, FY is females on hormone replacement therapy

Height is subject's height

bwpre is subject's baseline body weight

bmipre is subject's baseline body mass index

rmtlprekg is subject's baseline muscle strength for training leg

rmdkg is the change in muscle strength with strength training

```
proc mixed data=one covtest;
class race hrt_sex igf1 igfbp3 calbb;
model rmdkg=rmtlprekg
                    race
                    height
                    igf1
                    igfbp3
                    calbb
                    age
                    bwpre
                    hrt_sex
                    bmipre
                    igfbp3*race
                calbb*igf1
                    / outp=resids ddfm=kr htype=3 solution;
                                  *hrt_sex      FN    FY    MN;
estimate 'females vs males '       hrt_sex      0.5   0.5   -1/E;
estimate 'mean for females ' rmtlprekg 24.77 height 167.62 age 64.11 bwpre 78.21
bmipre 27.79 intercept 1 hrt_sex   0.5   0.5   0/E;
lsmeans race hrt_sex igf1 igfbp3 calbb race*igfbp3 igf1*calbb/pdiff;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;
```

Results:

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
RMTLPREKG	1	104	0.31	0.5789
Race	1	104	8.57	0.0042
Height	1	104	0.74	0.3912
IGF1	2	104	0.68	0.5101
IGFBP3	2	104	1.75	0.1796
Calbb	1	104	0.02	0.8961
Age	1	104	1.40	0.2388
bwpre	1	104	0.14	0.7080
hrt_sex	2	104	4.33	0.0157
bmipre	1	104	0.17	0.6821
Race*IGFBP3	2	104	2.42	0.0935
IGF1*Calbb	2	104	2.70	0.0716

Least Squares Means

	Estimate	Standard Error	DF	t Value	Pr > |t|
females vs males	-3.1988	1.1580	104	-2.76	0.0068
mean for females	5.6628	0.7208	104	7.86	<.0001

Least Squares Means

Effect	hrt_sex	Race	IGF1	IGFBP3	Calbb	Estimate	Standard Error	DF	t Value	Pr > |t|
Race		1				5.3969	0.5715	104	9.44	<.0001
Race		2				8.0610	0.8077	104	9.98	<.0001
hrt_sex	FN					5.5325	0.6658	104	8.31	<.0001
hrt_sex	FY					5.7929	1.1154	104	5.19	<.0001
hrt_sex	MN					8.8614	0.8382	104	10.57	<.0001
IGF1			1			6.5863	0.8108	104	8.12	<.0001
IGF1			2			7.3696	0.6590	104	11.18	<.0001
IGF1			3			6.2310	0.9653	104	6.45	<.0001
IGFBP3				11		7.8620	0.7802	104	10.08	<.0001
IGFBP3				12		6.5637	0.6506	104	10.09	<.0001
IGFBP3				22		5.7611	0.9598	104	6.00	<.0001
Calbb					11	6.6712	0.5413	104	12.32	<.0001
Calbb					12	6.7867	0.8136	104	8.34	<.0001
Race*IGFBP3		1		11		5.3205	0.8356	104	6.37	<.0001
Race*IGFBP3		1		12		5.9448	0.6934	104	8.57	<.0001
Race*IGFBP3		1		22		4.9255	0.8333	104	5.91	<.0001
Race*IGFBP3		2		11		10.4036	1.2474	104	8.34	<.0001
Race*IGFBP3		2		12		7.1826	0.9830	104	7.31	<.0001
Race*IGFBP3		2		22		6.5968	1.7143	104	3.85	0.0002
IGF1*Calbb			1		11	6.9285	0.8086	104	8.57	<.0001
IGF1*Calbb			1		12	6.2440	1.3022	104	4.79	<.0001
IGF1*Calbb			2		11	8.3677	0.6599	104	12.68	<.0001
IGF1*Calbb			2		12	6.3715	1.0568	104	6.03	<.0001
IGF1*Calbb			3		11	4.7174	0.8858	104	5.33	<.0001
IGF1*Calbb			3		12	7.7445	1.6558	104	4.68	<.0001

Differences of Least Squares Means

Effect	hrt_sex	Race	IGF1	IGFBP3	CalbB	_hrt_sex	_Race	_IGF1	_IGFBP3	_CalbB	Estimate	Standard Error	P[1]
Race		1					2				-2.6641	0.9098	0.0042
hrt_sex	FN					FY					-0.2603	1.1386	1.0000
hrt_sex	FN					MN					-3.3289	1.1443	0.0132
hrt_sex	FY					MN					-3.0686	1.4215	0.0996
IGF1			1					2			-0.7833	0.9178	1.0000
IGF1			1					3			0.3553	1.2002	1.0000
IGF1			2					3			1.1387	1.1156	0.9294
IGFBP3				11					12		1.2983	0.9339	0.5022
IGFBP3				11					22		2.1009	1.1693	0.2259
IGFBP3				12					22		0.8026	1.0379	1.0000
Calbb					11					12	-0.1155	0.8830	0.8961
Race*IGFBP3		1		11			1		12		-0.6243	0.9361	1.0000
Race*IGFBP3		1		11			1		22		0.3950	1.0255	1.0000
Race*IGFBP3		1		11			2		11		-5.0831	1.4400	0.0054
Race*IGFBP3		1		12			1		22		1.0193	0.8678	1.0000
Race*IGFBP3		1		12			2		12		-1.2378	1.0959	1.0000
Race*IGFBP3		1		22			2		22		-1.6713	1.8924	1.0000
Race*IGFBP3		2		11			2		12		3.2209	1.5626	0.3762
Race*IGFBP3		2		11			2		22		3.8068	2.1130	0.6705
Race*IGFBP3		2		12			2		22		0.5859	1.8987	1.0000
IGF1*Calbb			1		11			1		12	0.6844	1.4387	1.0000
IGF1*Calbb			1		11			2		11	-1.4392	0.8778	0.9369
IGF1*Calbb			1		11			3		11	2.2111	1.1061	0.4338
IGF1*Calbb			1		12			2		12	-0.1275	1.5958	1.0000
IGF1*Calbb			1		12			3		12	-1.5005	2.0798	1.0000
IGF1*Calbb			2		11			2		12	1.9961	1.1692	0.8172
IGF1*Calbb			2		11			3		11	3.6503	0.9951	0.0036
IGF1*Calbb			2		12			3		12	-1.3730	1.9577	1.0000
IGF1*Calbb			3		11			3		12	-3.0272	1.8235	0.8991

[1] With 104 df.

Model for change in muscle volume with strength training:

IGF1 is the IGF1 genotype, 1 is 192 homozygote, 2 is 192 heterozygotes,
3 is non-carriers of the 192 allele

IGFBP3 is the IGFBP3 genotype, 11 is AA homozygotes, 12 is AC heterozygotes, 11 is CC homozygotes

Calbb is the calcineurin B genotype, 11 is the II homozygotes, 12 is the D-allele carriers

Race is subject's race: 1 Caucasian or 2 African American

Age is subject's age

hrt_sex is hormone replacement therapy status variable: MN is male, FN is females not on hormone replacement therapy, FY is females on hormone replacement therapy

Height is subject's height

bwpre is subject's baseline body weight

bmipre is subject's baseline body mass index

mvtb is baseline muscle volume for training (exercising) leg

mvca is change in muscle volume for the trained leg also correcting for change in untrained leg

```
proc mixed data=one;
class race hrt_sex igf1 igfbp3 calbb;
model mvca= mvtb
                    igf1
                    igfbp3
                    calbb
                    age
                    race
                    hrt_sex
                    bmipre
                    height
                    bwpre
                /outp=resids ddfm=kr htype=3 solution;
                              *hrt_sex      FN      FY      MN;
estimate 'females vs males'     hrt_sex     0.5     0.5     -1/E;
estimate 'mean for females' height 167.57 age 64.14 bwpre 78.62 bmipre 27.89 mvtb
1468.25 intercept 1    hrt_sex 0.5 0.5 0/E;
lsmeans race hrt_sex igf1 igfbp3 calbb/pdiff;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;
```

Results:

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
MVTB	1	106	2.77	0.0989
IGF1	2	106	1.04	0.3561
IGFBP3	2	106	0.09	0.9133
CalbB	1	106	3.60	0.0607
Age	1	106	1.14	0.2874
Race	1	106	1.06	0.3059
hrt_sex	2	106	1.70	0.1875
bmipre	1	106	0.02	0.8907
Height	1	106	0.02	0.9025
bwpre	1	106	0.03	0.8587

Least Squares Means

	Estimate	Standard Error	DF	t Value	Pr > |t|
females vs males	-38.0975	23.4381	106	-1.63	0.1070
mean for females	106.15	14.1046	106	7.53	<.0001

Least Squares Means

Effect	hrt_sex	Race	IGF1	IGFBP3	CalbB	Estimate	Standard Error	DF	t Value	Pr > |t|
Race		1				110.49	11.1311	106	9.93	<.0001
Race		2				127.22	13.8641	106	9.18	<.0001
hrt_sex	FN					102.39	12.4963	106	8.19	<.0001
hrt_sex	FY					109.92	22.2137	106	4.95	<.0001
hrt_sex	MN					144.25	15.6256	106	9.23	<.0001
IGF1			1			106.06	13.8205	106	7.67	<.0001
IGF1			2			126.12	10.9311	106	11.54	<.0001
IGF1			3			124.39	14.7591	106	8.43	<.0001
IGFBP3				11		122.09	13.2685	106	9.20	<.0001
IGFBP3				12		119.59	11.3179	106	10.57	<.0001
IGFBP3				22		114.88	14.6880	106	7.82	<.0001
CalbB					11	133.08	10.2493	106	12.98	<.0001
CalbB					12	104.63	13.8383	106	7.56	<.0001

Differences of Least Squares Means

Effect	hrt_sex	Race	IGF1	IGFBP3	CalbB	_hrt_sex	_Race	_IGF1	_IGFBP3	_CalbB	Estimate	Standard Error	P[1]
Race		1					2				-16.7266	16.2588	0.3059
hrt_sex	FN					FY					-7.5310	22.4331	1.0000
hrt_sex	FN					MN					-41.8630	22.7002	0.2040
hrt_sex	FY					MN					-34.3320	28.8966	0.7125
IGF1			1					2			-20.0608	14.2409	0.4857
IGF1			1					3			-18.3347	17.7056	0.9084
IGF1			2					3			1.7261	15.5227	1.0000
IGFBP3				11					12		2.5065	14.6943	1.0000
IGFBP3				11					22		7.2093	17.3346	1.0000
IGFBP3				12					22		4.7028	14.6802	1.0000
CalbB					11					12	28.4556	15.0071	0.0607

[1] With 106 df.

Model for change in muscle quality with strength training:

IGF1 is the IGF1 genotype, 1 is 192 homozygote, 2 is 192 heterozygotes,
3 is non-carriers of the 192 allele

IGFBP3 is the IGFBP3 genotype, 11 is AA homozygotes, 12 is AC heterozygotes, 11 is CC homozygotes

Calbb is the calcineurin B genotype, 11 is the II homozygotes, 12 is the D-allele carriers

Race is subject's race: 1 Caucasian or 2 African American

Age is subject's age

hrt_sex is hormone replacement therapy status variable: MN is male, FN is females not on hormone replacement therapy, FY is females on hormone replacement therapy

Height is subject's height

bwpre is subject's baseline body weight

bmipre is subject's baseline body mass index

mqb is baseline muscle quality (strength per muscle volume) for training leg

mqc is change in muscle quality for trained leg

```
proc mixed data=one covtest scoring=10 convh=1E-5 covtest;
class race hrt_sex igf1 igfbp3 calbb;
model mqc=mqb
                age
                race
                height
                bwpre
                igf1
                igfbp3
                calbb
                igf1*calbb
                hrt_sex
                bmipre
          /outp=resids ddfm=kr htype=3 solution;

                                *hrt_sex      FN      FY      MN;
estimate 'females vs males'       hrt_sex      0.5     0.5     -1/E;
estimate 'mean for females' mqb 16.74 height 167.62 bwpre 78.59 bmipre 27.92 age
64.51 intercept 1       hrt_sex 0.5     0.5     0/E;
lsmeans race hrt_sex igf1 igfbp3 calbb igf1*calbb/pdiff;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
```

Results:

Type 3 Tests of Fixed Effects

Effect	Num DF	De DF	F Value	Pr > F
MQB	1	97	28.39	<.0001
Age	1	97	3.59	0.0610
Race	1	97	3.90	0.0511
Height	1	97	1.59	0.2102
bwpre	1	97	1.03	0.3130
IGF1	2	97	0.37	0.6930
IGFBP3	2	97	0.41	0.6632
CalbB	1	97	0.15	0.6980
IGF1*CalbB	2	97	3.07	0.0509
hrt_sex	2	97	1.71	0.1871
bmipre	1	97	0.60	0.4417

Least Squares Means

	Estimate	Standard Error	DF	t Value	Pr > |t|
females vs males	-0.7121	0.5911	97	-1.20	0.2312
mean for females	2.7837	0.4174	97	6.67	<.0001

Least Squares Means

Effect	hrt_sex	Race	IGF1	IGFBP3	CalbB	Estimate	Standard Error	DF	t Value	Pr > |t|
Race		1				2.5774	0.3268	97	7.89	<.0001
Race		2				3.4675	0.4152	97	8.35	<.0001
hrt_sex	FN					2.4911	0.3707	97	6.72	<.0001
hrt_sex	FY					3.0791	0.6678	97	4.61	<.0001
hrt_sex	MN					3.4972	0.3884	97	9.00	<.0001
IGF1			1			3.1891	0.4809	97	6.63	<.0001
IGF1			2			3.1755	0.3384	97	9.38	<.0001
IGF1			3			2.7027	0.5220	97	5.18	<.0001
IGFBP3				11		2.8610	0.4115	97	6.95	<.0001
IGFBP3				12		3.2426	0.3547	97	9.14	<.0001
IGFBP3				22		2.9638	0.4414	97	6.72	<.0001
CalbB					11	2.9288	0.3096	97	9.46	<.0001
CalbB					12	3.1160	0.4443	97	7.01	<.0001
IGF1*CalbB			1	11		3.2783	0.4531	97	7.23	<.0001
IGF1*CalbB			1	12		3.1000	0.7950	97	3.90	0.0002
IGF1*CalbB			2	11		3.6860	0.3676	97	10.03	<.0001
IGF1*CalbB			2	12		2.6650	0.5332	97	5.00	<.0001
IGF1*CalbB			3	11		1.8222	0.4821	97	3.78	0.0003
IGF1*CalbB			3	12		3.5831	0.8809	97	4.07	<.0001

Differences of Least Squares Means

Effect	hrt_sex	Race	IGF1	IGFBP3	CalbB	_hrt_sex	_Race	_IGF1	_IGFBP3	_CalbB	Estimate	Standard Error	P[1]
Race		1					2				-0.8901	0.4507	0.0511
hrt_sex	FN					FY					-0.5880	0.6854	1.0000
hrt_sex	FN					MN					-1.0061	0.5636	0.2322
hrt_sex	FY					MN					-0.4181	0.7848	1.0000
IGF1			1					2			0.01362	0.5221	1.0000
IGF1			1					3			0.4865	0.6741	1.0000
IGF1			2					3			0.4729	0.5730	1.0000
IGFBP3				11					12		-0.3816	0.4628	1.0000
IGFBP3				11					22		-0.1028	0.5160	1.0000
IGFBP3				12					22		0.2788	0.4360	1.0000
CalbB					11					12	-0.1872	0.4809	0.6980
IGF1*CalbB			1	11				1		12	0.1783	0.8658	1.0000
IGF1*CalbB			1	11				2		11	-0.4078	0.4858	1.0000
IGF1*CalbB			1	11				3		11	1.4561	0.5887	0.1359
IGF1*CalbB			1	12				2		11	-0.5860	0.8087	1.0000
IGF1*CalbB			1	12				2		12	0.4350	0.9362	1.0000
IGF1*CalbB			1	12				3		12	-0.4831	1.1874	1.0000
IGF1*CalbB			2	11				2		12	1.0210	0.6171	0.9117
IGF1*CalbB			2	11				3		11	1.8638	0.5228	0.0054
IGF1*CalbB			2	12				3		11	0.8428	0.6871	1.0000

[1] With 97 df

APPENDIX G

Final Statistical Models and Results for Percent Change with Strength Training

APPENDIX G: FINAL STATISTICAL MODELS AND RESULTS FOR PERCENT CHANGE WITH STRENGTH TRAINING

Model for relative percent change in muscle strength with strength training:

IGF1 is the IGF1 genotype, 1 is 192 homozygote, 2 is 192 heterozygotes,
3 is non-carriers of the 192 allele

IGFBP3 is the IGFBP3 genotype, 11 is AA homozygotes, 12 is AC heterozygotes, 11 is CC homozygotes

Calbb is the calcineurin B genotype, 11 is the II homozygotes, 12 is the D-allele carriers

Race: 1 Caucasian or 2 African American
Age
sex: 1 male or 2 female

hrt_sex is hormone replacement variable: MN is male, FN is females not on hormone replacement therapy, FY is females on hormone replacement therapy
Height
bwpre is baseline body weight

bmipre is baseline body mass index

RMTLPREKG is baseline muscle strength for training leg

pctchange is the relative percent change in muscle strength with strength training

```
proc mixed data=one covtest;
class race hrt_sex igf1 igfbp3 calbb;
model pctchange=rmtlprekg
                race
                height
                igf1
                igfbp3
                calbb
                age
                bwpre
                hrt_sex
                bmipre
                igfbp3*race
                calbb*igf1
                / outp=resids ddfm=kr htype=3 solution;
                        *hrt_sex        FN      FY      MN;
estimate  'male vs female'          hrt_sex     1       1       -2/divisor=2;
estimate  'mean for females' rmtlprekg 24.77 height 167.62 age 64.11 bwpre 78.21
bmipre 27.79 intercept 1 hrt_sex      0.5     0.5     0/E;
lsmeans race hrt_sex igf1 igfbp3 calbb igfbp3*race igf1*calbb/pdiff;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;
```

Results:

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
RMTLPREKG	1	104	33.67	<.0001
Race	1	104	10.72	0.0014
Height	1	104	1.06	0.3062
IGF1	2	104	0.14	0.8682
IGFBP3	2	104	0.69	0.5030
Calbb	1	104	0.11	0.7399
Age	1	104	3.29	0.0726
bwpre	1	104	0.03	0.8559
hrt_sex	2	104	3.75	0.0268
bmipre	1	104	0.06	0.8059
Race*IGFBP3	2	104	4.35	0.0153
IGF1*Calbb	2	104	4.14	0.0187

Least Squares Means

Label	Estimate	Standard Error	DF	t Value	Pr > |t|
male vs female	-10.5686	4.9487	104	-2.14	0.0351
mean for females	27.4827	3.0802	104	8.92	<.0001

Least Squares Means

Effect	hrt_sex	Race	IGF1	IGFBP3	Calbb	Estimate	Standard Error	DF	t Value	Pr > |t|
Race		1				24.6361	2.4421	104	10.09	<.0001
Race		2				37.3639	3.4519	104	10.82	<.0001
hrt_sex	FN					24.8662	2.8453	104	8.74	<.0001
hrt_sex	FY					30.0882	4.7664	104	6.31	<.0001
hrt_sex	MN					38.0457	3.5821	104	10.62	<.0001
IGF1			1			30.8396	3.4648	104	8.90	<.0001
IGF1			2			32.2410	2.8164	104	11.45	<.0001
IGF1			3			29.9195	4.1252	104	7.25	<.0001
IGFBP3				11		34.0902	3.3341	104	10.22	<.0001
IGFBP3				12		30.1448	2.7804	104	10.84	<.0001
IGFBP3				22		28.7651	4.1018	104	7.01	<.0001
Calbb					11	30.3720	2.3133	104	13.13	<.0001
Calbb					12	31.6281	3.4769	104	9.10	<.0001
Race*IGFBP3		1		11		22.8375	3.5710	104	6.40	<.0001
Race*IGFBP3		1		12		29.6551	2.9632	104	10.01	<.0001
Race*IGFBP3		1		22		21.4158	3.5609	104	6.01	<.0001
Race*IGFBP3		2		11		45.3429	5.3306	104	8.51	<.0001
Race*IGFBP3		2		12		30.6346	4.2009	104	7.29	<.0001
Race*IGFBP3		2		22		36.1143	7.3261	104	4.93	<.0001
IGF1*Calbb			1		11	30.7326	3.4554	104	8.89	<.0001
IGF1*Calbb			1		12	30.9465	5.5650	104	5.56	<.0001
IGF1*Calbb			2		11	37.8550	2.8200	104	13.42	<.0001
IGF1*Calbb			2		12	26.6271	4.5160	104	5.90	<.0001
IGF1*Calbb			3		11	22.5283	3.7852	104	5.95	<.0001
IGF1*Calbb			3		12	37.3107	7.0761	104	5.27	<.0001

Differences of Least Squares Means

Effect	hrt_sex	Race	IGF1	IGFBP3	Calbb	_hrt_sex	_Race	_IGF1	_IGFBP3	_Calbb	Estimate	Standard Error	P[1]
Race		1					2				-12.7278	3.8880	0.0014
hrt_sex	FN					FY					-5.2220	4.8658	0.8571
hrt_sex	FN					MN					-13.1796	4.8902	0.0246
hrt_sex	FY					MN					-7.9576	6.0748	0.5793
IGF1			1					2			-1.4015	3.9221	1.0000
IGF1			1					3			0.9201	5.1289	1.0000
IGF1			2					3			2.3216	4.7676	1.0000
IGFBP3				11					12		3.9454	3.9911	0.9756
IGFBP3				11					22		5.3251	4.9971	0.8670
IGFBP3				12					22		1.3798	4.4354	1.0000
Calbb					11					12	-1.2561	3.7734	0.7399
Race*IGFBP3		1		11			1		12		-6.8175	4.0002	0.8217
Race*IGFBP3		1		11			1		22		1.4217	4.3826	1.0000
Race*IGFBP3		1		11			2		11		-22.5053	6.1538	0.0036
Race*IGFBP3		1		12			1		22		8.2392	3.7085	0.2565
Race*IGFBP3		1		12			2		12		-0.9795	4.6832	1.0000
Race*IGFBP3		1		22			2		22		-14.6984	8.0873	0.6480
Race*IGFBP3		2		11			2		12		14.7083	6.6776	0.2682
Race*IGFBP3		2		11			2		22		9.2286	9.0298	1.0000
Race*IGFBP3		2		12			2		22		-5.4797	8.1141	1.0000
IGF1*Calbb			1		11			1		12	-0.2139	6.1481	1.0000
IGF1*Calbb			1		11			2		11	-7.1224	3.7512	0.5436
IGF1*Calbb			1		11			3		11	8.2044	4.7269	0.7704
IGF1*Calbb			1		12			2		12	4.3194	6.8196	1.0000
IGF1*Calbb			1		12			3		12	-6.3642	8.8881	1.0000
IGF1*Calbb			2		11			2		12	11.2279	4.9966	0.2403
IGF1*Calbb			2		11			3		11	15.3267	4.2525	0.0045
IGF1*Calbb			2		12			3		12	-10.6836	8.3663	1.0000
IGF1*Calbb			3		11			3		12	-14.7824	7.7927	0.5454

[1] With 104 df

Model for relative percent change in muscle volume with strength training:

```
IGF1 is the IGF1 genotype, 1 is 192 homozygote, 2 is 192 heterozygotes,
3 is non-carriers of the 192 allele

IGFBP3 is the IGFBP3 genotype, 11 is AA homozygotes, 12 is AC
heterozygotes, 11 is CC homozygotes

Calbb is the calcineurin B genotype, 11 is the II homozygotes, 12 is
the D-allele carriers

Race: 1 is Caucasian or 2 is African American

Age is the subject's age

hrt_sex is hormone replacement therapy status variable: MN is male, FN
is females not on hormone replacement therapy, FY is females on hormone
replacement therapy

Height is the subject's height

bwpre is baseline body weight

bmipre is baseline body mass index

MVTB is baseline muscle volume for training (exercising) leg

pctchange is the relative change in muscle volume with strength
training
```

```
proc mixed data=one;
class race hrt_sex igf1 igfbp3 calbb;
model pctchange= mvtb
                 igf1
                 igfbp3
                 calbb
                 age
                 race
                 hrt_sex
                 bmipre
                 height
                 bwpre
                 /outp=resids ddfm=kr htype=3 solution;
                       *hrt_sex      FN     FY     MN;
estimate 'females vs males'    hrt_sex      0.5    0.5    -1/E;
estimate 'mean for females' height 167.57 age 64.14 bwpre 78.62 bmipre 27.89 mvtb
1468.25 intercept 1          hrt_sex  0.5    0.5    0/E;
lsmeans race hrt_sex igf1 igfbp3 calbb/pdiff;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;
```

Results:

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
MVTB	1	106	1.32	0.2535
IGF1	2	106	1.45	0.2382
IGFBP3	2	106	0.01	0.9887
CalbB	1	106	4.38	0.0388
Age	1	106	1.47	0.2281
Race	1	106	0.74	0.3919
hrt_sex	2	106	2.09	0.1293
bmipre	1	106	0.31	0.5806
Height	1	106	0.77	0.3830
bwpre	1	106	0.30	0.5835

Least Squares Means

Label	Estimate	Standard Error	DF	t Value	Pr > |t|
females vs males	-2.8997	1.6460	106	-1.76	0.0810
mean for females	7.0891	0.9905	106	7.16	<.0001

Least Squares Means

Effect	hrt_sex	Race	IGF1	IGFBP3	Calb B	Estimate	Standard Error	DF	t Value	Pr > |t|
Race		1				7.5640	0.7817	106	9.68	<.0001
Race		2				8.5455	0.9737	106	8.78	<.0001
hrt_sex	FN					6.7344	0.8776	106	7.67	<.0001
hrt_sex	FY					7.4420	1.5600	106	4.77	<.0001
hrt_sex	MN					9.9879	1.0974	106	9.10	<.0001
IGF1			1			6.9332	0.9706	106	7.14	<.0001
IGF1			2			8.4307	0.7677	106	10.98	<.0001
IGF1			3			8.8003	1.0365	106	8.49	<.0001
IGFBP3				11		8.1383	0.9318	106	8.73	<.0001
IGFBP3				12		8.0686	0.7948	106	10.15	<.0001
IGFBP3				22		7.9574	1.0315	106	7.71	<.0001
CalbB					11	9.1574	0.7198	106	12.72	<.0001
CalbB					12	6.9521	0.9718	106	7.15	<.0001

Differences of Least Squares Means

Effect	hrt_sex	Race	IGF1	IGFBP3	Calb B	_hrt_sex	_Race	_IGF1	_IGFBP3	_Calb B	Estimate	Standard Error	P[1]
Race		1					2				-0.9816	1.1418	0.3919
hrt_sex	FN					FY					-0.7076	1.5754	1.0000
hrt_sex	FN					MN					-3.2535	1.5942	0.1314
hrt_sex	FY					MN					-2.5459	2.0294	0.6372
IGF1			1					2			-1.4976	1.0001	0.4119
IGF1			1					3			-1.8672	1.2434	0.4086
IGF1			2					3			-0.3696	1.0901	1.0000
IGFBP3				11					12		0.06971	1.0320	1.0000
IGFBP3				11					22		0.1809	1.2174	1.0000
IGFBP3				12					22		0.1111	1.0310	1.0000
CalbB					11					12	2.2054	1.0539	0.0388

[1] With 106 df

Model for relative percent change in muscle quality with strength training:

IGF1 is the IGF1 genotype, 1 is 192 homozygote, 2 is 192 heterozygotes, 3 is non-carriers of the 192 allele

IGFBP3 is the IGFBP3 genotype, 11 is AA homozygotes, 12 is AC heterozygotes, 11 is CC homozygotes

Calbb is the calcineurin B genotype, 11 is the II homozygotes, 12 is the D-allele carriers

Race: 1 is Caucasian or 2 is African American

Age is the subject's age

hrt_sex is hormone replacement variable: MN is male, FN is females not on hormone replacement therapy, FY is females on hormone replacement therapy

Height is the subject's height

bwpre is baseline body weight

bmipre is baseline body mass index

mqb is baseline muscle quality (strength per muscle volume) for training leg

logdifference is the difference between the logarithms for baseline muscle quality and muscle quality after strength training

```
proc mixed data=one covtest scoring=10 convh=1E-5 covtest;
class race hrt_sex igf1 igfbp3 calbb;
model logdifference=mqb
                    age
                    race
                    height
                    bwpre
                    igf1
                    igfbp3
                    calbb
                    igf1*calbb
                    hrt_sex
                    bmipre
                    igfbp3*race
              /outp=resids ddfm=kr htype=3 solution;
                                  *hrt_sex        FN      FY      MN;
estimate 'females vs males'     hrt_sex         0.5     0.5     -1/E;
estimate 'mean for females' mqb 16.74 height 167.62 bwpre 78.59 bmipre 27.92 age
64.51 intercept 1   hrt_sex 0.5         0.5     0/E;
lsmeans hrt_sex race igf1 igfbp3 calbb igf1*calbb igfbp3*race/pdiff;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;
```

Results:

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
MQB	1	95	57.45	<.0001
Age	1	95	2.30	0.1323
Race	1	95	6.26	0.0141
Height	1	95	2.58	0.1117
bwpre	1	95	1.61	0.2078
IGF1	2	95	0.19	0.8250
IGFBP3	2	95	0.14	0.8711
CalbB	1	95	0.64	0.4241
IGF1*CalbB	2	95	4.56	0.0128
hrt_sex	2	95	1.28	0.2834
bmipre	1	95	1.00	0.3187
Race*IGFBP3	2	95	2.65	0.0756

Least Squares Means

Label	Estimate	Standard Error	DF	t Value	Pr > |t|
females vs males	-0.01407	0.01362	95	-1.03	0.3042
mean for females	0.07357	0.009649	95	7.62	<.0001

Least Squares Means

Effect	hrt_sex	Race	IGF1	IGFBP3	CalbB	Estimate	Standard Error	DF	t Value	Pr > |t|
hrt_sex	FN					0.06757	0.008609	95	7.85	<.0001
hrt_sex	FY					0.07967	0.01539	95	5.18	<.0001
hrt_sex	MN					0.08769	0.009179	95	9.55	<.0001
Race		1				0.06449	0.007559	95	8.53	<.0001
Race		2				0.09213	0.01009	95	9.13	<.0001
IGF1			1			0.08306	0.01116	95	7.44	<.0001
IGF1			2			0.07849	0.008375	95	9.37	<.0001
IGF1			3			0.07337	0.01210	95	6.06	<.0001
IGFBP3				11		0.07852	0.01003	95	7.83	<.0001
IGFBP3				12		0.07491	0.008624	95	8.69	<.0001
IGFBP3				22		0.08149	0.01223	95	6.66	<.0001
CalbB					11	0.07385	0.007159	95	10.32	<.0001
CalbB					12	0.08277	0.01041	95	7.95	<.0001
IGF1*CalbB			1		11	0.08266	0.01050	95	7.87	<.0001
IGF1*CalbB			1		12	0.08345	0.01840	95	4.54	<.0001
IGF1*CalbB			2		11	0.09202	0.008691	95	10.59	<.0001
IGF1*CalbB			2		12	0.06497	0.01302	95	4.99	<.0001
IGF1*CalbB			3		11	0.04686	0.01110	95	4.22	<.0001
IGF1*CalbB			3		12	0.09988	0.02057	95	4.86	<.0001
Race*IGFBP3		1		11		0.05793	0.01132	95	5.12	<.0001
Race*IGFBP3		1		12		0.07613	0.008785	95	8.67	<.0001
Race*IGFBP3		1		22		0.05941	0.01086	95	5.47	<.0001
Race*IGFBP3		2		11		0.09912	0.01585	95	6.26	<.0001
Race*IGFBP3		2		12		0.07369	0.01313	95	5.61	<.0001
Race*IGFBP3		2		22		0.1036	0.02111	95	4.91	<.0001

Differences of Least Squares Means

Effect	hrt_sex	Race	IGF1	IGFBP3	CalbB	_hrt_sex	_Race	_IGF1	_IGFBP3	_CalbB	Estimate	Standard Error	P[1]
hrt_sex	FN					FY					-0.01210	0.01580	1.0000
hrt_sex	FN					MN					-0.02012	0.01306	0.3798
hrt_sex	FY					MN					-0.00802	0.01804	1.0000
Race		1					2				-0.02764	0.01105	0.0141
IGF1			1					2			0.004565	0.01212	1.0000
IGF1			1					3			0.009685	0.01566	1.0000
IGF1			2					3			0.005120	0.01381	1.0000
IGFBP3				11					12		0.003609	0.01205	1.0000
IGFBP3				11					22		-0.00296	0.01475	1.0000
IGFBP3				12					22		-0.00657	0.01304	1.0000
CalbB					11					12	-0.00892	0.01111	0.4241
IGF1*CalbB			1		11			1		12	-0.00079	0.01999	1.0000
IGF1*CalbB			1		11			2		11	-0.00936	0.01124	1.0000
IGF1*CalbB			1		11			3		11	0.03580	0.01369	0.0936
IGF1*CalbB			1		12			2		12	0.01849	0.02161	1.0000
IGF1*CalbB			1		12			3		12	-0.01643	0.02771	1.0000
IGF1*CalbB			2		11			2		12	0.02705	0.01232	0.5823
IGF1*CalbB			2		11			3		11	0.04515	0.01447	0.0036
IGF1*CalbB			2		12			3		12	-0.03491	0.02417	1.0000
IGF1*CalbB			3		11			3		12	-0.05302	0.02251	0.1854
Race*IGFBP3		1		11			1		12		-0.01820	0.01222	1.0000
Race*IGFBP3		1		11			1		22		-0.00148	0.01351	1.0000
Race*IGFBP3		1		11			2		11		-0.04119	0.01887	0.2835
Race*IGFBP3		1		12			1		22		0.01673	0.01112	1.0000
Race*IGFBP3		1		12			2		12		0.002440	0.01420	1.0000
Race*IGFBP3		1		12			2		22		-0.02743	0.02200	1.0000
Race*IGFBP3		1		22			2		22		-0.04416	0.02300	0.5202
Race*IGFBP3		2		11			2		12		0.02542	0.02036	1.0000
Race*IGFBP3		2		11			2		22		-0.00445	0.02676	1.0000
Race*IGFBP3		2		12			2		22		-0.02987	0.02368	1.0000

[1] With 95 df

APPENDIX H

Frequency Tables for Genotype Groups for Gene by Gene and Gene by Race Interactions

APPENDIX H: FREQUENCY TABLES FOR GENOTYPE GROUPS FOR GENE BY GENE AND GENE BY RACE INTERACTIONS

Table of frequencies for *IGF1* and *PPP3R1* genotype groups for change in muscle strength with strength training

	***PPP3R1* Genotype Group**	
***IGF1* Genotype Group**	**II Homozygotes**	**D-Allele Carriers**
192 Homozygotes	**28**	**8**
192 Heterozygotes	**49**	**13**
Noncarriers of the 192 Allele	**19**	**5**

Table of frequencies for *IGFBP3* and Race groups for change in muscle strength with strength training

	Race	
***IGFBP3* Genotype Group**	**African American**	**Caucasian**
AA Homozygotes	**10**	**22**
AC Heterozygotes	**15**	**43**
CC Homozygotes	**5**	**27**

Table of frequencies for *IGF1* and *PPP3R1* genotype groups for change in muscle quality with strength training

	***PPP3R1* Genotype Group**	
***IGF1* Genotype Group**	**II Homozygotes**	**D-Allele Carriers**
192 Homozygotes	**26**	**6**
192 Heterozygotes	**44**	**13**
Noncarriers of the 192 Allele	**19**	**5**

APPENDIX I

Genotype data tables and figures for baseline muscle phenotypes and for changes in muscle phenotypes with strength training

APPENDIX I: GENOTYPE DATA TABLES AND FIGURES FOR BASELINE MUSCLE PHENOTYPES AND FOR CHANGES IN MUSCLE PHENOTYPES WITH STRENGTH TRAINING

Table 7. Physical characteristics for *IGF1* 192 homozygotes (n = 32-36), *IGF1* 192 heterozygotes (n = 57-62), and *IGF1* noncarriers of the 192 allele (n = 24-26) at baseline for all muscle phenotypes

	192 Homozygotes (n = 32-36)[1]		192 Heterozygotes (n = 57-62)[1]		Noncarriers of the 192 Allele (n = 24-26)[1]	
	Baseline	**After ST**	**Baseline**	**After ST**	**Baseline**	**After ST**
Age	62 (6)	--	65 (9)	--	64 (9)	--
Height (cm)	169 (9)	--	166 (8)	--	170 (9)	--
Weight (kg)	77.9 (14.0)	78.1 (14.2)	77.5 (14.1)	77.7 (14.4)	80.5(15.4)	80.6 (15.7)
Body Fat (%)	33.9 (7.7)	33.6 (7.5)	33.9 (7.8)	33.6 (7.9)	33.3 (7.4)	32.5 (6.9)
FFM (kg)	51.6 (11.7)	51.7 (11.3)	50.9 (10.2)	51.3 (10.3)	53.8(11.7)	54.5 (11.9)
1 RM (kg)	24 ± 1.1		26 ± 0.9		27 ± 1.2	
MV (cm^3)	1440 ± 36		1480 ± 29		1490 ± 39	
MQ (kg/cm^3)*10^{-3}	16.2 ± 0.63		17.3 ± 0.52		17.5 ± 0.67	
Male/Female	15-16/ 17-20	--	26-28/ 31-34	--	12/ 12-14	--
African American/Caucasian	3-4/ 29-32	--	15-16/ 42-46	--	10-12/ 14	--

Values are means (SD) FFM = Fat Free Mass MV = Muscle Volume MQ = Muscle Quality

Values for 1 RM, MV, and Q are least square means ± SE 1 RM = Knee extension one repetition maximum

[1]Sample size variability was due to missing data for muscle phenotypes

Table 8. Physical characteristics for *IGFBP3* AA homozygotes (n = 29-32), *IGFBP3* AC heterozygotes (n = 55-61), and *IGFBP3* CC homozygotes (n = 29-32) at baseline for all muscle phenotypes

	AA Homozygotes (n = 29-32)[1]		AC Heterozygotes (n = 55-61)[1]		CC Homozygotes (n = 29-32)[1]	
	Baseline	**After ST**	**Baseline**	**After ST**	**Baseline**	**After ST**
Age	63 (10)	--	65 (8)	--	65 (7)	--
Height (cm)	166 (10)	--	167 (8)	--	170 (9)	--
Weight (kg)	78.5 (16.3)	78.8 (16.6)	77.4(12.8)	77.6 (13.2)	79.4(15.1)	79.4 (15.2)
Body Fat (%)	34.1 (7.4)	33.7 (7.6)	34.2 (8.4)	33.8 (8.2)	32.9 (6.5)	32.3 (6.4)
FFM (kg)	51.8 (12.5)	52.2 (12.7)	50.8 (9.9)	51.2 (9.8)	53.1 (11.2)	53.5 (11.1)
1 RM (kg)	24 ± 1.1		24 ± 1.0		28 ± 1.4	
MV (cm^3)	1470 ± 35		1450 ± 30		1500 ± 39	
MQ(kg/cm^3)*10^{-3}	16.1 ± 0.61		16.5 ± 0.55		18.5 ± 0.77	
Male/Female	12-13/ 17-19	--	23-26/ 32-35	--	18-19/ 11-13	--
African Americans/Caucasians	10-11/ 19-22	--	13-15/ 42-46	--	5-6/ 23-27	--

Values are means (SD) FFM = Fat Free Mass MV = Muscle Volume MQ = Muscle Quality

Values for 1 RM, MV, and Q are least square means ± SE 1 RM = Knee extension one repetition maximum

[1]Sample size variability was due to missing data for muscle phenotypes

Table 9. Physical characteristics for *PPP3R1* II homozygotes (n = 89-96) and *PPP3R1* D-allele carriers (n = 24-26) at baseline for all muscle phenotypes

	II Homozygotes (n = 89-96)[1]		D-Allele Carriers (n = 24-26)[1]	
	Baseline	**After ST**	**Baseline**	**After ST**
Age	65 (8)	--	62 (9)	--
Height (cm)	168 (9)	--	167 (6)	--
Weight (kg)	78.7 (15.1)	78.8 (15.3)	76.3(10.8)	76.9 (11.3)
Body Fat (%)	33.6 (7.7)	33.1 (7.6)	34.5 (7.4)	34.3 (7.4)
FFM (kg)	52.1 (11.5)	52.5 (11.5)	49.8(8.4)	50.4 (8.6)
1 RM (kg)	24 ± 0.8		27 ± 1.2	
MV (cm^3)	1460 ± 27		1490 ± 36	
MQ (kg/cm^3)*10^{-3}	16.6 ± 0.47		17.4 ± 0.64	
Male/Female	44-47/45-49	--	9-10/15-17	--
African Americans/Caucasians	16-18/73-79	--	12-14/12-13	--

Values are means (SD) FFM = Fat Free Mass MV = Muscle Volume MQ = Muscle Quality

Values for 1 RM, MV, and Q are least square means ± SE 1 RM = Knee extension one repetition maximum

[1]Sample size variability was due to missing data for muscle phenotypes

Table 10. Change in muscle strength with strength training for *IGF1* 192 homozygotes (n = 36), *IGF1* 192 heterozygotes (n = 62), and *IGF1* noncarriers of the 192 allele (n = 24)

	192 Homozygotes (n = 36)	192 Heterozygotes (n = 62)	Noncarriers of the 192 Allele (n = 24)
Age	62 (6)	65 (9)	64 (9)
Height (cm)	169 (9)	166 (8)	170 (9)
Weight (kg)	77.9 (14.0)	77.5 (14.1)	80.5 (15.4)
Baseline Body Fat (%)	33.9 (7.7)	33.9 (7.8)	33.3 (7.4)
Baseline FFM (kg)	51.6 (11.7)	50.9 (10.2)	53.8(11.7)
Baseline 1 RM (kg)	24 ± 1.1	26 ± 1.0	27 ± 1.3
Δ 1 RM (kg)	6.6 ± 0.81	7.4 ± 0.66	6.2 ± 0.97
Male/Female	16/20	28/34	12/12
African American/Caucasian	4/32	16/46	10/14

Values are means (SD)
Values for Δ 1 RM are least square means ± SE
FFM = Fat Free Mass
1 RM = Knee extension one repetition maximum

Table 11. Change in muscle strength with strength training for *IGFBP3* AA homozygotes (n = 32), *IGFBP3* AC heterozygotes (n = 58), and *IGFBP3* CC homozygotes (n = 32)

	AA Homozygotes (n = 32)	AC Heterozygotes (n = 58)	CC Homozygotes (n = 32)
Age	63 (10)	65 (8)	65 (7)
Height (cm)	166 (10)	167 (8)	170 (9)
Baseline Weight (kg)	78.5 (16.3)	77.4 (12.8)	79.4 (15.1)
Baseline Body Fat (%)	34.1 (7.4)	34.2 (8.4)	32.9 (6.5)
Baseline FFM (kg)	51.8 (12.5)	50.8 (9.9)	53.1 (11.2)
Baseline 1 RM (kg)	24 ± 1.1	24 ± 1.0	28 ± 1.4
Δ 1 RM (kg)	7.9 ± 0.78	6.6 ± 0.65	5.8 ± 0.96
Male/Female	13/19	24/34	19/13
African Americans/Caucasians	10/22	15/43	5/27

Values are means (SD)
Values for Δ 1 RM are least square means ± SE
FFM = Fat Free Mass
1 RM = Knee extension one repetition maximum

Table 12. Change in muscle strength with strength training for *PPP3R1* II homozygotes (n = 96) and *PPP3R1* D-allele carriers (n = 26)

	II Homozygotes (n = 96)	**D-Allele Carriers (n = 26)**
Age	65 (8)	62 (9)
Height (cm)	168 (9)	167 (6)
Baseline Weight (kg)	78.7 (15.1)	76.3 (10.8)
Baseline Body Fat (%)	33.6 (7.7)	34.5 (7.4)
Baseline FFM (kg)	52.1 (11.5)	49.8 (8.4)
Baseline 1 RM (kg)	24 ± 0.8	27 ± 1.2
Δ 1 RM (kg)	6.7 ± 0.54	6.8 ± 0.81
Male/Female	47/49	9/17
African Americans/Caucasians	17/79	13/13

Values are means (SD)
Values for Δ 1 RM are least square means ± SE
FFM = Fat Free Mass
1 RM = Knee extension one repetition maximum

Table 13. Change in muscle volume with strength training for *IGF1* 192 homozygotes (n = 35), *IGF1* 192 heterozygotes (n = 59), and *IGF1* noncarriers of the 192 allele (n = 26)

	192 Homozygotes (n = 35)	192 Heterozygotes (n = 59)	Noncarriers of the 192 Allele (n = 26)
Age	63 (6)	65 (9)	64 (9)
Height (cm)	168 (9)	167 (8)	169 (9)
Baseline Weight (kg)	77.7 (14.4)	78.5 (15.0)	80.2 (15.0)
Baseline Body Fat (%)	33.8 (7.7)	33.9 (7.9)	33.3 (7.4)
Baseline FFM (kg)	51.5 (12.0)	51.5 (10.7)	53.2 (11.4)
Baseline MV (cm^3)	1440 ± 36	1480 ± 29	1490 ± 39
Δ MV (cm^3)	110 ± 14	130 ± 11	120 ± 15
Male/Female	16/19	28/31	12/14
African American/Caucasian	4/31	16/43	12/14

Values are means (SD)
Values for Δ MV are least square means ± SE
FFM = Fat Free Mass
MV = Muscle Volume

Table 14. Change in muscle volume for *IGFBP3* AA homozygotes (n = 30), *IGFBP3* AC heterozygotes (n = 61), and *IGFBP3* CC homozygotes (n = 29)

	AA Homozygotes (n = 30)	AC Heterozygotes (n = 61)	CC Homozygotes (n = 29)
Age	64 (10)	65 (8)	65 (7)
Height (cm)	165 (9)	167 (8)	171 (8)
Baseline Weight (kg)	78.4 (16.4)	77.9 (13.9)	80.5 (14.8)
Baseline Body Fat (%)	34.1 (7.7)	34.1 (8.2)	33.0 (6.6)
Baseline FFM (kg)	51.6 (12.7)	51.1 (10.6)	53.7 (10.9)
Baseline MV (cm^3)	1470 ± 35	1450 ± 30	1500 ± 39
Δ MV (cm^3)	120 ± 13	120 ± 11	110 ± 15
Male/Female	12/18	26/35	18/11
African Americans/Caucasians	11/19	15/46	6/23

Values are means (SD)
Values for Δ MV are least square means ± SE
FFM = Fat Free Mass
MV = Muscle Volume

Table 15. Change in muscle volume with strength training for *PPP3R1* II homozygotes (n = 94) and *PPP3R1* D-allele carriers (n = 26)

	II Homozygotes (n = 94)	**D-Allele Carriers (n = 26)**
Age	64 (8)	63 (8)
Height (cm)	168 (9)	166 (6)
Baseline Weight (kg)	79.0 (15.6)	77.1 (10.9)
Baseline Body Fat (%)	33.6 (7.8)	34.6 (7.3)
Baseline FFM (kg)	52.3 (11.7)	50.3 (8.8)
Baseline MV (cm^3)	1460 ± 27	1490 ± 36
Δ MV (cm^3)	130 ± 10	100 ± 14
Male/Female	46/48	10/16
African Americans/Caucasians	18/76	14/12

Values are means (SD)
Values for Δ MV are least square means ± SE
FFM = Fat Free Mass
MV = Muscle Volume

Table 16. Change in muscle quality with strength training for *IGF1* 192 homozygotes (n = 32), *IGF1* 192 heterozygotes (n = 57), and *IGF1* noncarriers of the 192 allele (n = 24)

	192 Homozygotes (n = 32)	192 Heterozygotes (n = 57)	Noncarriers of the 192 Allele (n = 24)
Age	63 (6)	66 (9)	64 (9)
Height (cm)	168 (9)	167 (8)	170 (9)
Baseline Weight (kg)	78.3 (14.3)	77.9 (13.9)	80.5 (15.4)
Baseline Body Fat (%)	34.1 (8.0)	34.2 (7.9)	33.3 (7.4)
Baseline FFM (kg)	51.7 (12.1)	50.9 (10.0)	53.8 (11.7)
Baseline MQ (kg/cm^3)*10^{-3}	16.2 ± 0.63	17.3 ± 0.52	17.5 ± 0.67
Δ MQ (kg/cm^3)*10^{-3}	3.2 ± 0.48	3.2 ± 0.34	2.7 ± 0.52
Male/Female	15/17	26/31	12/12
African American/Caucasian	3/29	15/42	10/14

Values are means (SD)
Values for Δ MQ are least square means ± SE

FFM = Fat Free Mass
MQ = Muscle Quality

Table 17. Change in muscle quality with strength training for *IGFBP3* AA homozygotes (n = 29), *IGFBP3* AC heterozygotes (n = 55), and *IGFBP3* CC homozygotes (n = 29)

	AA Homozygotes (n = 29)	AC Heterozygotes (n = 55)	CC Homozygotes (n = 29)
Age	63 (10)	65 (8)	65 (7)
Height (cm)	165 (10)	167 (8)	170 (8)
Baseline Weight (kg)	78.2 (16.7)	77.8 (12.7)	80.5 (14.8)
Baseline Body Fat (%)	33.9 (7.7)	34.6 (8.4)	33.0 (6.6)
Baseline FFM (kg)	51.8 (12.9)	50.7 (9.9)	53.7 (10.9)
Baseline MQ (kg/cm^3)*10^{-3}	16.1 ± 0.61	16.5 ± 0.55	18.5 ± 0.77
Δ MQ(kg/cm^3)*10^{-3}	2.9 ± 0.41	3.2 ± 0.35	3.0 ± 0.44
Male/Female	12/17	23/32	18/11
African Americans/Caucasians	10/19	13/42	5/24

Values are means (SD)
Values for Δ MQ are least square means ± SE
FFM = Fat Free Mass
MQ = Muscle Quality

Table 18. Change in muscle quality with strength training for *PPP3R1* II homozygotes (n = 89) and *PPP3R1* D-allele carriers (n = 24) at baseline for muscle quality

	II Homozygotes (n = 89)	**D-Allele Carriers (n = 24)**
Age	65 (8)	63 (8)
Height (cm)	168 (9)	166 (6)
Baseline Weight (kg)	79.0 (15.1)	76.9 (11.0)
Baseline Body Fat (%)	33.8 (7.8)	34.8 (7.5)
Baseline FFM (kg)	52.2 (11.5)	50.0 (8.6)
Baseline MQ (kg/cm^3)*10^{-3}	16.6 ± 0.47	17.4 ± 0.64
Δ MQ (kg/cm^3)*10^{-3}	2.9 ± 0.31	3.1 ± 0.44
Male/Female	44/45	9/15
African Americans/Caucasians	16/73	12/12

Values are means (SD)
Values for Δ MQ are least square means ± SE
FFM = Fat Free Mass
MQ = Muscle Quality

Table 19. Change in muscle strength with strength training (ST) for *PPP3R1* by *IGF1* genotype groups

	***PPP3R1* II and *IGF1* 192/192 (n = 28)**	***PPP3R1* D-allele carriers and *IGF1* 192/192 (n = 8)**	***PPP3R1* II and *IGF1* 192/- (n = 49)**	***PPP3R1* D-allele carriers and *IGF1* 192/- (n = 13)**	***PPP3R1* II and *IGF1* -/- (n = 19)**	***PPP3R1* D-allele carriers and *IGF1* -/- (n = 5)**
Age	62 (6)	61 (9)	66 (9)	63 (9)	65 (9)	62 (8)
Height (cm)	169 (9)	168 (7)	166 (9)	167 (7)	171 (10)	164 (4)
Baseline Weight (kg)	77.9 (14.6)	78.0 (12.8)	78.1 (14.8)	74.9 (10.8)	81.3 (16.9)	77.4 (8.4)
Baseline Body Fat (%)	35.1 (7.4)	29.7 (7.6)	33.3 (7.9)	36.5 (7.3)	32.4 (7.9)	36.9 (4.1)
Baseline FFM (kg)	50.8 (12.8)	54.2 (6.1)	51.8 (10.4)	47.5 (9.4)	55.1 (12.5)	48.9 (7.0)
Baseline 1 RM (kg)	22 ± 1.3	29 ± 2.2	25 ± 1.0	27 ± 1.6	26 ± 1.4	25 ± 2.7
Δ 1 RM (kg)	6.9 ± 0.81	6.2 ± 1.30	8.4 ± 0.66*	6.4 ± 1.06	4.7 ± 0.89	7.7 ± 1.66
Male/Female	12/16	4/4	24/25	4/9	11/8	1/4
African Americans/Caucasians	2/26	2/6	9/40	7/6	6/13	4/1

Values are means (SD)
Values for Δ 1 RM are least square means ± SE
FFM = Fat Free Mass
1 RM = Knee extension one repetition maximum
192/192 = *IGF1* 192 Homozygotes
192/- = *IGF1* 192 Heterozygotes
-/- = *IGF1* non-carriers if the 192 allele
* Significantly greater than *PPP3R1* II and *IGF1* -/-, $P < 0.05$

Table 20. Change in muscle strength with strength training (ST) for *IGF1* by *IGFBP3* genotype groups

	IGFBP3 **AA and** ***IGF1*** **192/192 (n = 9)**	***IGFBP3*** **AC and** ***IGF1*** **192/192 (n= 19)**	***IGFBP3*** **CC and** ***IGF1*** **192/192 (n = 8)**	***IGFBP3*** **AA and** ***IGF1*** **192/- (n = 19)**	***IGFBP3*** **AC and** ***IGF1*** **192/- (n = 26)**	***IGFBP3*** **CC and** ***IGF1*** **192/- (n = 17)**	***IGFBP3*** **AA and** ***IGF1*** **-/- (n = 4)**	***IGFBP3*** **AC and** ***IGF1*** **-/- (n = 13)**	***IGFBP3*** **CC and** ***IGF1*** **-/- (n= 7)**
Age	60 (7)	62 (6)	62 (8)	64 (11)	65 (8)	67 (7)	59 (11)	67 (10)	62 (6)
Height (cm)	169 (12)	167 (8)	172 (5)	163 (8)	167 (8)	169 (10)	170 (10)	169 (9)	170 (11)
Baseline Weight (kg)	81.1 (19.4)	75.9 (12.6)	79.0 (10.9)	76.7 (15.7)	77.7 (12.9)	78.0 (14.8)	80.9 (14.2)	78.9 (13.4)	83.2 (20.9)
Baseline Body Fat (%)	32.2 (8.4)	35.5 (7.8)	32.2(6.3)	34.8 (7.0)	34.1(9.4)	32.6 (6.1)	35.0 (8.6)	32.3 (7.1)	34.3 (8.2)
Baseline FFM (kg)	55.1(15.0)	49.1(11.1)	53.4(8.3)	49.9(11.5)	50.7(8.9)	52.1(11.1)	52.9(13.1)	53.3(10.1)	55.2(15.20
Baseline 1 RM (kg)	24 ± 2.0	24 ± 1.6	30 ± 2.8	23 ± 1.4	25 ± 1.4	30 ± 2.3	18 ± 3.5	25 ± 1.7	29 ± 2.5
Δ 1 RM (kg)	7.2 ± 1.54	6.7 ± 1.19	7.9±2.16	8.8 ± 0.96	7.5±0.95	6.8 ± 1.68	8.6 ± 2.39	5.9 ± 1.16	6.2 ± 1.75
Male/Female	4/5	7/12	5/3	7/12	11/15	10/7	2/2	6/7	4/3
African Americans/Caucasians	1/8	3/16	0/8	8/11	7/19	1/16	1/3	5/8	4/3

Values are means (SD)
Values for Δ 1 RM are least square means ± SE
FFM = Fat Free Mass
1 RM = Knee extension one repetition maximum

AA = *IGFBP3* AA Homozygotes
AC = *IGFBP3* AC Heterozygotes
CC = *IGFBP3* CC Homozygotes

192/192 = *IGF1* 192 Homozygotes
192/- = *IGF1* 192 Heterozygotes
-/- = *IGF1* non-carriers of the 192 allele

Table 21. Change in muscle strength with strength training (ST) for *PPP3R1* by *IGFBP3* genotype groups

	***PPP3R1* II and *IGFBP3* AA (n = 25)**	***PPP3R1* D-allele carriers and *IGFBP3* AA (n = 10)**	***PPP3R1* II and *IGFBP3* AC (n = 43)**	***PPP3R1* D-allele carriers and *IGFBP3* AC (n = 12)**	***PPP3R1* II and *IGFBP3* CC (n = 28)**	***PPP3R1* D-allele carriers and *IGFBP3 CC* (n = 4)**
Age	65 (10)	58 (6)	64 (7)	65 (10)	65 (8)	64 (6)
Height (cm)	166 (11)	164 (6)	167 (8)	170 (7)	170 (9)	165 (3)
Baseline Weight (kg)	79.7 (16.7)	74.4 (14.6)	77.1 (13.7)	79.2 (8.2)	80.4 (15.9)	72.5 (4.3)
Baseline Body Fat (%)	33.3 (7.4)	33.9 (8.0)	34.6 (8.8)	34.5 (7.1)	32.5 (6.2)	35.8 (8.7)
Baseline FFM (kg)	53.3 (13.4)	48.9 (10.1)	50.2 (10.3)	51.7 (6.8)	54.1 (11.4)	46.4 (8.3)
Baseline 1 RM (kg)	24 ± 1.5	23 ± 1.8	23 ± 1.1	26 ± 1.6	26 ± 1.4	32 ± 2.8
Δ 1 RM (kg)	8.3 ± 1.03	7.5 ± 1.46	6.6 ± 0.74	6.8 ± 1.11	6.0 ± 1.07	7.6 ± 2.02
Male/Female	12/13	3/7	17/26	5/7	18/10	1/3
African Americans/Caucasians	5/20	6/4	8/35	6/6	4/24	1/3

Values are means (SD)
Values for Δ 1 RM are least square means ± SE
FFM = Fat Free Mass
1 RM = Knee extension one repetition maximum
AA = *IGFBP3* AA Homozygotes
AC = *IGFBP3* AC Heterozygotes
CC = *IGFBP3* CC Homozygotes

Table 22. Change in muscle volume with strength training (ST) for *PPP3R1* by *IGF1* genotype groups

	***PPP3R1* II and *IGF1* 192/192** (n = 28)	***PPP3R1* D-allele carriers and *IGF1* 192/192** (n = 7)	***PPP3R1* II and *IGF1* 192/-** (n = 46)	***PPP3R1* D-allele carriers and *IGF1* 192/-** (n = 13)	***PPP3R1* II and *IGF1* -/-** (n = 20)	***PPP3R1* D-allele carriers and *IGF1* -/-** (n = 6)
Age	62 (5)	65 (8)	65 (9)	63 (9)	65 (9)	61 (7)
Height (cm)	168 (9)	166 (7)	167 (9)	167 (7)	171 (10)	164 (4)
Baseline Weight (kg)	76.5 (14.7)	82.2 (12.9)	79.5 (15.9)	74.9 (10.8)	81.4 (16.4)	76.0 (8.2)
Baseline Body Fat (%)	35.0 (7.5)	29.3 (7.7)	33.2 (8.0)	36.5 (7.3)	32.8 (8.0)	36.7 (3.7)
Baseline FFM (kg)	50.0 (12.7)	57.4 (5.4)	52.7 (10.8)	47.5 (9.4)	54.8 (12.2)	48.2 (6.5)
Baseline MV (cm^3)	1450 ± 48	1500 ± 79	1490 ± 37	1510 ± 56	1460 ± 45	1450 ± 99
Δ MV (cm^3)	90 ± 24	60 ± 30	130 ± 14	120 ± 21	140 ± 17	100 ± 34
Male/Female	11/17	5/2	24/22	4/9	11/9	1/5
African Americans/Caucasians	2/26	2/5	9/37	7/6	7/13	5/1

Values are means (SD)
Values for Δ MV are least square means ± SE
FFM = Fat Free Mass
MV = Muscle Volume

192/192 = *IGF1* 192 Homozygotes
192/- = *IGF1* 192 Heterozygotes
-/- = *IGF1* non-carriers of the 192 allele

Table 23. Change in muscle volume with strength training (ST) for *IGF1* by *IGFBP3* genotype groups

	***IGFBP3* AA and *IGF1* 192/192 (n = 7)**	***IGFBP3* AC and *IGF1* 192/192 (n= 21)**	***IGFBP3* CC and *IGF1* 192/192 (n = 7)**	***IGFBP3* AA and *IGF1* 192/- (n = 19)**	***IGFBP3* AC and *IGF1* 192/- (n = 26)**	***IGFBP3* CC and *IGF1* 192/- (n = 14)**	***IGFBP3* AA and *IGF1* -/- (n = 5)**	***IGFBP3* AC and *IGF1* -/- (n = 13)**	***IGFBP3* CC and *IGF1* -/- (n= 8)**
Age	62 (8)	63 (5)	64 (7)	64 (11)	65 (8)	66 (7)	61 (10)	67 (10)	62 (6)
Height (cm)	168 (13)	167 (8)	171 (5)	163 (8)	167 (8)	171 (8)	168 (10)	169 (9)	169 (10)
Baseline Weight (kg)	81.2(21.1)	75.4(13.1)	80.9(10.3)	75.6(16.0)	80.0(14.8)	79.7(14.3)	81.2(12.3)	78.9(13.4)	81.5(20.0)
Baseline Body Fat (%)	31.6 (9.6)	35.2 (7.5)	31.9 (6.7)	34.3 (6.8)	34.2 (9.4)	32.7 (6.4)	36.2 (8.0)	32.3 (7.1)	34.4 (7.7)
Baseline FFM (kg)	55.6(16.4)	49.0(11.3)	54.8 (7.9)	49.6(11.6)	52.1(10.3)	53.0(10.5)	52.0(11.5)	53.3(10.1)	53.9(14.6)
Baseline MV (cm^3)	1450 ± 70	1390 ± 48	1560 ± 85	1480 ± 44	1440 ± 42	1570 ± 69	1430 ± 86	1500 ± 53	1490 ± 69
Δ MV (cm^3)	60 ± 29	80 ± 22	90 ± 38	150 ±16	110 ± 16	90 ± 28	130 ± 32	130 ± 20	110 ± 26
Male/Female	3/4	8/13	5/2	7/12	12/14	9/5	2/3	6/7	4/4
African Americans/Caucasians	1/6	3/18	0/7	8/11	7/19	1/13	2/3	5/8	5/3

Values are means (SD)
Values for Δ MV are least square means ± SE
FFM = Fat Free Mass
MV = Muscle volume

AA = *IGFBP3* AA Homozygotes
AC = *IGFBP3* AC Heterozygotes
CC = *IGFBP3* CC Homozygotes

192/192 = *IGF1* 192 Homozygotes
192/- = *IGF1* 192 Heterozygotes
-/- = *IGF1* non-carriers of the 192 allele

Table 24. Change in muscle volume with strength training (ST) for *PPP3R1* by *IGFBP3* genotype groups

	***PPP3R1* II and *IGFBP3* AA (n = 21)**	***PPP3R1* D-allele carriers and *IGFBP3* AA (n = 9)**	***PPP3R1* II and *IGFBP3* AC (n = 49)**	***PPP3R1* D-allele carriers and *IGFBP3* AC (n = 12)**	***PPP3R1* II and *IGFBP3* CC (n = 24)**	***PPP3R1* D-allele carriers and *IGFBP3* CC (n = 5)**
Age	66 (10)	59 (6)	64 (7)	67 (9)	64 (7)	62 (6)
Height (cm)	166 (11)	164 (6)	167 (8)	169 (7)	172 (8)	165 (3)
Baseline Weight (kg)	79.7 (17.1)	75.2 (15.2)	77.1 (15.0)	80.8 (8.2)	82.3 (15.6)	71.8 (4.0)
Baseline Body Fat (%)	34.2 (7.5)	33.8 (8.5)	34.0 (8.5)	34.7 (6.9)	32.4 (6.5)	35.7 (7.5)
Baseline FFM (kg)	52.6 (13.6)	49.5 (10.6)	50.7 (11.2)	52.7 (7.7)	55.3 (10.9)	46.0 (7.3)
Baseline MV (cm^3)	1490 ± 45	1450 ± 61	1430 ± 34	1450 ± 53	1470 ± 47	1580 ± 79
Δ MV(cm^3)	120 ± 16	130 ± 23	140 ± 12	90 ± 20	130 ± 16	100 ± 30
Male/Female	9/12	3/6	20/29	6/6	17/7	¼
African Americans/Caucasians	5/16	6/3	9/40	6/6	4/20	2/3

Values are means (SD)
Values for Δ MV are least square means ± SE
FFM = Fat Free Mass
MV= Muscle Volume

AA = *IGFBP3* AA Homozygotes
AC = *IGFBP3* AC Heterozygotes
CC = *IGFBP3* CC Homozygotes

Table 25. Change in muscle quality with strength training (ST) for *PPP3R1* by *IGF1* genotype groups

	***PPP3R1* II and *IGF1* 192/192** (n = 26)	***PPP3R1* D-allele carriers and *IGF1* 192/192** (n = 6)	***PPP3R1* II and *IGF1* 192/-** (n = 44)	***PPP3R1* D-allele carriers and *IGF1* 192/-** (n = 13)	***PPP3R1* II and *IGF1* -/-** (n = 19)	***PPP3R1* D-allele carriers and *IGF1* -/-** (n = 5)
Age	62 (6)	65 (8)	66 (8)	63 (9)	65 (8)	62 (8)
Height (cm)	168 (9)	167 (7)	166 (9)	167 (7)	171 (10)	164 (4)
Weight (kg)	77.7 (14.6)	81.0 (13.7)	78.8 (14.7)	74.9 (10.8)	81.3 (16.9)	77.4 (8.4)
Body Fat (%)	35.2 (7.7)	29.4 (8.4)	33.5 (8.0)	36.5 (7.3)	32.4 (7.9)	36.9 (4.1)
FFM (kg)	50.6 (13.0)	56.3 (4.9)	51.9 (10.1)	47.5 (9.4)	55.1 (12.5)	48.9 (7.0)
Baseline MQ (kg/cm^3)*10^{-3}	15.7 ± 0.68	17.3 ± 1.21	17.0 ± 0.57	17.6 ± 0.85	17.2 ± 0.73	17.4 ± 1.35
Δ MQ (kg/cm^3)*10^{-3}	3.3 ± 0.45	3.1 ± 0.80	3.7 ± 0.37*	2.7 ± 0.53	1.8 ± 0.48	3.6 ± 0.88
Male/Female	11/15	4/2	22/22	4/9	11/8	1/4
African Americans/Caucasians	2/24	1/5	8/36	7/6	6/13	4/1

Values are means (SD)
Values for Δ MV are least square means ± SE
FFM = Fat Free Mass
MQ = Muscle Quality
192/192 = *IGF1* 192 Homozygotes
192/- = *IGF1* 192 Heterozygotes
-/- = *IGF1* non-carriers of the 192 allele
* Significantly greater than *PPP3R1* II and *IGF1* -/-, $P < 0.05$

Table 26. Change in muscle quality with strength training (ST) for *IGF1* by *IGFBP3* genotype groups

	IGFBP3 **AA and** ***IGF1*** **192/192 (n = 7)**	***IGFBP3*** **AC and** ***IGF1*** **192/192 (n=18)**	***IGFBP3*** **CC and** ***IGF1*** **192/192 (n = 7)**	***IGFBP3*** **AA and** ***IGF1*** **192/- (n = 18)**	***IGFBP3*** **AC and** ***IGF1*** **192/- (n = 24)**	***IGFBP3*** **CC and** ***IGF1*** **192/- (n = 15)**	***IGFBP3*** **AA and** ***IGF1*** **-/- (n =4)**	***IGFBP3*** **AC and** ***IGF1*** **-/- (n = 13)**	***IGFBP3*** **CC and** ***IGF1*** **-/- (n= 7)**
Age	62 (8)	63 (5)	64 (7)	65 (11)	66 (8)	66 (2)	59 (11)	67 (10)	62 (60
Height (cm)	168 (13)	167 (8)	171 (5)	163 (8)	167 (8)	170 (8)	170 (10)	169 (9)	170 (11)
Baseline Weight (kg)	81.2(21.1)	76.2(12.9)	80.9(10.3)	76.4(16.1)	78.4(12.6)	79.0(14.1)	80.9(14.2)	78.9(13.4)	83.2(20.9)
Baseline Body Fat (%)	31.6 (9.6)	36.0 (7.7)	31.9 (6.7)	34.5 (7.0)	34.8 (9.5)	32.8 (6.2)	35.0 (8.6)	32.3 (7.1)	34.3 (8.3)
Baseline FFM (kg)	55.6(16.4)	48.9(11.4)	54.8 (7.9)	50.0(11.8)	50.6 (8.6)	52.5(10.3)	52.9(13.1)	53.3(10.1)	55.2(15.2)
Baseline MQ $(kg/cm^3)*10^{-3}$	16.4 ± 1.19	16.0 ± 1.04	18.2 ± 1.58	15.7 ± 0.78	17.3 ± 0.79	18.9 ± 1.27	14.2 ± 1.94	16.8± 0.94	19.4 ± 1.37
Δ MQ $(kg/cm^3)*10^{-3}$	3.5 ± 0.85	2.6 ± 0.77	4.5 ± 1.20	2.8 ± 0.51	3.7 ± 0.53	3.9 ± 0.88	3.7 ± 1.26	2.7 ± 0.61	3.7 ± 0.92
Male/Female	3/4	7/11	5/2	7/11	10/14	9/6	2/2	6/7	4/3
African Americans/Caucasians	1/6	2/16	0/7	8/10	6/18	1/14	1/3	5/8	4/3

Values are means (SD)
Values for Δ MQ are least square means ± SE
FFM = Fat Free Mass
allele
AA = *IGFBP3* AA Homozygotes
AC = *IGFBP3* AC Heterozygotes
CC = *IGFBP3* CC Homozygotes
MQ = Muscle Quality
192/192 = *IGF1* 192 Homozygotes
192/- = *IGF1* 192 Heterozygotes
-/- = *IGF1* non-carriers of the 192

Table 27. Change in muscle quality with strength training (ST) for *PPP3R1* by *IGFBP3* genotype groups

	***PPP3R1* II and *IGFBP3* AA (n = 20)**	***PPP3R1* D-allele carriers and *IGFBP3* AA (n = 9)**	***PPP3R1* II and *IGFBP3* AC (n = 44)**	***PPP3R1* D-allele carriers and *IGFBP3* AC (n = 11)**	***PPP3R1* II and *IGFBP3* CC (n = 25)**	***PPP3R1* D-allele carriers and *IGFBP3* CC (n = 4)**
Age	66 (11)	59 (6)	65 (7)	67 (9)	65 (7)	64 (6)
Height (cm)	166 (11)	164 (6)	167 (9)	169 (7)	171 (9)	165 (3)
Baseline Weight (kg)	79.6 (17.5)	75.2 (15.2)	77.3 (13.6)	80.0 (8.1)	81.7 (15.5)	72.5 (4.3)
Baseline Body Fat (%)	33.9 (7.5)	33.8 (8.5)	34.4 (8.8)	35.3 (6.9)	32.5 (6.4)	35.8 (8.7)
Baseline FFM (kg)	52.8 (13.9)	49.5 (10.6)	50.5 (10.5)	51.7 (7.2)	54.9 (10.9)	46.4 (8.3)
Baseline MQ (kg/cm^3)*10^{-3}	15.9 ± 0.83	15.3 ± 1.23	16.1 ± 0.62	17.4 ± 0.95	18.0 ± 0.81	19.8 ± 1.53
Δ MQ (kg/cm^3)*10^{-3}	3.3± 0.52	2.4 ± 0.75	3.0 ± 0.39	3.2 ± 0.61	2.9 ± 0.53	4.6 ± 0.98
Male/Female	9/11	3/6	18/26	5/6	17/8	1/3
African Americans/Caucasians	4/16	6/3	8/36	5/6	4/21	1/3

Values are means (SD)
Values for Δ MQ are least square means ± SE
FFM = Fat Free Mass
MQ = Muscle Quality
AA = *IGFBP3* AA Homozygotes
AC = *IGFBP3* AC Heterozygotes
CC = *IGFBP3* CC Homozygotes

Figure 5 Baseline Muscle Strength for Race by *IGFBP3* Genotype Groups

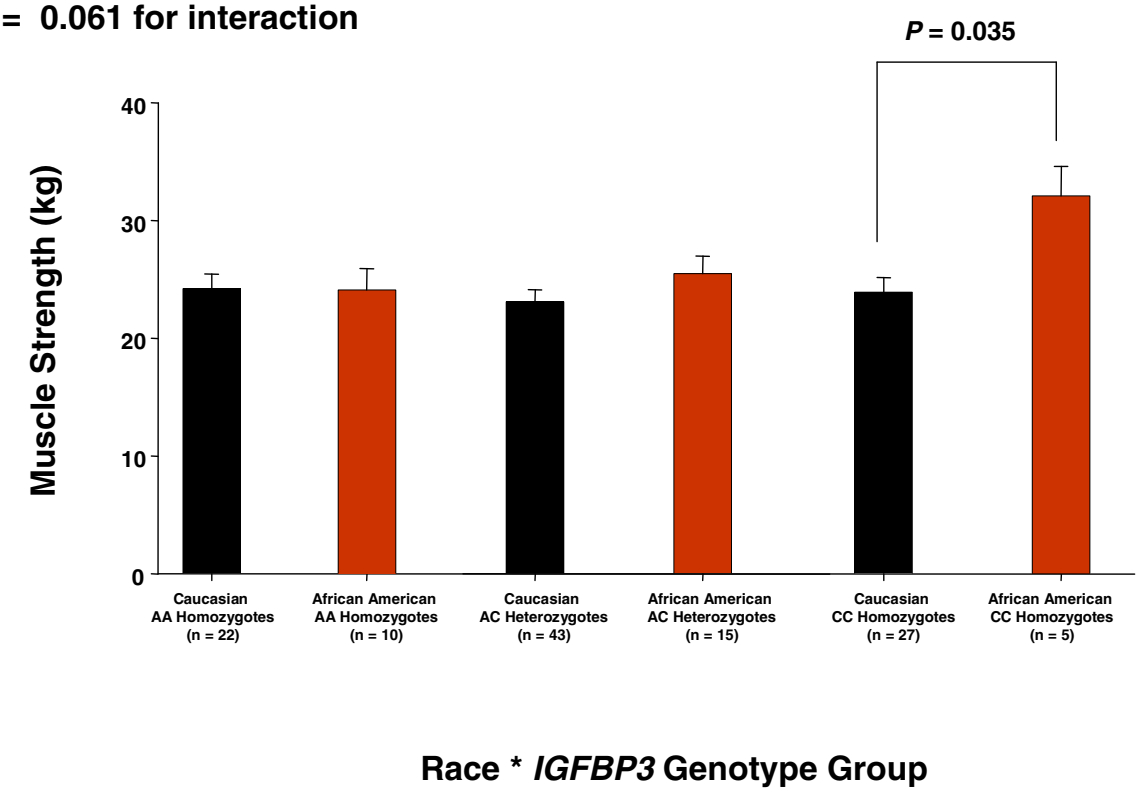


Figure 6 Baseline Muscle Quality for Race by *IGFBP3* Genotype Groups

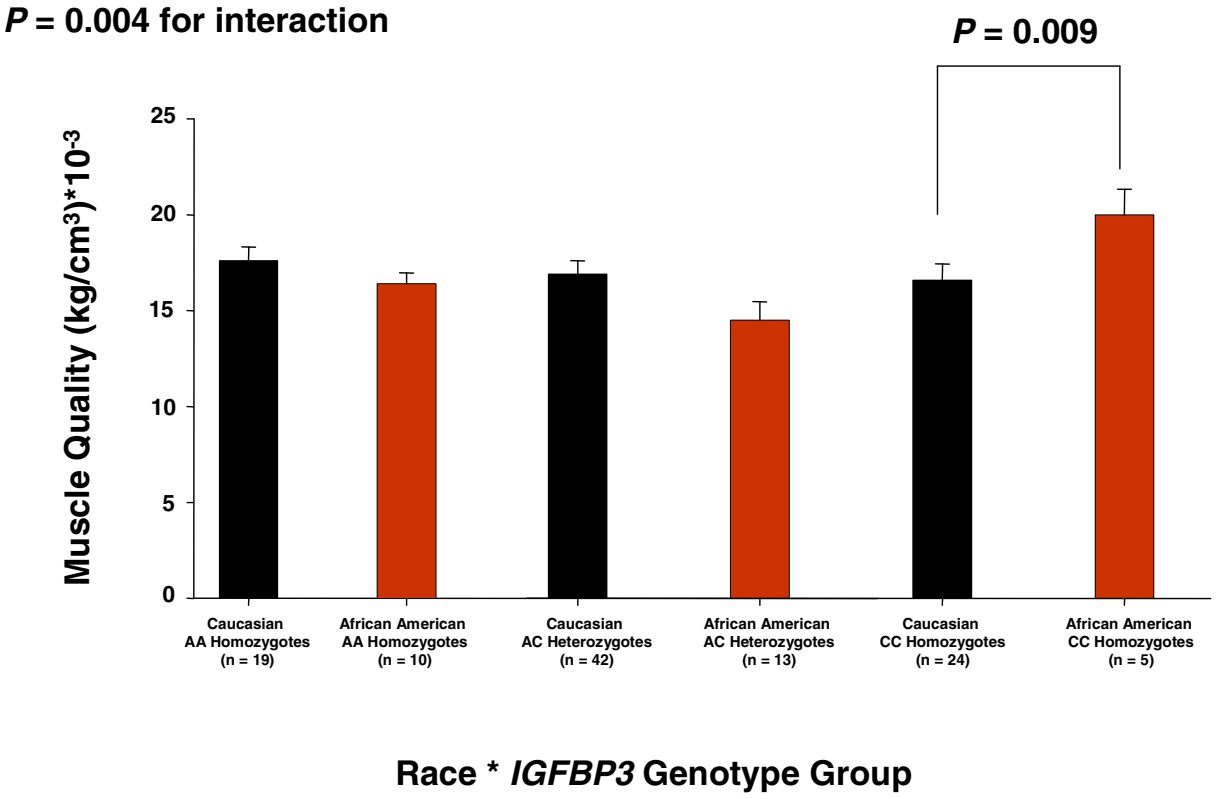


Figure 7 Percent Change in Muscle Strength with Strength Training by Race and Insulin-like Growth Factor Binding Protein 3 (*IGFBP3*) Genotype Group

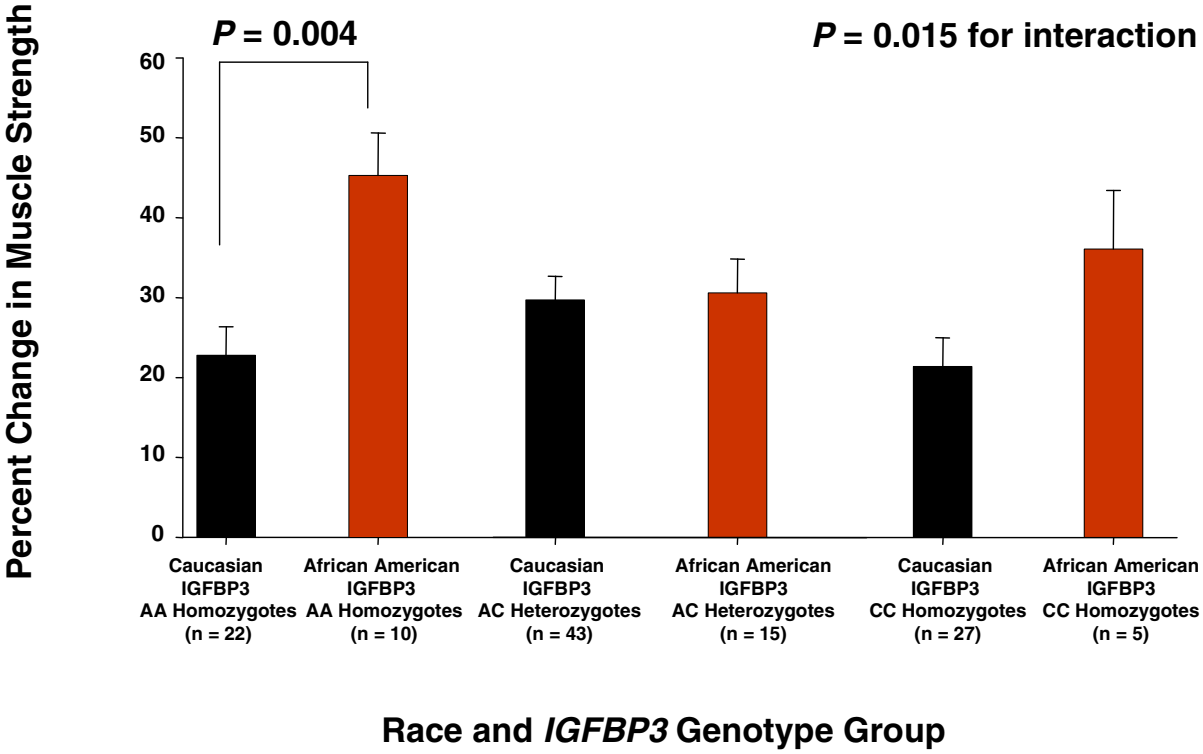


Figure 8 Relative Change in Muscle Quality by Race and Insulin-like Growth Factor Binding Protein 3 (IGFBP3) Genotype Group

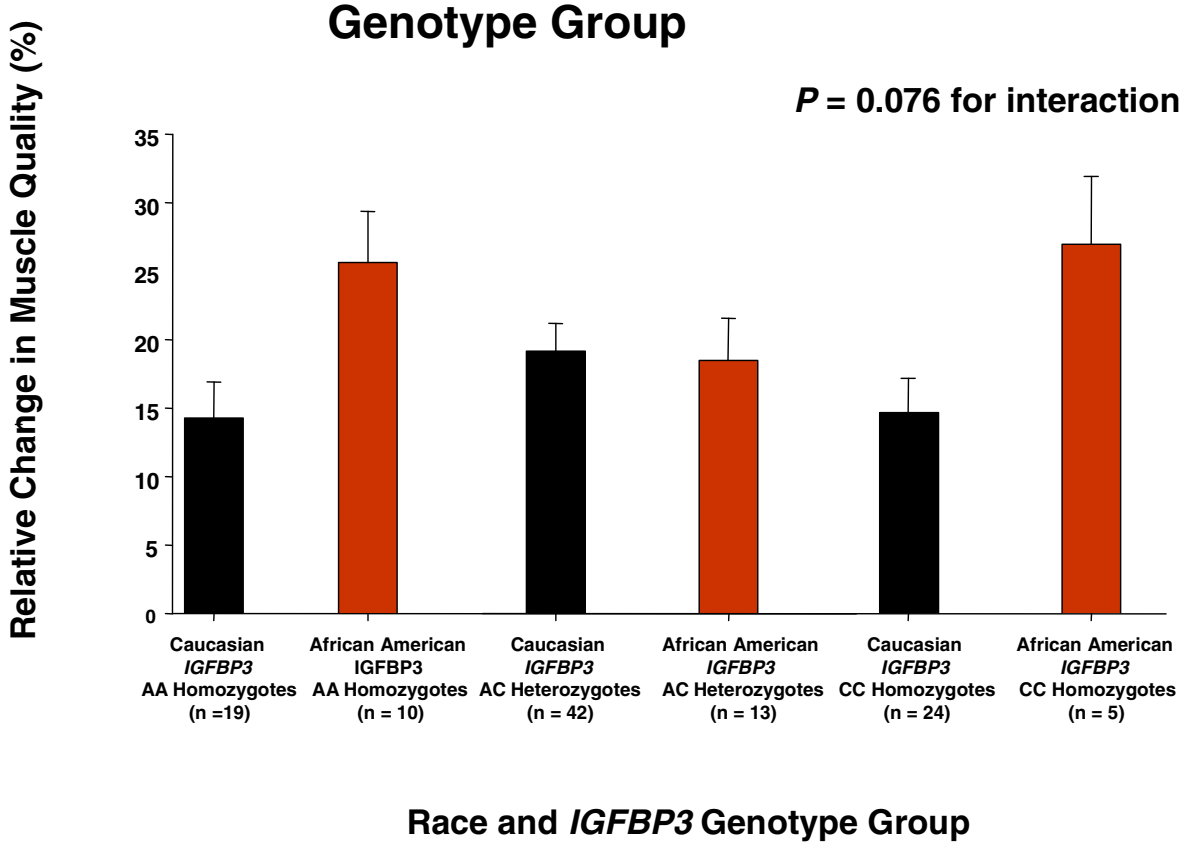


Figure 9 Change in Muscle Volume with Strength Training for Insulin-like Growth Factor 1 (*IGF1*) Genotype Groups

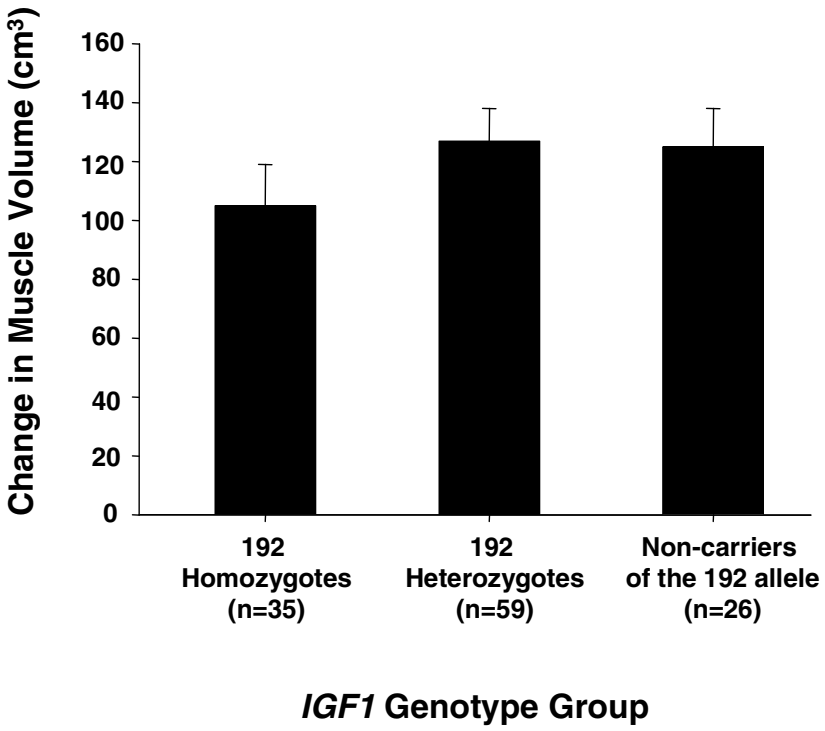


Figure 10 Change in Muscle Volume with Strength Training for Insulin-like Growth Factor Binding Protein 3 (*IGFBP3)* Genotype Groups

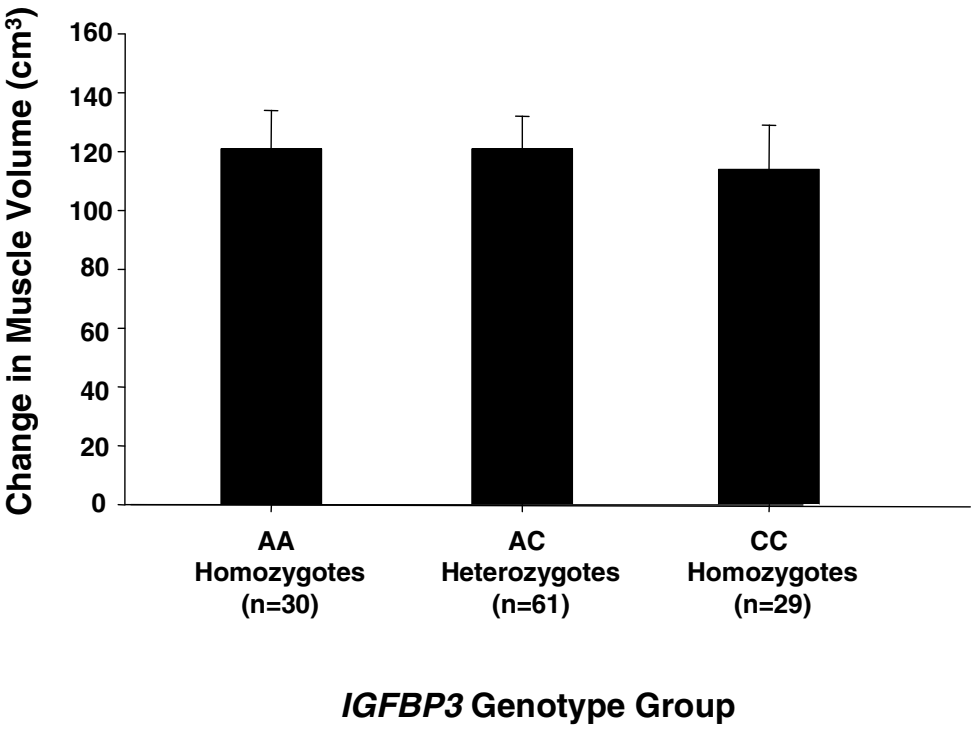
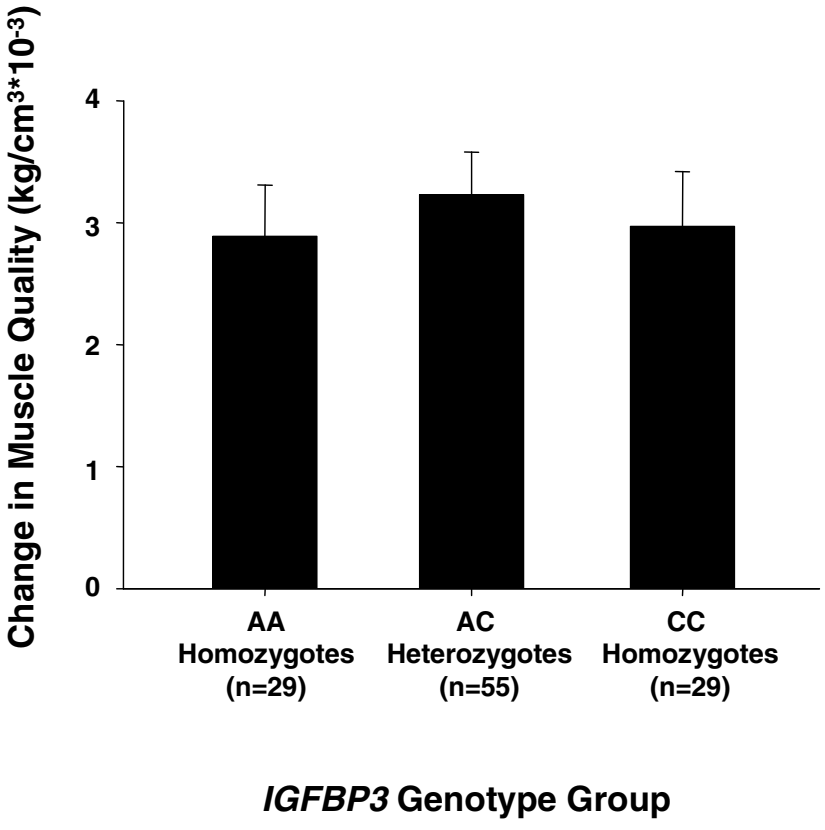


Figure 11 Change in Muscle Quality with Strength Training for Insulin-like Growth Factor Binding Protein 3 (*IGFBP3*) Genotype Group



APPENDIX J

Models and Results for Calculating Percent Variability

APPENDIX J: MODELS AND RESULTS FOR CALCULATING PERCENT VARIABILITY

Model for calculating percent variability for change in muscle strength with strength training attributable to genotypes:

RMTLPREKG is baseline muscle strength

rmdkg is change in muscle strength with strength training

igf1 is subject's insulin-like growth factor 1 genotype

igfbp3 is subject's insulin-like growth factor binding protein 3 genotype

calbb is subject's calcineurin B (*PPP3R1*) genotype

bwpre is subject's baseline body weight

bmipre is subject's baseline body mass index

hrt_sex is subject's hormone replacement status

```
proc means data=one n css;
var rmdkg;
quit;

proc mixed data=one method=type3 covtest boxplot;
class race hrt_sex igf1 igfbp3 calbb;
model rmdkg=rmtlprekg
                    race
                    height
                    igf1
                    igfbp3
                    calbb
                    age
                    bwpre
                    hrt_sex
                    bmipre
                    igfbp3*race
                    calbb*igf1
                    / ddfm=sat solution residuals;

lsmeans igf1 igfbp3 calbb igfbp3*race igf1*calbb/pdiff at means;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;
```

Results:

Type 3 Analysis of Variance

Source	DF	Sum of Squares	Mean Square	Error DF	F Value	Pr > F
RMTLPREKG	1	3.614304	3.614304	104	0.31	0.5789
Race	1	99.966343	99.966343	104	8.57	0.0042
Height	1	8.642697	8.642697	104	0.74	0.3912
IGF1	2	15.800191	7.900095	104	0.68	0.5101
IGFBP3	2	40.699811	20.349906	104	1.75	0.179
Calbb	1	0.199613	0.199613	104	0.02	0.8961
Age	1	16.368561	16.368561	104	1.40	0.2388
bwpre	1	1.644461	1.644461	104	0.14	0.7080
hrt_sex	2	100.878464	50.439232	104	4.33	0.0157
bmipre	1	1.967392	1.967392	104	0.17	0.6821
Race*IGFBP3	2	56.527655	28.263828	104	2.42	0.0935
IGF1*Calbb	2	63.061851	31.530925	104	2.70	0.0716
Residual	104	1212.521814	11.658864	.	.	.

Covariance Parameter Estimates

Cov Parm	Estimate	Standard Error	Z Value	Pr Z
Residual	11.6589	1.6168	7.21	<.0001

Fit Statistics

-2 Res Log Likelihood	622.0
AIC (smaller is better)	624.0
AICC (smaller is better)	624.1
BIC (smaller is better)	626.7

Solution for Fixed Effects

Effect	hrt_sex	Race	IGF1	IGFBP3	Calbb	Estimate	Standard Error	t Value	Pr > |t|[1]
Intercept						-23.2374	43.4170	-0.54	0.5936
RMTLPREKG						-0.03551	0.06378	-0.56	0.5789
Race		1				-1.6713	1.8924	-0.88	0.3792
Race		2				0	.	.	.
Height						0.2197	0.2552	0.86	0.3912
IGF1			1			-1.5005	2.0798	-0.72	0.4723
IGF1			2			-1.3730	1.9577	-0.70	0.4847
IGF1			3			0	.	.	.
IGFBP3				11		3.8068	2.1130	1.80	0.0745
IGFBP3				12		0.5859	1.8987	0.31	0.7583
IGFBP3				22		0	.	.	.
Calbb					11	-3.0272	1.8235	-1.66	0.0999
Calbb					12	0	.	.	.
Age						-0.05539	0.04675	-1.18	0.2388
bwpre						-0.1025	0.2730	-0.38	0.7080
hrt_sex	FN					-3.3289	1.1443	-2.91	0.0044
hrt_sex	FY					-3.0686	1.4215	-2.16	0.0332
hrt_sex	MN					0	.	.	.
bmipre						0.3096	0.7536	0.41	0.6821
Race*IGFBP3		1		11		-3.4118	2.3587	-1.45	0.1511
Race*IGFBP3		1		12		0.4335	2.0994	0.21	0.8368
Race*IGFBP3		1		22		0	.	.	.
Race*IGFBP3		2		11		0	.	.	.
Race*IGFBP3		2		12		0	.	.	.
Race*IGFBP3		2		22		0	.	.	.
IGF1*Calbb			1		11	3.7116	2.3102	1.61	0.1112
IGF1*Calbb			1		12	0	.	.	.
IGF1*Calbb			2		11	5.0233	2.1604	2.33	0.0220
IGF1*Calbb			2		12	0	.	.	.
IGF1*Calbb			3		11	0	.	.	.
IGF1*Calbb			3		12	0	.	.	.

[1]with 104 DF

Model for calculating percent variability for change in muscle volume with strength training attributable to genotypes:

mvtb is baseline muscle volume

mvca is change in muscle volume with strength training

igf1 is subject's insulin-like growth factor 1 genotype

igfbp3 is subject's insulin-like growth factor binding protein 3 genotype

calbb is subject's calcineurin B (*PPP3R1*) genotype

bwpre is subject's baseline body weight

bmipre is subject's baseline body mass index

hrt_sex is subject's hormone replacement status

```
proc means data=one n css;
var mvca;
quit;


proc mixed data=one method=type3 covtest boxplot;
class race hrt_sex igf1 igfbp3 calbb;
model mvca=mvtb
                        age
                        race
                        hrt_sex
                        bmipre
                        height
                        bwpre
                        igf1
                        igfbp3
                        calbb

                        /ddfm=sat solution residuals;

lsmeans igf1 igfbp3 calbb/pdiff at means;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;
```

Results:

Type 3 Analysis of Variance

Source	DF	Sum of Squares	Mean Square	Error DF	F Value	Pr > F
MVTB	1	11072	11072	106	2.77	0.0989
IGF1	2	8332.125558	4166.062779	106	1.04	0.3561
IGFBP3	2	725.618650	362.809325	106	0.09	0.9133
CalbB	1	14365	14365	106	3.60	0.0607
Age	1	4566.843505	4566.843505	106	1.14	0.2874
Race	1	4228.496532	4228.496532	106	1.06	0.3059
hrt_sex	2	13588	6794.016230	106	1.70	0.1875
bmipre	1	75.755552	75.755552	106	0.02	0.8907
Height	1	60.254168	60.254168	106	0.02	0.9025
bwpre	1	127.297106	127.297106	106	0.03	0.8587
Residual	106	423504	3995.322087	.	.	.

Covariance Parameter Estimates

Cov Parm	Estimate	Standard Error	Z Value	Pr Z
Residual	3995.32	548.80	7.28	<.0001

Fit Statistics

-2 Res Log Likelihood	1254.4
AIC (smaller is better)	1256.4
AICC (smaller is better)	1256.4
BIC (smaller is better)	1259.1

Solution for Fixed Effects

Effect	hrt_sex	Race	IGF1	IGFBP3	CalbB	Estimate	Standard Error	t Value	Pr > |t|[1]
Intercept						171.39	462.22	0.37	0.7115
MVTB						0.06110	0.03670	1.66	0.0989
IGF1			1			-18.3347	17.7056	-1.04	0.3028
IGF1			2			1.7261	15.5227	0.11	0.9117
IGF1			3			0	.	.	.
IGFBP3				11		7.2093	17.3346	0.42	0.6783
IGFBP3				12		4.7028	14.6802	0.32	0.7493
IGFBP3				22		0	.	.	.
CalbB					11	28.4556	15.0071	1.90	0.0607
CalbB					12	0	.	.	.
Age						-0.8738	0.8173	-1.07	0.2874
Race		1				-16.7266	16.2588	-1.03	0.3059
Race		2				0	.	.	.
hrt_sex	FN					-41.8630	22.7002	-1.84	0.0680
hrt_sex	FY					-34.3320	28.8966	-1.19	0.2375
hrt_sex	MN					0	.	.	.
bmipre						1.0920	7.9300	0.14	0.8907
Height						-0.3215	2.6177	-0.12	0.9025
bwpre						-0.5302	2.9702	-0.18	0.85
Residual						.	.		

[1] with 106 DF

Model for calculating percent variability for change in muscle quality with strength training attributable to genotypes:

mqb is baseline muscle volume

mqc is change in muscle volume with strength training

igf1 is subject's insulin-like growth factor 1 genotype

igfbp3 is subject's insulin-like growth factor binding protein 3 genotype

calbb is subject's calcineurin B (*PPP3R1*) genotype

bwpre is subject's baseline body weight

bmipre is subject's baseline body mass index

hrt_sex is subject's hormone replacement status

```
proc means data=one n css;
var mqc;
quit;

proc mixed data=one method=type3 covtest boxplot;
class race hrt_sex igf1 igfbp3 calbb;
model mqc=mqb
                age
                race
                height
                hrt_sex
                bwpre
                bmipre
                igf1
                igfbp3
                calbb
                igf1*calbb
                /ddfm=sat solution residuals;

lsmeans igf1 igfbp3 calbb igf1*calbb/pdiff at means;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;
```

Results:

Type 3 Analysis of Variance

Source	DF	Sum of Squares	Mean Square	DF	F Value	Pr > F
MQB	1	94.083090	94.083090	97	28.39	<.0001
Age	1	11.907632	11.907632	97	3.59	0.0610
Race	1	12.927397	12.927397	97	3.90	0.0511
Height	1	5.273079	5.273079	97	1.59	0.2102
bwpre	1	3.409480	3.409480	97	1.03	0.3103
IGF1	2	2.440301	1.220151	97	0.37	0.6930
IGFBP3	2	2.733374	1.366687	97	0.41	0.6632
CalbB	1	0.502028	0.502028	97	0.15	0.6980
IGF1*CalbB	2	20.358235	10.179117	97	3.07	0.0509
hrt_sex	2	11.301844	5.650922	97	1.71	0.1871
bmipre	1	1.977592	1.977592	97	0.60	0.4417
Residual	97	321.457894	3.313999	.	.	

Covariance Parameter Estimates

Cov Parm	Estimate	Standard Error	Z Value	Pr Z
Residual	3.3140	0.4759	6.96	<.0001

Fit Statistics

-2 Res Log Likelihood	457.7
AIC (smaller is better)	459.7
AICC (smaller is better)	459.7
BIC (smaller is better)	462.3

Solution for Fixed Effects

Effect	hrt_sex	Race	IGF1	IGFBP3	CalbB	Estimate	Standard Error	t Value	Pr > |t|[1]
Intercept						-14.3454	24.2313	-0.59	0.5552
MQB						-0.3414	0.06407	-5.33	<.0001
Age						-0.04674	0.02466	-1.90	0.0610
Race		1				-0.8901	0.4507	-1.98	0.0511
Race		2				0	.	.	.
Height						0.1821	0.1444	1.26	0.2102
bwpre						-0.1522	0.1501	-1.01	0.3130
IGF1			1			-0.4831	1.1874	-0.41	0.6850
IGF1			2			-0.9181	1.0069	-0.91	0.3641
IGF1			3			0	.	.	.
IGFBP3				11		-0.1028	0.5160	-0.20	0.8425
IGFBP3				12		0.2788	0.4360	0.64	0.5240
IGFBP3				22		0	.	.	.
CalbB					11	-1.7609	0.9628	-1.83	0.0705
CalbB					12	0	.	.	.
IGF1*CalbB			1		11	1.9392	1.3021	1.49	0.1397
IGF1*CalbB			1		12	0	.	.	.
IGF1*CalbB			2		11	2.7819	1.1229	2.48	0.0150
IGF1*CalbB			2		12	0	.	.	.
IGF1*CalbB			3		11	0	.	.	.
IGF1*CalbB			3		12	0	.	.	.
hrt_sex	FN					-1.0061	0.5636	-1.79	0.0774
hrt_sex	FY					-0.4181	0.7848	-0.53	0.5955
hrt_sex	MN					0	.	.	.
bmipre						0.3207	0.4152	0.77	0.4417

[1] with 97 DF

APPENDIX K

Calculations for Percent Variability for all Genotypes and each Gene by Gene Interaction of Interest

APPENDIX K: CALCULATIONS FOR PERCENT VARIABILITY FOR ALL GENOTYPES AND EACH GENE BY GENE INTERACTION OF INTEREST

To determine the percent variability of the muscle phenotype attributable to each genotype and each gene by gene interaction of interest, r^2 was determined from the Type III sums of squares.

SS = sums of squares
M = model
E = error
T = Total

$r^2 = SS_M/SS_T = SS_M/(SS_M + SS_E)$

For this model only random (due to error) and genetic effects of interest were included, so the model sums of squares included all genotypes and those gene by gene interactions which were significant or exhibited a trend. Covariates were not included in the model because they should not play a role because they are being controlled for. Example: BMI would not be expected to contribute to the change in muscle strength with strength training (if it does it is controlled for by using as a covariate).

So if there was a significant *IGF1*PPP3R1* interaction or a trend towards a significant interaction the r^2 terms would be the following:

$r^2_{IGF1\text{average}} = SS_{IGF1}/(SS_{IGF1} + SS_{IGFBP3} + SS_{PPP3R1} + SS_{IGF1*PPP3R1} + \text{Error (or } SS_{\text{residual}}))$

$r^2_{IGFBP3\text{average}} = SS_{IGFBP3}/(SS_{IGF1} + SS_{IGFBP3} + SS_{PPP3R1} + SS_{IGF1*PPP3R1} + \text{Error (or } SS_{\text{residual}}))$

$r^2_{PPP3R1\text{average}} = SS_{PPP3R1}/(SS_{IGF1} + SS_{IGFBP3} + SS_{PPP3R1} + SS_{IGF1*PPP3R1} + \text{Error (or } SS_{\text{residual}}))$

$r^2_{IGF1*PPP3R1\text{average}} = SS_{IGF1*PPP3R1}/(SS_{IGF1} + SS_{IGFBP3} + SS_{PPP3R1} + SS_{IGF1*PPP3R1} + \text{Error (or } SS_{\text{residual}}))$

However, for each gene involved in a significant or trend towards a significant interaction some of the sums of squares is contributed by the sums of squares for the interaction. It is not possible to determine this contribution so it was estimated that each gene involved in an interaction contributed half of the percent variability.

For change in muscle strength with strength training. There were trends for a significant interaction gene by gene interaction for *IGF1* by *PPP3R1* (*P* = 0.0716) and for a significant gene by race interaction for *IGFBP3* by race (*P* = 0.0935):

SS_{IGF1} = 15.80
SS_{IGFBP3} = 40.70
SS_{PPP3R1} = 0.20
$SS_{IGF1*PPP3R1}$ = 63.06
$SS_{IGFBP3*Race}$ = 56.53
$SS_{RESIDUAL\ (ERROR)}$ = 1212.52

$r^2_{IGF1AVG}$ = 15.80/(15.80+40.70+0.20+63.06+56.53+1212.52) = 15.80/1388.81 = 1.14%

$r^2_{IGFBP3AVG}$ = 40.70/1388.81 = 2.93%

$r^2_{PPP3R1AVG}$ = 0.20/1388.81 = 0.01%

$r^2_{IGF1*PPP3R1}$ = 63.06/1388.81 = 4.54%

$r^2_{IGFBP3*Race}$ = 56.53/1388.81 = 4.07%

r^2_{IGF1} ~ 4.54/2 + 1.14 ~ 3.41%

r^2_{IGFBP3} ~ 4.07/2 + 2.93 ~ 4.97%

r^2_{PPP3R1} ~ 4.54/2 + 0.01 ~ 2.28%

For change in muscle volume with strength training. There was a trend for a significant influence of the *PPP3R1* gene polymorphism (*P* = 0.0607):

SS_{IGF1} = 8332
SS_{IGFBP3} = 726
SS_{PPP3R1} = 14365
$SS_{RESIDUAL\ (ERROR)}$ = 423504

r^2_{IGF1} = 8332/(8332+726+14365+423504) = 8332/446927 = 1.86%

r^2_{IGFBP3} = 726/446927 = 0.16%

r^2_{PPP3R1} = 14365/446927 = 3.21%

For change in muscle quality with strength training. There was a trend for a significant gene by gene interaction for *IGF1* by *PPP3R1* (*P* = 0.0509):

SS_{IGF1} = 2.44
SS_{IGFBP3} = 2.73
SS_{PPP3R1} = 0.50
$SS_{IGF1*PPP3R1}$ = 20.36
$SS_{RESIDUAL\ (ERROR)}$ = 321.46

$r^2_{IGF1AVG}$ = 2.44/(2.44+2.73+0.50+20.36+321.46) = 2.44/347.49= 0.70%

$r^2_{IGFBP3AVG}$ = 2.73/347.49 = 0.79%

$r^2_{PPP3R1AVG}$ = 0.50/347.49 = 0.14%

$r^2_{IGF1*PPP3R1}$ = 20.36/347.49 = 5.86%

r^2_{IGF1} ~ 5.86/2 + 0.70 ~ 3.63%

r^2_{IGFBP3} = 0.79%

r^2_{PPP3R1} ~ 5.86/2 + 0.14 ~ 3.07%

APPENDIX L

Models and Results for Total Gene Effects for Analyses in Which a Trend for a Significant Interaction Occurred

APPENDIX L: MODELS AND RESULTS FOR TOTAL GENE EFFECTS FOR ANALYSES IN WHICH A TREND FOR A SIGNIFICANT INTERACTION OCCURRED

Model for change in strength with strength training for *IGF1*:

IGF1 is the IGF1 genotype, 1 is 192 homozygote, 2 is 192 heterozygotes,
3 is non-carriers of the 192 allele

IGFBP3 is the IGFBP3 genotype, 11 is AA homozygotes, 12 is AC heterozygotes, 11 is CC homozygotes

Calbb is the calcineurin B genotype, 11 is the II homozygotes, 12 is the D-allele carriers

Race: 1 Caucasian or 2 African American

Age is subject's age

sex: 1 male or 2 female

hrt_sex is hormone replacement therapy status variable: MN is male, FN is females not on hormone replacement therapy, FY is females on hormone replacement therapy

Height is subject's height

bwpre is baseline body weight

bmipre is baseline body mass index

```
/*analysis for gene effect for IGF1 for change in muscle strength*/
/*full model*/
proc means data=one n css;
var rmdkg;
quit;

proc mixed data=one method=type3 covtest boxplot;
class race hrt_sex igf1 igfbp3 calbb;
model rmdkg=rmtlprekg
                        race
                        height
                        igf1
                        igfbp3
                        calbb
                        age
                        bwpre
                        hrt_sex
```

```
                    bmipre
                    igfbp3*race
                igf1*calbb
                /ddfm=sat solution residuals;

lsmeans igf1 igfbp3 calbb igfbp3*race igf1*calbb/pdiff at means;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;

/*model without IGF1*/
proc means data=one n css;
var rmdkg;
quit;

proc mixed data=one method=type3 covtest boxplot;
class race hrt_sex igfbp3 calbb;
model rmdkg=rmtlprekg
                    race
                    height
                    calbb
                    age
                    bwpre
                    hrt_sex
                    bmipre
            igfbp3
            igfbp3*race
                /ddfm=sat solution residuals;

lsmeans igfbp3 calbb igfbp3*race/pdiff at means;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;
```

Results:

Full Model:

Type 3 Analysis of Variance

Source	DF	Sum of Squares	Mean Square
RMTLPREKG	1	3.614304	3.614304
Race	1	99.966343	99.966343
Height	1	8.642697	8.642697
IGF1	2	15.800191	7.900095
IGFBP3	2	40.699811	20.349906
Calbb	1	0.199613	0.199613
Age	1	16.368561	16.368561
bwpre	1	1.644461	1.644461
hrt_sex	2	100.878464	50.439232
bmipre	1	1.967392	1.967392
Race*IGFBP3	2	56.527655	28.263828
IGF1*Calbb	2	63.061851	31.530925
Residual	104	1212.521814	11.658864

Constrained Model:

Source	DF	Sum of Squares	Mean Square
RMTLPREKG	1	4.825644	4.825644
Race	1	80.303996	80.303996
Height	1	10.189801	10.189801
Calbb	1	6.328011	6.328011
Age	1	17.423118	17.423118
bwpre	1	4.571200	4.571200
hrt_sex	2	128.552162	64.276081
bmipre	1	5.734234	5.734234
IGFBP3	2	53.554319	26.777160
Race*IGFBP3	2	65.893174	32.946587
Residual	108	1382.954162	12.805131

Model for change in strength with strength training for *IGFBP3*:

IGF1 is the IGF1 genotype, 1 is 192 homozygote, 2 is 192 heterozygotes,
3 is non-carriers of the 192 allele

IGFBP3 is the IGFBP3 genotype, 11 is AA homozygotes, 12 is AC heterozygotes, 11 is CC homozygotes

Calbb is the calcineurin B genotype, 11 is the II homozygotes, 12 is the D-allele carriers

Race: 1 Caucasian or 2 African American

Age is subject's age

sex: 1 male or 2 female

hrt_sex is hormone replacement therapy status variable: MN is male, FN is females not on hormone replacement therapy, FY is females on hormone replacement therapy

Height is subject's height

bwpre is baseline body weight

bmipre is baseline body mass index

```
/*analysis for gene effect for IGFBP3 for change in muscle strength*/
/*full model*/
proc means data=one n css;
var rmdkg;
quit;

proc mixed data=one method=type3 covtest boxplot;
class race hrt_sex igf1 igfbp3 calbb;
model rmdkg=rmtlprekg
                        race
                        height
                        igf1
                        igfbp3
                        calbb
                        age
                        bwpre
                        hrt_sex
                        bmipre
                        igfbp3*race
            igf1*calbb
                /ddfm=sat solution residuals;
```

```
lsmeans igf1 igfbp3 calbb igfbp3*race igf1*calbb/pdiff at means;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;


/*model without IGFBP3*/

proc means data=one n css;
var rmdkg;
quit;

proc mixed data=one method=type3 covtest boxplot;
class race hrt_sex igf1 calbb;
model rmdkg=rmtlprekg
                        race
                        height
                        calbb
                        age
                        bwpre
                        hrt_sex
                        bmipre
            igf1
            igf1*calbb
                /ddfm=sat solution residuals;
lsmeans igf1 calbb igf1*calbb /pdiff at means;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;
```

Results:

Full Model:

Type 3 Analysis of Variance

Source	DF	Sum of Squares	Mean Square
RMTLPREKG	1	3.614304	3.614304
Race	1	99.966343	99.966343
Height	1	8.642697	8.642697
IGF1	2	15.800191	7.900095
IGFBP3	2	40.699811	20.349906
Calbb	1	0.199613	0.199613
Age	1	16.368561	16.368561
bwpre	1	1.644461	1.644461
hrt_sex	2	100.878464	50.439232
bmipre	1	1.967392	1.967392
Race*IGFBP3	2	56.527655	28.263828
IGF1*Calbb	2	63.061851	31.530925
Residual	104	1212.521814	11.658864

Constrained Model:

Type 3 Analysis of Variance

Source	DF	Sum of Squares	Mean Square
RMTLPREKG	1	11.868777	11.868777
Race	1	120.215997	120.215997
Height	1	6.103380	6.103380
Calbb	1	0.847680	0.847680
Age	1	40.082231	40.082231
bwpre	1	0.747230	0.747230
hrt_sex	2	127.353545	63.676773
bmipre	1	0.986788	0.986788
IGF1	2	45.420302	22.710151
IGF1*Calbb	2	35.524215	17.762107
Residual	108	1289.747279	11.942104

Model for change in strength with strength training for *PPP3R1*:

IGF1 is the IGF1 genotype, 1 is 192 homozygote, 2 is 192 heterozygotes,
3 is non-carriers of the 192 allele

IGFBP3 is the IGFBP3 genotype, 11 is AA homozygotes, 12 is AC heterozygotes, 11 is CC homozygotes

Calbb is the calcineurin B (PPP3R1) genotype, 11 is the II homozygotes, 12 is the D-allele carriers

Race: 1 Caucasian or 2 African American

Age is subject's age

sex: 1 male or 2 female

hrt_sex is hormone replacement therapy status variable: MN is male, FN is females not on hormone replacement therapy, FY is females on hormone replacement therapy

Height is subject's height

bwpre is baseline body weight

bmipre is baseline body mass index

```
/*analysis for gene effect for PPP3R1 for change in muscle strength*/
/*full model*/
proc means data=one n css;
var rmdkg;
quit;

proc mixed data=one method=type3 covtest boxplot;
class race hrt_sex igf1 igfbp3 calbb;
model rmdkg=rmtlprekg
                        race
                        height
                        igf1
                        igfbp3
                        calbb
                        age
                        bwpre
                        hrt_sex
                        bmipre
                        igfbp3*race
            igf1*calbb
```

```
                /ddfm=sat solution residuals;

lsmeans igf1 igfbp3 calbb igfbp3*race igf1*calbb/pdiff at means;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;


/*model without PPP3R1*/

proc means data=one n css;
var rmdkg;
quit;

proc mixed data=one method=type3 covtest boxplot;
class race hrt_sex igf1 igfbp3;
model rmdkg=rmtlprekg
                        race
                        height
                        age
                        bwpre
                        hrt_sex
                        bmipre
            igf1
            igfbp3
            igfbp3*race
            /ddfm=sat solution residuals;
lsmeans igf1 igfbp3 igfbp3*race /pdiff at means;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;
```

Results:

Full Model:

Type 3 Analysis of Variance

Source	DF	Sum of Squares	Mean Square
RMTLPREKG	1	3.614304	3.614304
Race	1	99.966343	99.966343
Height	1	8.642697	8.642697
IGF1	2	15.800191	7.900095
IGFBP3	2	40.699811	20.349906
Calbb	1	0.199613	0.199613
Age	1	16.368561	16.368561
bwpre	1	1.644461	1.644461
hrt_sex	2	100.878464	50.439232
bmipre	1	1.967392	1.967392
Race*IGFBP3	2	56.527655	28.263828
IGF1*Calbb	2	63.061851	31.530925
Residual	104	1212.521814	11.658864

Constrained Model:

Type 3 Analysis of Variance

Source	DF	Sum of Squares	Mean Square
RMTLPREKG	1	5.860671	5.860671
Race	1	96.472287	96.472287
Height	1	4.166675	4.166675
Age	1	23.396079	23.396079
bwpre	1	0.370524	0.370524
hrt_sex	2	120.701509	60.350754
bmipre	1	0.638072	0.638072
IGF1	2	108.328174	54.164087
IGFBP3	2	20.301794	10.150897
Race*IGFBP3	2	30.520656	15.260328
Residual	107	1280.953999	11.971533

Model for change in muscle quality with strength training for *IGF1*:

IGF1 is the IGF1 genotype, 1 is 192 homozygote, 2 is 192 heterozygotes,
3 is non-carriers of the 192 allele

IGFBP3 is the IGFBP3 genotype, 11 is AA homozygotes, 12 is AC heterozygotes, 11 is CC homozygotes

Calbb is the calcineurin B genotype, 11 is the II homozygotes, 12 is the D-allele carriers

Race: 1 Caucasian or 2 African American

Age is subject's age

sex: 1 male or 2 female

hrt_sex is hormone replacement therapy status variable: MN is male, FN is females not on hormone replacement therapy, FY is females on hormone replacement therapy

Height is subject's height

bwpre is baseline body weight

bmipre is baseline body mass index

```
/*analysis for gene effect for IGF1 for change in muscle quality*/
/*full model*/
proc means data=one n css;
var mqc;
quit;

proc mixed data=one method=type3 covtest boxplot;
class race hrt_sex igf1 igfbp3 calbb;
model mqc=mqb
                age
                race
                height
                bwpre
                igf1
                igfbp3
                calbb
                hrt_sex
                bmipre
                igf1*calbb
                /ddfm=sat solution residuals;
```

```
lsmeans igf1 igfbp3 calbb igf1*calbb/pdiff at means;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;

/*model without IGF1*/
proc means data=one n css;
var mqc;
quit;

proc mixed data=one method=type3 covtest boxplot;
class race hrt_sex igfbp3 calbb;
model mqc=mqb
                age
                race
                height
                bwpre
                igfbp3
                calbb
                hrt_sex
                bmipre

                /ddfm=sat solution residuals;

lsmeans igfbp3 calbb/pdiff at means;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;
```

Results:

Full Model:

Type 3 Analysis of Variance

Source	DF	Sum of Squares	Mean Square
MQB	1	94.083090	94.083090
Age	1	11.907632	11.907632
Race	1	12.927397	12.927397
Height	1	5.273079	5.273079
bwpre	1	3.409480	3.409480
IGF1	2	2.440301	1.220151
IGFBP3	2	2.733374	1.366687
CalbB	1	0.502028	0.502028
hrt_sex	2	11.301844	5.650922
bmipre	1	1.977592	1.977592
IGF1*CalbB	2	20.358235	10.179117
Residual	97	321.457894	3.313999

Constrained Model:

Type 3 Analysis of Variance

Source	DF	Sum of Squares	Mean Square
MQB	1	110.944409	110.944409
Age	1	13.963383	13.963383
Race	1	9.836652	9.836652
Height	1	5.764891	5.764891
bwpre	1	5.110641	5.110641
IGFBP3	2	3.449142	1.724571
CalbB	1	0.432539	0.432539
hrt_sex	2	19.036949	9.518474
bmipre	1	3.420044	3.420044
Residual	101	367.281512	3.636451

Model for change in muscle quality with strength training for *PPP3R1*:

IGF1 is the IGF1 genotype, 1 is 192 homozygote, 2 is 192 heterozygotes,
3 is non-carriers of the 192 allele

IGFBP3 is the IGFBP3 genotype, 11 is AA homozygotes, 12 is AC heterozygotes, 11 is CC homozygotes

Calbb is the calcineurin B (PPP3R1) genotype, 11 is the II homozygotes, 12 is the D-allele carriers

Race: 1 Caucasian or 2 African American

Age is subject's age

sex: 1 male or 2 female

hrt_sex is hormone replacement therapy status variable: MN is male, FN is females not on hormone replacement therapy, FY is females on hormone replacement therapy

Height is subject's height

bwpre is baseline body weight

bmipre is baseline body mass index

```
/*analysis for gene effect for PPP3R1 for change in muscle quality*/
/*full model*/
proc means data=one n css;
var mqc;
quit;

proc mixed data=one method=type3 covtest boxplot;
class race hrt_sex igf1 igfbp3 calbb;
model mqc=mqb
                age
                race
                height
                bwpre
                igf1
                igfbp3
                calbb
                hrt_sex
                bmipre
                igf1*calbb
                /ddfm=sat solution residuals;
```

```
lsmeans igf1 igfbp3 calbb igf1*calbb/pdiff at means;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;

/*model without PPP3R1*/
proc means data=one n css;
var mqc;
quit;

proc mixed data=one method=type3 covtest boxplot;
class race hrt_sex igf1 igfbp3;
model mqc=mqb
                age
                race
                height
                bwpre
                igfbp3
                igf1
                hrt_sex
                bmipre

                /ddfm=sat solution residuals;

lsmeans igfbp3 igf1/pdiff at means;
ods output tests3=tests3;
ods output diffs=diffs;
ods output lsmeans=lsm;
quit;
```

Results:

Full Model:

Type 3 Analysis of Variance

Source	DF	Sum of Squares	Mean Square
MQB	1	94.083090	94.083090
Age	1	11.907632	11.907632
Race	1	12.927397	12.927397
Height	1	5.273079	5.273079
bwpre	1	3.409480	3.409480
IGF1	2	2.440301	1.220151
IGFBP3	2	2.733374	1.366687
CalbB	1	0.502028	0.502028
hrt_sex	2	11.301844	5.650922
bmipre	1	1.977592	1.977592
IGF1*CalbB	2	20.358235	10.179117
Residual	97	321.457894	3.313999

Constrained Model:

Type 3 Analysis of Variance

Source	DF	Sum of Squares	Mean Square
MQB	1	93.612824	93.612824
Age	1	11.802626	11.802626
Race	1	14.629462	14.629462
Height	1	3.356136	3.356136
bwpre	1	2.330282	2.330282
IGFBP3	2	6.204668	3.102334
IGF1	2	25.151528	12.575764
hrt_sex	2	13.155892	6.577946
bmipre	1	1.279626	1.279626
Residual	100	342.562523	3.425625

APPENDIX M

Calculation for Total Gene Effects for Analyses in Which a Trend for a Significant Interaction Occurred

APPENDIX M: CALCULATION FOR TOTAL GENE EFFECTS FOR ANALYSES IN WHICH A TREND FOR A SIGNIFICANT INTERACTION OCCURRED

To determine the significance of the total gene effect for change in muscle phenotype the full model sums of squares (with all gene effects and error term) was compared with the constrained model sums of squares (in which all gene effects of interest were removed). The difference in sums of squares for the error term for these two models was the contribution to the sums of squares due to that particular gene effect. This difference in sums of squares was divided by the degrees of freedom for that gene effect (the difference in degrees of freedom for the error terms for the full and constrained models). The mean square for the gene effect was then calculated as the quotient of the sums of squares due to the gene effect divided by the degrees of freedom for the gene effect. The F-ratio was then calculated as the ratio of the mean square for the gene effect and the mean square for the error term for the full model. The level of significance was tested using F tables with the numerator degrees of freedom (df1 in tables) equal to the degrees of freedom for the gene effect and the denominator degrees of freedoms (df2 in tables) as the error term degrees of freedom.

Effects of *IGF1* genotype on change in muscle strength with ST:

For full model:
Error sums of squares = 1212.52
Mean Square = 11.66
Degrees of freedom = 104

For constrained model (without sums of squares for *IGF1* and *IGF1*PPP3R1*):
Error sums of squares = 1382.95
Mean Square = 12.81
Degrees of freedom = 108

Differences in sums of squares for two models = 1382.95 – 1212.52 = 170.43

Degrees of freedom due to *IGF1* gene effects = 108 – 104 = 4

Mean Square for *IGF1* gene effects = 170.43/4 = 42.61

F = 42.61/11.66 = 3.61

df1 = 4
df2 = 104

Using F tables $P < 0.01$ (F = 3.51 for df1 = 4 and df2 = 100 for $P = 0.01$)

Effects of *IGFBP3* genotype on change in muscle strength with ST:

For full model:
Error sums of squares = 1212.52
Mean Square = 11.66
Degrees of freedom = 104

For constrained model (without sums of squares for *IGFBP3* and *IGFBP3**Race):
Error sums of squares = 1289.74
Mean Square = 11.94
Degrees of freedom = 108

Differences in sums of squares for two models = 1289.74 – 1212.52 = 77.22

Degrees of freedom due to *IGFBP3* gene effects = 108 – 104 = 4

Mean Square for *IGFBP3* gene effects = 77.22/4 = 19.31

F = 19.31/11.66 = 1.66

df1 = 4
df2 = 104

Using F tables $P > 0.05$ (F = 2.46 for df1 = 4 and df2 = 100 for $P = 0.05$) so non-significant

Effects of *PPP3R1* genotype on change in muscle strength with ST:

For full model:
Error sums of squares = 1212.52
Mean Square = 11.66
Degrees of freedom = 104

For constrained model (without sums of squares for *PPP3R1* and *PPP3R1*IGF1):*
Error sums of squares = 1280.95
Mean Square = 11.97
Degrees of freedom = 107

Differences in sums of squares for two models = 1280.95 – 1212.52 = 68.43

Degrees of freedom due to *PPP3R1* gene effects = 107 – 104 = 3

Mean Square for *PPP3R1* gene effects = 68.43/3 = 22.81

F = 22.81/11.66 = 1.96

df1 = 3
df2 = 104

Using F tables $P > 0.05$ (F = 2.70 for df1 = 3 and df2 = 100 for $P = 0.05$) so non-significant

Effects of *IGF1* genotype on change in muscle quality with ST:

For full model:
Error sums of squares = 321.46
Mean Square = 3.31
Degrees of freedom = 97

For constrained model (without sums of squares for *IGF1* and *IGF1*PPP3R1*):
Error sums of squares = 367.28
Mean Square = 3.64
Degrees of freedom = 101

Differences in sums of squares for two models = 367.28 – 321.46 = 45.82

Degrees of freedom due to *IGF1* gene effects = 101 – 97 = 4

Mean Square for *IGF1* gene effects = 45.82/4 = 11.46

F = 11.46/3.31 = 3.46

df1 = 4
df2 = 97

Using F tables $P < 0.05$ (F = 2.46 for df1 = 4 and df2 = 100 for $P = 0.05$)

Effects of *PPP3R1* genotype on change in muscle quality with ST:

For full model:
Error sums of squares = 321.46
Mean Square = 3.31
Degrees of freedom = 97

For constrained model (without sums of squares for *IGF1* and *IGF1*PPP3R1*):
Error sums of squares = 342.56
Mean Square = 3.43
Degrees of freedom = 100

Differences in sums of squares for two models = 342.56 – 321.46 = 21.10

Degrees of freedom due to *PPP3R1* gene effects = 100 – 97 = 3

Mean Square for *PPP3R1* gene effects = 21.10/3 = 7.03

F = 7.03/3.31 = 2.12

df1 = 3
df2 = 97

Using F tables $P > 0.05$ (F = 2.70 for df1 = 3 and df2 = 100 for $P = 0.05$) so non-signficant

APPENDIX N: LITERATURE REVIEW

Causes and consequences of sarcopenia

Effects of aging on the components of sarcopenia

Potential mechanisms of sarcopenia

Strength training as an intervention for sarcopenia

Genetic influences on phenotypes related to sarcopenia

Physiology of IGF-1 pathway gene polymorphisms

APPENDIX N: LITERATURE REVIEW

The following review of literature provides background information relevant to the understanding of the influence of insulin-like growth factor pathway genes on the muscle phenotype adaptations to ST. This review will focus on the following topics: 1) Causes and consequences of sarcopenia, 2) Effects of aging on the components of sarcopenia, 3) Potential mechanisms of sarcopenia, 4) Strength training (ST) as an intervention for sarcopenia, 5) Genetic influences on muscle phenotypes related to sarcopenia, and 6) Physiology of *IGF1* pathway gene polymorphisms.

Causes and consequences of sarcopenia: Sarcopenia is a Greek word literally meaning "loss of flesh", which was first coined by Rosenberg in 1989 (223). It refers to the loss of skeletal muscle mass with aging that further results in loss of skeletal muscle function, including loss of strength, muscle quality, and power (134, 149). There are many factors occurring naturally with aging that may contribute to the loss of muscle size and function. However, there is a relatively large inter-individual variability in the magnitude of loss in muscle mass and muscle function with age, as well as the factors that explain these losses. Some of these factors include: decreases in alpha motor neurons, motor units, protein synthesis, expression of myosin heavy chains, and a rise in catabolic stimuli, including cytokines (e.g. IL-6 and TNF-α) (33, 150, 242). Hormonal and growth factors include, reduction in the levels of sex steroids and impairments in the growth hormone (GH)/insulin-like growth factor (IGF) pathway (152, 244, 277). There are also environmental factors, such as nutrition and physical inactivity that can have a profound influence on sarcopenia (167).

The first study to define and determine the prevalence of sarcopenia in a large group of individuals was the New Mexico study reported by Baumgartner et al. (20). These investigators defined sarcopenia as occurring in an individual whose muscle mass was ≥ 2 standard deviations below the mean appendicular muscle mass for young healthy adults. Using dual-energy x-ray absorptiometry (DXA) to measure appendicular muscle mass, Baumgartner et al. (20) found in elderly Hispanic and Caucasian males and females that the prevalence of sarcopenia increased from 13 to 24% of persons aged 65-70 years to over 50% of those older than 80 years. In addition, sarcopenic women had 3.6 times higher rates of disability, and sarcopenic men had 4.1 times higher disability rates compared with study participants with normal muscle mass. In another study in which DXA was used to measure muscle mass, Iannuzzi-Sucich et al. (105) reported that the prevalence of sarcopenia was 22.6% for women aged 64-93 years and 26.8% for men aged 64-92 years. These authors also reported that the prevalence of sarcopenia for women and men older than 80 years was 31% and 45%, respectively.

In addition to these studies, the losses of muscle mass and muscle function due to sarcopenia have been well-documented in cross-sectional and longitudinal studies (68, 114, 132, 141, 147), and have many significant health consequences ranging from decreased functional ability to increased mortality. These consequences include: increased risk of falls (142, 144), hip fractures (9), bone mineral density loss (243), and physical disability (276). Loss of strength is often related to dysfunction in the elderly (18, 189, 204) and is a powerful predictor of future disability, especially in women (204). Loss of muscle mass with age may also lead to glucose intolerance (25). Finally, it has been shown that sarcopenia is associated with increased mortality (158, 159, 231). Miller

et al. (161) showed that corrected arm muscle area is a better predictor of long term mortality than BMI, which is often used as a predictor of mortality in older adults. Also, several studies have reported an association between low muscle strength and increased mortality rates (79, 133, 205). For example, Metter et al. (158) reported that both hand grip strength and change in grip strength were predictors of mortality, independent of physical activity or muscle mass.

Using the standard criteria for sarcopenia, Baumgartner et al. (20) estimated the prevalence of sarcopenia to be about 9 million in the U.S. (20). With an aging society, it is estimated that the incidence of sarcopenia will increase significantly, resulting in major increases in health care cost. In the United States, census data reported that there were 35 million Americans over the age of 65. By 2015, this number is projected to increase to 46 million (U.S. Census Bureau, 2000). Consequently, health care costs will increase for the elderly. In 2001, projects spending totaled 103 billion for nursing home stays, and by 2010, this will increase by 77% to 183 billion (Health Care Financing Administration, 2000). Because society is aging, it is imperative to address this disease process through a better understanding of its causes, prevalence, and treatment.

Effects of aging on the components of sarcopenia: Muscle mass and strength reach a peak between 40 and 50 yrs of age and remain relatively stable until the sixth decade. After age 50 an accelerated decline in muscle strength (~12-14%/decade) usually occurs (132, 141, 157), while muscle mass declines at a rate of ~ 6%/decade (147). These losses in muscle strength and muscle mass result in a loss of muscle function of ~ 40% by the 8^{th} decade of life, often resulting in disability and morbidity, and possibly even mortality (158, 161).

The decline in muscle mass with age is strongly correlated with strength, and the losses associated with aging (76, 207). However, depending on the measurement method used, it has been reported that muscle mass declines at a slower rate with aging than muscle strength (154). Various measurement techniques have been used to estimate losses in muscle mass with age (e.g. ultra-sound, computed tomography scans [CT], magnetic resonance imaging [MRI], ^{40}K counting, creatinine excretion, DXA, and hydrodensiometry), however, little information is available from direct measurement of muscle mass. A post-mortem examination of cadavers would allow for a more direct measurement of muscle mass and would overcome certain ethical and logistical problems.

Metter et al. (158) estimated fat-free mass (FFM) via creatinine excretion in ~ 950 subjects from the Baltimore Longitudinal Study on Aging (BLSA) and found that FFM loss of ~ 33% occurs during the adult life span. Lexell et al. (138) employed a whole muscle post-mortem examination to quantify size of whole muscle, number of fibers, and fiber size to measure total age-related changes in muscle. For this study, these investigators examined autopsied cross-sections of whole vastus lateralis muscle from 43 previously healthy men between the ages of 15 and 83 years. The results showed that sarcopenia begins around the age of 25 years and accelerates thereafter. These investigators reported that this muscle decline is caused mainly by a decrease in fiber number, with no preferential loss of any particular fiber type, and to a lesser degree by a loss of fiber size, mostly of type II fibers. Further supporting evidence for these findings was provided by Overend et al. (184) who performed CT scans on thigh muscles of young and older men and found that comparisons of relative leg muscle strength in these

subjects may be misleading due to the decreases in muscle tissue associated with aging. These authors stressed that appropriate measurement of muscle size and cross-sectional area (CSA) needed to be performed prior to making such comparisons. More recently, Trappe et al. (270) reported that in men and women each of the four muscles comprising the quadriceps, atrophy similarly with aging, such that CSA in elderly subjects is ~ 27% lower than in younger subjects as measured by CT.

Age-related declines in muscle strength are related to changes in number of motor units, altered muscle pennation angle, fiber type grouping, loss of muscle fibers, decreased expression of myosin heavy chain (MHC) proteins, and increases in connective tissue and fat infiltration (12, 124, 130, 138). The age-related decline in muscle strength has been demonstrated by several cross-sectional and longitudinal studies, which have shown that there is considerable loss of muscle strength beginning after the 50s for men, and somewhat earlier for women (141, 147). However, investigations that examine aging effects often employ cross-sectional designs. These studies cannot establish cause and effect relationships, but only associations between variables and are confounded by factors such as diet, physical activity, or generational differences when comparing subjects of different ages and/or generations. Even when using longitudinal data to assess age-related changes, these confounding factors may still persist. Despite the methodological constraints with cross-sectional studies, these studies can provide important contributions to the literature, especially when using large sample sizes and when combined with other studies.

Using cross-sectional data from the BLSA, in which grip strength was measured in 847 men aged 20-89 years, Kallman et al. (118) reported that muscle strength is

highest in the 30s and subsequently declines in a curvilinear fashion after the age of 40. After the 80s strength declined by ~37%. On the other hand, longitudinal analysis of these data showed that ~15% of the subjects over age 60 years demonstrated no strength decline during an ~ 9 year follow-up. These results suggest that there is a significant inter-individual variability in age-related strength losses. A follow-up report from the BLSA suggested that concentric, eccentric, and isometric knee and elbow flexor and extensor strength declines with aging, when ~ 650 men and women aged 20-93 years were examined (141). In addition, Era et al. (61) reported the isometric strength levels in five muscle groups for men in their 30s, 50s, and 70s. The results showed significant age-related differences between these age groups for isometric handgrip, elbow flexion, knee extension, trunk extension and flexion strength that was similar to the BLSA results reported by Kallman et al. (118). Both studies examined strength differences over a similar portion of the adult life span. Arm flexor and extensor data show that the age-related declines in arm strength are similar to the declines that occur in leg strength, but these declines begin at a later age. To investigate the relationship between muscle strength, age, and body composition, Frontera et al. (76), in an earlier cross-sectional study, measured isokinetic strength of the elbow and knee extensors and flexors in 200 healthy, 45-78 year old men and women. They measured peak torque for the knee at 60 and 240 degrees/s and for the elbow at 60 and 180 degrees/s. Strength in all muscle groups at both testing speeds was significantly lower (15.5-26.7%) in the 65-78 year old age group compared with the 45-54 year old age group. However, when strength was adjusted for FFM, age-associated differences among age groups were not significant in all muscle groups, except in the knee extensors at high velocity (240 degrees/s). These

results support the hypothesis that age-related declines in muscle mass are at least partially responsible for the losses in muscle strength. This conclusion also confirms an earlier report by Borges (26), who measured maximal isometric and isokinetic knee extension and flexion muscle torque at slow, medium, and fast velocities (12, 90, 150 degrees/s) in ~140 healthy men and women from 20-70 years of age. Both isokinetic and isometric torque were lower with increased age for both sexes. Isokinetic torque decreased significantly between 20 and 30 years of age in men and between 40 and 50 years of age in women. A significant decrease in torque was also observed between the ages of 60 and 70 years in both men and women. There was a significant decrease in maximum isometric torque between 60 and 70 years in both sexes. Peak torque was significantly correlated with body mass, height, and body surface area in these subjects.

Cross-sectional data at the muscle fiber level provide additional support for these results. In this regard, Frontera et al. (78) reported a 35% reduction in type II muscle fiber force production in older men (~ 75 yrs) compared to younger men. In addition, Trappe et al. (267) reported in a cross-sectional study that older women had 25-40% less power in single fibers than young women, old men, and young men. These results showed that older women have attenuated force production in single skeletal muscle fibers.

These findings suggest that the decline in whole muscle strength is at least partially caused by the decrease in force generating capacity of individual muscle fibers with aging. However, if older subjects are unable to maximally recruit existing motor units, then limited force production of muscle fibers may be a limiting factor. Maximal voluntary contraction with twitch interpolation provides evidence that elderly subjects

can fully and maximally contract their musculature (43, 102, 126), although one report found that less than full activation (as low as 69%) of musculature occurred in older adults (250). On the other hand, Jakobi et al. (109) reported that with sufficient attempts, elderly men can fully activate their elbow flexors and extensors, as well as younger men, even if an impairment previously existed. These findings highlight a design flaw in many previous studies that assessed muscle strength without providing an adequate familiarization period prior to strength testing.

Due to logistical difficulties and expenses, longitudinal studies are not as common as cross-sectional investigations. Furthermore, longitudinal studies are subject to other problems, such as loss to follow-up and observations that are often not equally spaced. However, longitudinal designs are preferable for assessing the effects of aging. Typically, longitudinal studies on sarcopenia report a more rapid rate of decline in muscle strength than do cross-sectional studies. For example, Bassey and Harries (19) reported that in men and women > 65 years, strength declined ~2% per year. However, a four-year follow-up on 620 survivors showed that grip strength had declined by 12% in men and by 19% in women, and these strength losses were significantly related to age (19). These authors also found a significant decline in physical activity and functional capacity in these subjects. These findings were supported by Sowers et al. (248), who found almost 9% of women had at least a 6% loss (>2.5 kg) of lean mass over a three-year observation period in African American and Caucasian women aged 34-58 years. This loss of muscle mass was associated with decreased physical functioning as determined by slower walking velocity and decreased leg strength. Further support is offered by Aniansson et al. (8), who reported that over a seven-year period, between the age of 70

and 75, there was a significant decline in knee extensor, elbow extensor and flexor strength in both men and women, with a larger decrease occurring in isokinetic as compared with isometric strength. Men with a higher level of physical activity had greater isokinetic muscle strength in the knee flexors and extensors than those men with lower activity level. Seven-year follow-up results showed a body mass decrease of 6% and a quadriceps muscle strength decrease of 10-22% over this period (7). During this time span there was also a reduction in fast-twitch fiber area in the quadriceps. Seven-year follow-up data from this cohort showed that in these active elderly men between the ages of 76 to 80 years, isokinetic strength at 30 degrees/s decreased significantly at a rate of 2-3% per year (6). Both type I and type II fiber areas significantly increased during this time, which was interpreted as a compensatory adaptation for the loss of motor units that occur with aging (6).

These findings were supported by Rantanen et al. (203) in a study which investigated age-related changes in strength over a 5-year period in ~100 men and ~185 women with baseline age of 75 years. They found a substantial inter-individual variability in the percent change in strength over the five-year period ranging from a 4% increase in knee extension strength in men and women to a 16% decrease in hand grip strength in women. Reduced grip strength was more extensive in women than men. The more active men in this study maintained their trunk extension strength better than sedentary men. In women who decreased their activity levels over the five-year period, the rate of decline in grip and elbow flexion strength was 32% and 27% respectively, which was greater than other similarly aged subjects who either remained sedentary or were more active. The more active women retained their knee extension strength at a

higher level than the other groups. Those subjects who died before their follow-up tests exhibited poorer strength at baseline, indicating the possibility that low muscle strength is a predictor of mortality. The results from this study also suggest that participation in everyday physical tasks (i.e. household work, walking, and gardening), which are also the most common physically demanding activities of older people, may be essential for maintaining strength at a sufficient level to maintain functional ability. This conclusion is supported by other findings that examined muscle strength thresholds that are associated with compromised performance or ambulatory tasks. For example, cross-sectional data from the BLSA (131) indicated that with increasing knee extensor peak torque, gait time decreases, then plateaus at higher strength levels (> 130 Nm for normal gait, and > 190 Nm for faster gait). In a more recent study, it was reported that subjects with isometric leg extension peak torque to body weight ratio < 3.0 Nm/kg are at a substantial risk for impaired function in chair rise, gait speed, and stair ascent and descent tasks (193).

The above findings by Rantanen et al. (203) concur with more recent findings by Frontera et al. (75), who investigated age-associated changes in skeletal muscle mass and function over a 12 year span. For this study, isokinetic strength of the knee and elbow flexors and extensors were measured in twelve healthy, older (~65 yrs), sedentary men. Both knee and elbow flexor and extensor strength declined from 20 to 30% at slow and fast velocities. These subjects also had an ~ 16% loss in quadriceps cross-sectional area (CSA), as assessed by CT scans. Linear regression analysis showed that strength at baseline and changes in CSA over time were independent predictors of strength after 12 years. In addition, vastus lateralis muscle biopsies showed a 30% reduction of type I

fiber percentage, but showed no change in mean area of either fiber type. These authors suggested that the preferential loss of type I fibers was surprising in light of previous findings suggesting no change in fiber-type distribution with age (196) and may be explained by methodological shortcomings (139) or coexpression of myosin heavy chain isoforms (5). In spite of these potential issues, Frontera et al. (75) concluded that a loss in muscle CSA is a major contributor to the decrease in muscle strength with advancing age, and together with muscle strength at baseline, accounts for ~90% of the variability in strength during the 12-year period. These findings are supported by other recent data that showed a smaller mid-thigh CSA and greater fat infiltration in the muscle are associated with lower strength (175) and functional ability in older men and women (279).

Muscle quality (MQ), sometimes referred to as specific tension or strength per unit of muscle, also appears to be influenced by age. MQ considers neuromuscular effects and is considered a better estimate of skeletal muscle function than overall fat-free mass (FFM). MQ declines both at the whole muscle (147) and single muscle fiber level (78). Early studies provided conflicting results. Young et al. (290) reported no difference in MQ of the knee extensors of older women compared to younger controls when strength was measured isometrically. Young et al. (291) also reported that, in contrast to the findings in women, older men showed a 19% lower MQ than younger men. Lynch et al. (147) reported a difference in leg MQ between young and older adults, and that arm MQ decreased to a similar extent in men and women. However, leg MQ declined approximately 20% more than arm MQ with increasing age in women. Frontera et al. (78) studied single muscle fibers in younger and older men and women and reported a difference in muscle fiber quality in men, with fibers from young men having greater

capacity for force production than fibers from older men. More recently in a cross-sectional study comprised of ~2600 men and women between the ages of 70-79, Newman et al. (175) found that upper and lower extremity MQ decreased with increasing age. Thus, these data show that MQ decreases with age, but the magnitude of this decline seems to depend on sex and the muscle group studied.

Potential mechanisms of sarcopenia: There has been no single cause identified that explains the decline of muscle size and function that occurs with aging. However, there are many interrelated factors that appear to contribute to sarcopenia. These include: loss of alpha motor neurons and motor units, declines in testosterone, estrogen, growth hormone, IGF-1, protein synthesis rate, changes in myosin heavy chain (MHC) gene expression, and an elevation in catabolic stimuli including cytokines. The total number of central nervous system and muscle neurons decreases with age (31, 219), and in particular those neurons of the fast motor unit (51, 52). Muscle contractile and mitochondrial protein synthesis rates decline with aging (12, 173, 220, 221), as do whole body muscle protein synthesis rates, and MHC levels (12, 95). Also, hormone levels, including testosterone, estrogen, growth hormone, IGF-1 (16, 93, 191), have been shown to decrease with age. Finally, catabolic stimuli, including cytokines, have been shown to increase with aging (230).

Strength training (ST) as an intervention for sarcopenia: Strength training (ST) has been shown to be the most effective and safest intervention for the prevention of sarcopenia in the elderly (24, 101, 195). ST has been shown to increase muscle strength and muscle mass substantially in the elderly in as little as 8 wks (65). Several training studies have shown the efficacy of ST in increasing muscle strength and muscle mass in

men and women aged 50-98 yrs (29, 64, 65, 77, 108). Additionally, the muscle adaptations due to ST have been shown to positively affect functional ability in elderly men and women (30, 234).

Most studies have shown that ST increases muscle strength ~25 to 45% in the elderly (64, 108, 121, 135, 268). At least one study has shown that ST can increase muscle strength in individuals up to the age of 98 yrs (65). Sullivan et al. (255) reported strength increases of 74% in recuperating nursing home patients whose mean age was 83 yrs. Most studies have suggested that there is little or no effect of age in the muscle strength response to ST. However, Lemmer et al. (135) reported slightly, but not significantly greater strength gains (34%) in 20-30 year old men and women compared to 65-75 year old men and women (28%). However, there was no age difference in the response of muscle volume to the same ST program (108). These data suggest that in response to ST, elderly muscle adapts similarly as younger muscle in response to progressive muscle overload.

Dependent on the method of measurement, intensity of the training program, and possibly the age and sex of the subjects, total body muscle mass generally increases in response to ST, however the range in training studies has been from no significant increase to a 41% increase (33, 77). The discrepancy in these results may in large part be due to the difference in techniques used (hydrostatic weighing and K-40 counting or creatinine excretion), which have specific assumptions for estimating lean tissue mass. Furthermore, it is likely that the whole body lean tissue, assessed by these techniques, would not change much in a short-term study based on the findings of the change in actual muscle volume.

Change in muscle volume or CSA allows for the measurement of the specific muscle being stimulated and allows the differentiation of muscle, bone, and fat. Muscle volume or CSA is typically measured by computed tomography (CT) or magnetic resonance imaging (MRI). Several studies have shown that ST increases muscle CSA in the elderly by ~ 8% with the range from studies being 3-23% (65, 77, 84, 217). Studies which have measured muscle volume with ST instead of CSA, to determine changes in muscle size, have shown similar or greater increases in the muscle due to ST (108, 123, 265).

However, at the myofiber level, the increases in fiber size with ST are at least 10%, but often more than 30%. This may be due to the fact that MRI and CT measurements include connective and other tissues which do not change with ST. Both type I and type II fibers increase in size with ST (29, 34, 64, 77, 137). Trappe et al. (269) found increases in fiber area of 20% in type I fibers and 13% in type II fibers in elderly men after 12 wks of ST. Force increased by 35% in type II fibers and by 20% in type I fibers. Shortening velocity increased 75% in MHC I and 45% in MHC IIa. Additionally, power increased 56% in both fiber types combined. In a similar study in older women following 12 wks of ST, fiber diameter increased by 24% in type I fibers and did not change in type IIa fibers. Force increased by 33% in type I and 14% in type II fibers. Shortening velocity was unaltered in both fiber types following training, yet power increased 50% in type I and 25% in type II fibers (270).

Many of the non-muscle-mass components of strength loss are reversed with strength training (88, 122). For example, Welle et al. (284) studied the effect of ST on MQ (3-RM strength/muscle CSA) in young and older subjects. Their older subjects

exhibited a 32% increase in MQ of knee extensors, which was not significantly different from the increase in young subjects. Hakkinen et al. (87) found similar MQ improvements in older men and women in response to ST when muscle strength was assessed with an isometric test. In another study, Welle et al. (284) found that the increase in specific tension (3-RM strength/CSA) following 3 months of resistance training in young (22-31 yrs) and older (62-72 yrs) individuals was similar for elbow flexion (~20%) and knee extension (~35%), but was more than double in older subjects for knee flexion**.** Reeves et al. (209) found that ST increased vastus lateralis muscle-specific force by 19% in older men and women (mean age 74.3 ± 3.5 yr). Finally, studies by Ivey et al. (108) and Tracy et al. (265) have demonstrated an increase in MQ following ST. In response to a 9 wk ST program, Tracy et al. (265) reported a 14 and 16% increase in MQ (quantified by 1-RM and muscle volume) for older men and women, respectively.

Genetic influences on muscle phenotypes related to sarcopenia: Results from heritability studies, genome wide scans, and candidate gene studies have suggested the presence of a genetic influence on baseline and ST-induced muscle phenotypes. Several heritability studies have shown the influence of genetics on fat-free mass (FFM) at baseline. Bouchard et al. (27) estimated the transmissible variance of familial resemblance for FFM to be 40-50% in subjects from the Quebec Family Study. Other studies performed on monozygotic (MZ) and dizygotic (DZ) twin pairs have shown that the heritability in lean body mass ranges from 52-80% (10, 176, 239). In a recent study, Huygens et al. (103) reported that up to > 90% of the variance in baseline muscle mass is heritable in young male twins.

Several family studies, using parent-child and sib-sib correlations, have shown transmission coefficients for isometric strength (handgrip and arm pull) to vary between 0.20 and 0.60. Heritability estimates have been higher in twins and vary between 0.60 and 0.80. Jones et al. (112) used young MZ and DZ twins to determine the heritability of maximal isometric elbow extension force at 100° (180° = straight arm). These authors estimated the heritability to be 83%. In young adult male twins, Thomis et al. (262) found that additive genetic factors explained 66-78% of the variance in maximal isometric torque depending on the angle of measurement. Thomis et al. (261) investigated the influence of genetic factors on static and dynamic strength in young male MZ and DZ twins. They found that the genetic factor contribution to the variability in eccentric arm flexor strength was 62-82%, and 29-65% in concentric arm flexor strength. Tiainen et al. (263) investigated genetic components for maximal isometric handgrip, knee extension, and ankle plantar flexion strength in MZ and DZ twins aged 63-76 yr from the Finnish Twin Study. These authors reported that genetics accounted for 14% of the variance in handgrip strength and 31% of the variance in knee strength for these twins. Previous studies among older twins reported that genetics accounted for 22-52% of the variance in grip strength (10, 36, 72, 208). Arden et al. (10) reported a heritability of 46% for leg extensor strength in MZ and DZ postmenopausal women twins. In a more recent twins study, Huygens et al. (103) reported an ~ 60% heritability in baseline knee, trunk, and elbow isokinetic strength.

Variability of response to a standardized strength training protocol suggests that heritability may influence the response of muscle phenotypes to strength training, although probably accounting for a smaller percent of the variance in muscle phenotypes

than at baseline. For example, in 65-75 year old men and women, the responses to a standardized strength training protocol varied from 5-59% for increases in muscle strength and 1-20% for increases in muscle volume (108, 135). Thomis et al. (260) investigated the heritability of changes in arm strength after 10 weeks of strength training in young male MZ and DZ twins. These researchers found evidence for a genotype by training interaction for one-repetition maximum (1RM) strength and isometric strength with MZ intra-pair correlations of 0.46 and 0.30, respectively. These researchers found that 20% of the variation in post-training 1RM strength, isometric strength, and concentric moment at 120 degrees/sec was explained by training-specific genetic factors that were independent from genetic factors that explained variation in the pre-training phenotype (30-77%).

Few studies have been reported using genome-wide scans or linkage studies to identify genes or gene regions that may influence muscle phenotypes at baseline or after ST. Chagnon et al. (37) performed a genome-wide search for genes related to body composition and its changes after a 20-wk endurance-exercise training program. These researchers found evidence of significant linkage with changes in FFM and the IGF-1 gene. Huygens et al. (103) explored the potential role of the myostatin pathway in relation to muscle strength and estimated muscle CSA in humans using linkage analysis with a candidate gene approach. Linkage patterns were observed between knee extension and flexion peak torque with markers corresponding to the myostatin gene, the CDKN1A gene, and the MYOD1 gene with a maximum LOD score of 2.63 reported for the myostatin gene.

In contrast to the limited data available from genome-wide scans on the influence of genes on muscle phenotypes, there have been many candidate gene studies, including several studies on the *IGF1* and myostatin genes (as suggested by linkage studies) on baseline muscle phenotypes. For example, Sun et al. (256) found that the polymorphism in the promoter region of the *IGF1* gene displayed association and linkage with baseline FFM and the change in FFM due to endurance exercise training. Roth et al. (227) investigated the influence of the interleukin-6 -174 (G/C) promoter polymorphism on FFM in men and women aged 21-92 yrs. These investigators found a significantly lower total FFM for men in the C/C genotype group compared with those in the G/G genotype group, as well as significantly lower FFM of the lower limbs compared with the G/G group. Roth et al. (225) also reported that the C174T polymorphism in the ciliary neurotrophic factor receptor gene significantly influenced FFM in men and women aged 20-90 yrs. In another study, Roth's group reported that the FokI polymorphism was significantly associated with total and appendicular FFM in elderly men (210). Finally, Walsh et al. (280) from Roth's lab, reported that the CAG repeat polymorphism in exon 1 of the human androgen receptor gene was significantly associated with FFM in men aged 19-90 yrs. For this polymorphism, those men with a greater CAG repeat number had greater total FFM than those with fewer CAG repeats.

There have been several candidate gene studies which have investigated the influence of these genes on baseline muscle strength. Geusens et al. (81) reported significant differences in quadriceps muscle strength (23%) between vitamin D receptor BsmI genotype groups in nonobese women older than 70 years. Grundberg et al. (85) investigated the influence of the poly adenosine (A) repeat and the BsmI single

nucleotide polymorphisms in the vitamin D receptor on muscle strength and body composition in healthy 20-39 yr old women. These investigators found that individuals with shorter poly A repeat (ss) and/or absence of the linked BsmI restriction site (BB) had greater hamstring strength compared with women with a longer poly A repeat (LL) and/or presence of the linked BsmI restriction site (bb). Van Pottelbergh et al. (274) examined whether in community-dwelling men over 70 yrs, a polymorphic binding site of the Sp1 transcription factor in the gene encoding for the alpha1 chain of type I collagen (COL1A1 Sp1) was associated with muscle strength. They found that the presence of the s allele for this gene was associated with lower grip strength and biceps strength in the dominant arm, with the difference between ss and SS genotype groups of 21% and 30%, respectively. Roth et al. (226) investigated the relationship between ciliary neurotrophic factor (CNTF) genotype and muscle strength in men and women aged 20-90 yrs. They reported that individuals heterozygous for the CNTF null (A allele) mutation (G/A) exhibited significantly higher concentric peak torque of the knee extensors and knee flexors at 3.14 rad/sec than G/G homozygotes. Also, MQ of the knee extensors (peak torque at 3.14 rad/sec/muscle mass) was significantly greater in G/A heterozygotes. In subjects 60 years and older, A/A homozygotes demonstrated significantly lower eccentric peak torque at 0.52 rad/sec for both knee extensors and knee flexors compared to G/G and G/A genotype groups. These data indicated that individuals exhibiting the G/A genotype possess significantly greater muscular strength and MQ at relatively fast contraction speeds than do G/G individuals. Sayer et al. (235) studied the influence of the ApaI marker polymorphism in the insulin-like growth factor 2 (*IGF2*) gene on handgrip strength in older men and women. These investigators observed that

this polymorphism was significantly associated with grip strength in men, accounting for 1% of the variance in grip strength between G/G and A/A men. Schrager et al. (237) investigated the influence of this same polymorphism on FFM and muscle strength in men and women at several different time points across the adult age span. They reported that isokinetic arm strength (peak torque shortening) at the first time point was lower in ApaI A/A genotype men than in G/G men. With aging, G/G men had a significantly greater rate of loss in FFM compared to A/A men. Compared to G/G women, A/A women had lower total body FFM, lower isokinetic arm (peak torque lengthening and shortening) and leg (peak torque shortening) strength at the first time point, and lower values at age 35 for these muscle phenotypes. This difference between the genotype groups was maintained at age 65 and across the adult age span. Finally, Clarkson et al. (41) investigated the influence of the R577X polymorphism of the *ACTN3* gene on baseline muscle phenotypes in 355 women and 247 men aged 18 to 40 yrs and reported that this polymorphism accounted for about 2% of baseline MVC.

There are only a limited number of studies that have reported the influence of candidate genes on muscle phenotype response to any exercise training modality and an even fewer number using ST (41, 69, 107, 127, 211). Sun et al. (256) investigated the influence of the microsatellite marker in the insulin-like growth factor-1 (*IGF1*) gene and body composition phenotypes before and after 20 weeks of aerobic exercise training in the HERITAGE Family Study. They found significant differences in baseline FFM among *IGF1* genotype groups (192 bp homozygotes, heterozygotes, and noncarriers). There were also significant differences between *IGF1* genotype groups in the change in FFM with training, with 192 bp homozygotes gaining only half the amount of FFM

compared with the other two *IGF1* genotype groups. However, this type of training modality is not ideal for increasing FFM. Folland et al. (69) investigated the influence of ACE genotype on the quadriceps' strength response to 9 weeks of isometric or dynamic ST in healthy males. These investigators found a significant interaction between ACE genotype and isometric strength with greater strength gains in those with the D allele, and more specifically the ID genotype. Reichman et al. (211) reported that two polymorphisms in the interleukin-15 receptor-alpha gene (*IL15RA*) were associated with the muscle hypertrophic response to ST in young men and women. These authors found that a single nucleotide polymorphism in exon 7 of *IL15RA* was strongly associated with muscle hypertrophy and accounted for 7.1% of the variation. In addition, they found that a polymorphism in exon 4 of the *IL15RA* gene was also independently associated with muscle hypertrophy and accounted for an additional 3.5% of the variation in hypertrophy in response to 10 wks of ST. One potential weakness of this study was that changes in muscle mass were assessed using circumference measurements. Clarkson et al. (41) investigated the influence of the R577X polymorphism on the elbow flexor/extensor strength response to 12-wk standardized elbow flexor/extensor resistance training program of the nondominant arm. These authors found that this polymorphism was associated with the elbow flexor/extensor strength response to ST in women, but not in men. In women, this polymorphism accounted for ~ 2% of the gain in 1-RM strength. Finally, Kostek et al. (127) studied the influence of the dinucleotide CA repeat polymorphism near the promoter region of the *IGF1* gene on muscle phenotype responses to ST in Caucasians. These authors found that carriers of the 192 allele (192 homozygotes + 192 heterozygotes) gained significantly more strength with ST than those

with no 192 allele. Each of these previous candidate gene studies had the limitation of either no direct measurement of muscle tissue (69, 211), very small samples sizes (69, 107, 127), or only considered a single candidate gene (41, 69, 107, 127, 211).

Physiology of IGF-1 pathway gene polymorphisms: The *IGF1* gene, that encodes for the IGF-1 protein, is located on human chromosome 12 (12q22-q24.1) (168) and consists of 88,066 base pairs. This gene contains two known promoters, six exons, and five introns (247). Depending on the tissue of origin and transcriptional splicing the mRNA typically contains 153 amino acids and is eventually translated into a 70 amino acid protein with three disulfide bridges (140). The mRNA can produce at least three different transcripts, two of which are expressed in skeletal muscle (17, 153, 229, 254, 288).

The somatomedin hypothesis was developed from early experiments which investigated somatic growth caused by the pituitary gland. Results from these experiments suggested that growth hormone (GH) causes somatic growth indirectly by modulating levels of mediating growth factors, designated as somatomedin substance (46, 170, 233). This somatomedin substance regulated by GH was purified from rat serum and designated as insulin-like growth factor-1 (IGF-1) (213). This substance was termed "insulin-like" because of its ability to stimulate glucose uptake into fat and muscle cells, as well as its homology in amino acid sequence with insulin (202, 213). The primary structural difference between insulin and IGF-1 is that IGF-1 retains the C chain that is cleaved from proinsulin during post-transcriptional processing (213). Upon discovery of IGF-1, the somatomedin hypothesis was refined to suggest that GH secreted by the pituitary would target the liver to secrete IGF-1, which would then act on bodily tissues

to stimulate growth and provide feedback to the pituitary to control the level of GH secretion. However, D'Ercole et al. (45) first indicated the somatomedin hypothesis was incomplete when they discovered that explants of fetal mouse tissue maintained in serum-free media showed higher levels of IGF-1 in the culture medium as compared with extracts of the tissues themselves: liver, intestine, heart, brain, kidney, and lung. Other studies also showed that various tissues express IGF-1 and that this tissue-specific IGF-1 could be affected by and also act independent of plasma GH (145, 146, 216). Nevertheless, the direct effect of GH on non-hepatic tissues remained in question and it was subsequently shown that GH could affect tissues by stimulating local production of IGF-1 or by acting directly on tissues to cause growth (83). The latter process occurred without a mediating factor, but the resulting growth was not as dramatic as when IGF-1 was involved.

Action of IGF-1. IGF-1 displays numerous diverse functions during both embryonic development and postnatal growth. Studies have shown that mice carrying null mutations in the *IGF1* gene are born small and grow poorly postnatally (11, 197). Naturally occurring mutations in the *IGF1* gene are rare. It has been reported that only a single patient, with both intrauterine and postnatal growth retardation, has been found who had a deletion of the *IGF1* gene (287). The complete physiological functions of IGF-1 are beyond the scope of this review. Therefore, a brief background of IGF-1 action will be given with specific emphasis on skeletal muscle.

IGF-1 exerts some of its influence as an endocrine hormone circulating in the blood stream until reaching its target tissue. Unlike insulin, IGF-1 in the circulation is bound by one of six known insulin-like growth factor binding proteins (IGFBPs) (113).

These binding proteins act as carriers of IGF-1 to transport it out of circulation and prolong the half-life by protecting it from proteolytic degradation. In addition to their role in circulation, IGFBPs are often expressed in target tissues where they act to regulate IGF-1 function further. IGFBPs have been shown to augment and attenuate IGF-1 action depending on the target tissue (206).

The IGFBP is cleaved by proteases, releasing IGF-1, which can then bind to a tissue's insulin or IGF-1 receptor. The insulin and IGF-1 receptors structures are up to ~85% homologous, however, IGF-1 has a greater affinity for the IGF-1 receptor. Upon binding of IGF-1, the IGF-1 receptor undergoes rapid phosphorylation to activate tyrosine kinases (136, 253). These tyrosine kinases interact with intermediate signaling proteins, insulin receptor substrate (IRS-1), and src homology containing proteins (Shc), resulting in a complex and versatile modulation of cellular transcription and translation (67).

The activation of IRS-1 by IGF-1 binding to the IGF-1 receptor results in the activation of phosphatidylinositol 3-kinase (PI 3-K). The PI 3-K pathway has been shown to mediate skeletal muscle hypertrophy in mammalian muscle (169, 186). In addition, studies have shown that the binding of IGF-1 to its receptor signals the opening of a cell's calcium channels (48), releasing calcium into the cell to be bound by calmodulin, activating calcineurin, which can in turn stimulate muscle hypertrophy (172, 240).

The IGF-1 receptor has been shown to play many roles including: mediating amino acid uptake in muscle as well as decrease protein degradation, stimulating proliferation and differentiation of myocytes, and increasing DNA synthesis in muscle

satellite cells and regulating gene expression for proteins involved in growth and metabolism, including the c-fos and c-jun genes (40, 53, 62, 183, 294). Mice lacking the IGF-1 receptor die immediately after birth due to respiratory failure and severe growth deficiency (45% of normal) (143). Also a transgenic mouse study showed that IGF-1 mediates its proliferative and differentiative effects via the IGF-1 receptor (199).

Both gene knockout and transgenic animal studies have demonstrated the importance of IGF-1 in muscle development (96, 143, 171). In muscle, IGF-1 has been shown to stimulate satellite cell proliferation (38), increase amino acid uptake (155), suppress proteolysis (13), increase thymidine incorporation (82), stimulate myogenic differentiation (66), and stimulate myogenesis (236), and unlike other mitogenic factors, IGF-1 will separately stimulate both proliferation and differentiation of muscle cells in culture (200). Transgenic mice overexpressing the *IGF1* gene show enhanced myotube formation as well as increased mRNA levels of myogenic factors, Myo D and myogenin, and elevated mRNA for contractile proteins (42) and, in addition, demonstrate protection from the normal loss of muscle mass and strength that occurs with senescence and undergo muscle regeneration from cardiotoxin-induced muscle damage (171). Overexpression of IGF-1 in transgenic mice has also been shown to prevent muscle alterations in the neuromuscular junction, preserve spinal cord motor neuron innervation in the muscle, and decrease the loss of type IIb muscle fibers (156), as well as accelerate muscle and motor neuron regeneration after sciatic nerve crush injury (201). The regeneration or preservation of neural innervation is likely to be a causative factor in preventing muscle strength and mass loss with age.

Circulating IGF-1 and exercise. IGF-1 is produced by various tissues including skeletal muscle, however, the majority of the circulating form of IGF-1 is produced in the liver. Several studies have investigated the relation of circulating IGF-1 and exercise and have found an increase in circulating IGF-1 up to 20 minutes after high intensity cycling (35) and forearm resistance exercise (60). Nevertheless, ST studies did not show an increase in circulating IGF-1 (128, 179, 180), but did change levels of potential modulators of IGF-1 action, including IGFBP-2, IGFBP-3, and acid labile subunit (180). In contrast, it was reported that high intensity aerobic training (59) and eccentric exercise (14) increased muscle IGF-1 and muscle *IGF1* mRNA, respectively, but did not affect circulating levels of IGF-1. The results of these studies suggest that circulating IGF-1 levels are likely to play a minimal role in the response to exercise, but that locally expressed IGF-1 impact is more dramatic. The exact time course for the change in muscle *IGF1* gene expression and protein translation will require further study. Furthermore, Sjogren et al. (245) reported that liver specific deletion of the *IGF1* gene produced mice that lacked the circulating form of IGF-1, yet displayed normal growth. These results suggest that the endocrine form of IGF-1 may not be important for muscle growth or maintenance in adult humans.

Autocrine/paracrine role of IGF-1 in aging muscle. Circulating levels of GH and IGF-1, as well as levels of IGF-1 in muscle, decrease with age (275). This decline begins in the thirties and results in a 40% decrease by the age of 80. It is thought that the decrease in circulating levels of IGF-1 specifically is a causal factor in the decline in muscle function that occurs with aging. Compounding or possibly causing this decline is the reduction with age of the autocrine/paracrine form of IGF-1 produced by muscle.

The *IGF1* gene can express multiple isoforms, derived from alternative splicing, depending on the tissue of origin and the stimulus. The predominant circulating isoform of IGF-1, produced by the liver due to GH stimulation, has been termed IGF-1Eb and is produced by splicing out exon one and thus utilizes the exon two promoter. Skeletal muscle expresses two known isoforms of the *IGF1* gene when it is subjected to stretch or mechanical stimulation. The first muscle isoform is termed IGF-1Ea (229) and is initiated at the exon 2 promoter similar to the liver form, however in IGF-1Ea, exon 5 is removed by alternative splicing. Overexpression of this isoform in transgenic mice resulted in pronounced muscle hypertrophy and older mice displayed signs of protection against the normal loss of muscle mass associated with aging (171). Musaro et al. (171) concluded that overexpression of IGF-1Ea could preserve muscle architecture and the age-independent regenerative capacity of muscle.

The second IGF-1 isoform expressed in muscle, termed mechano-growth factor (MGF) or IGF-1Ec, is a splice variant resulting from a novel splice acceptor site in the intron preceding exon 6 and is generated in muscle subjected to stretch and overload (288). Structurally, the MGF mRNA differs from its liver counterpart because of the presence of a 49-base pair insert on the carboxyl end of the protein, which is derived from exon 5 of the *IGF1* gene. This isoform is not glycosylated, therefore, it is expected to have a shorter half-life than the liver IGF and is therefore likely to be designed to act in an autocrine/paracrine, rather than in a systemic fashion. Animal studies have shown significant upregulation of MGF with muscle stimulation (153, 288). Other studies have shown that locally produced IGF-1 can stimulate muscle hypertrophy through activation of satellite cells and increased protein synthesis rates (1, 98, 240, 289). In humans,

several studies have shown an increase in muscle IGF-1 with a single bout of resistance exercise (14, 64, 198), even in frail elders (64), although the specific IGF-1 isoform was not determined. However, reports from two studies have suggested that MGF mRNA and MGF protein levels will be increased less with muscle stimulation in older rats (185) and humans (89) than in those who are younger. These results suggest a reduced capacity of older muscle to be stimulated by resistance exercise. However, Hameed et al. (90) did report ~170% increase in MGF mRNA after 5 weeks of ST in elderly men.

Results from previous studies clearly show that ST induces local expression of IGF-1 and it is likely that this locally expressed IGF-1 is mediating many of the hypertrophic effects observed in skeletal muscle. However, as previously mentioned, there is significant variability observed in the strength and hypertrophic responses of skeletal muscle to ST. Additionally, the increases in IGF-1 mRNA that occur in response to resistance exercise have been shown to range from 2-864% (91), and a variation for IGF-1 increase with ST of ~137% has been observed in the elderly (64, 90). These results suggest that genetics could be affecting this response. Indeed, studies have shown that circulating levels of IGF-1 are almost completely under genetic control in healthy twin children and the variability in circulating levels in the elderly is estimated to be ~ 63% under genetic control (99, 119). To date, no studies have examined the heritability of *IGF1* muscle expression. An autosomal genome wide search for genes related to FFM and its changes with exercise training revealed that a polymorphism in the *IGF1* promoter region displayed significant linkage with changes in FFM (37). Additionally, this same polymorphism was shown to be associated and in linkage with baseline FFM and with the change in FFM resulting from aerobic exercise training (256). More

importantly, this polymorphism has been shown to influence the changes in strength with ST in Caucasian older men and women (127).

IGF1 CA dinucleotide repeat polymorphism. The *IGF1* polymorphism identified in a genome wide scan and most association studies is the CA dinucleotide repeat polymorphism near the promoter region of the *IGF1* gene in humans (283). Studies in rats and humans of a similar CA repeat near a promoter region have shown this repeat to influence gene expression (2, 228). The CA dinucleotide repeat polymorphism near the promoter region of the *IGF1* gene typically contains between 16 and 22 CA repeats and this polymorphism is commonly referred to by the base pair length of the amplified DNA fragment (e.g. 192 bp). The 192 allele (19 CA repeats at nucleotide position 1087-1127 in the human IGF-1 DNA sequence Genbank accession number AY260957, RS# 10665874) of the *IGF1* promoter gene polymorphism has been investigated in various contexts. Genotyping of this polymorphism is typically separated into three groups: 192 homozygotes, 192 heterozygotes, and noncarriers of the 192 allele. It has not been determined whether the 192 polymorphism is causally related to changes in IGF-1 function, yet, the 192 allele is the most prevalent allele in the majority of the populations studied to date. Although this polymorphism has not been proven to be functional, it has been proven to be a potential marker for disease-related phenotypes and possibly IGF-1 expression levels. Also, this polymorphism has been shown to influence muscle strength in Caucasians.

Rosen et al. (222) first implicated this polymorphism in influencing serum levels of IGF-1 and bone mineral density in older men and women. These investigators reported that 192 homozygotes had lower serum levels of IGF-1, and in a group of older

men, 192 homozygotes had a disproportionately high incidence of idiopathic osteoporosis (222). Since this report other groups have investigated the influence of the 192 allele on circulating IGF-1 levels with some studies showing decreased (71, 212), increased (125, 162, 215, 273), or no difference unless combined with oral contraceptive use (111, 292). Although results are inconclusive for the effect of the 192 polymorphism on IGF-1 levels, it seems possible that the *IGF1* 192 gene polymorphism may affect skeletal muscle-related phenotypes because of previous results showing positive associations of this polymorphism with FFM (37, 256) and with the change in muscle strength with ST (127). If the 192 allele itself is not functional it would appear to be at least a valid marker for phenotypes related to IGF-1 expression. Therefore, the possibility exists that the 192 polymorphism is in linkage disequilibrium with a functional polymorphism in the *IGF1* gene.

Physiology of IGFBP-3. Almost all IGFs released from tissue are bound with high affinity and specificity by IGFBPs. There have been at least six IGFBPs identified and they are designated IGFBP-1 to IGFBP-6. IGFBPs have several important functions, including: limiting the bioavailability of free IGFs to bind to IGF receptors, preventing IGF-induced hypoglycemia, regulating the transport of IGFs between intra- and extravascular space, enhancing the actions of IGFs by forming a slow-releasing pool of IGFs, affecting cellular proliferation/death via IGFBP receptors, and potentiating or inhibiting IGF action.

IGFBP-3 is a member of the family of IGFBPs. It has been reported that IGFBP-3 carries most of the 90% of IGFs in circulation which is bound by IGFBPs (22). Regulation of *IGFBP3* gene expression is complex and tissue specific. GH, insulin, and

insulin-like growth factors are hormones important in the regulation of *IGFBP3* expression (21, 259, 278), as are agents that induce growth inhibition/apoptosis, such as p53 (32), retinoic acid (86, 151), vitamin D (177), antiestrogens (104), antiandrogens (178), transforming growth factor-β (86, 181), and tumor necrosis factor-α (232). Also, it has been reported that IGFBP-3 levels are inversely associated with cigarette smoking (117). In addition, it has been reported that African Americans have lower circulating levels of IGFBP-3 than Caucasians (192, 272). As is the case with IGF-1, IGFBP-3 concentrations in the blood decline with age (115, 116, 293).

Because it is a major carrier of IGFs in circulation, IGFBP-3 appears to play an important role in the growth of tissues in early development. However, the role of IGFBP-3 in tissue growth in adults, especially in skeletal muscle, is not as clear. There is evidence that IGFBP-3 is present in skeletal muscle and that it may be a modulator of the autocrine/paracrine effect of IGFs expressed in skeletal muscle (4, 15, 249, 295). It has also been shown that increased secretion of IGFBP-3 in a primary adult human skeletal muscle cell model can be stimulated by IGF-1 (70).

IGFBP3 promoter region -202 polymorphism. The *IGFBP3* gene, which encodes for the IGFBP-3 protein, is highly conserved among species and is present on chromosome 7p14-p12 (58). Twin studies have shown that about half of the intra-individual variability in circulating IGFBP-3 levels is genetically determined (94). Deal et al. (47) detected five polymorphic sites on the *IGFBP3* gene, and identified the -202 locus in the promoter region of this gene as significantly influencing age-adjusted circulating IGFBP-3 concentration. For this polymorphism, the wild-type adenine allele is replaced with the variant cytosine allele with an allele frequency of 40% in those

subjects tested. These investigators found that A homozygotes had higher levels of circulating IGFBP-3 than AC heterozygotes who had higher circulating levels of IGFBP-3 than C homozygotes. Also, these authors reported significantly higher promoter activity for the A allele compared with the C allele in an in vitro study. This finding was consistent with the relationship observed between genotype and circulating IGFBP-3 levels. In addition, these investigators reported that body mass index (BMI) and height interacted with the -202 polymorphism to influence circulating IGFBP-3 levels, such that tall individuals or individuals with a BMI of 27 or greater had levels of circulating IGFBP-3 that were significantly higher when they possessed at least one A allele.

Other studies that have investigated the influence of this polymorphism on cancer risk have also shown that the A allele was associated with higher levels of IGFBP-3 (111, 210, 246). However, it was also reported that the -202 polymorphism interacted with body size indicators, ethnicity, use of aspirin/NSAIDS (246), and oral contraceptive status (111) to influence IGFBP-3 levels.

Physiology of calcineurin and its link with IGF-1. Calcineurin is a Ca^{2+}/calmodulin-dependent protein phosphatase, which plays a key role in mediating hypertrophic response. Calcineurin consists of a 58- to 59-kD catalytic subunit, designated as calcineurin A (CnA), and a 19-kD Ca^{2+}-binding regulatory subunit, designated as calcineurin B (281). There are 2 major isoforms, alpha and beta, of CnA encoded by separate genes located on different human chromosomes. A third isoform, A-gamma, is unique to the testis. Calcineurin B consists of only one isoform designated as alpha isoform 1. Calcineurin is highly expressed in muscle tissue at levels ten times higher than most other tissues. Calcineurin is activated by sustained increase in basal Ca^{2+}

concentration (44). Once activated, calcineurin dephosphorylates the nuclear factor of activated T-cell (NFAT) families or members of other transcriptional factor families, such as myocyte enhancer factor 2 (MEF2). These activated transcription factors translocate to the nucleus and then play an important role in the subsequent transcriptional activation of genes involved in hypertrophy (54, 55, 285) or genes which influence other muscle phenotypes (39, 165, 174, 188).

The role that calcineurin plays in cardiac muscle appears to be more clear than the role it plays in skeletal muscle. Several investigators have reported that calcineurin stimulates cardiac hypertrophy (92, 166, 214). Molkentin et al. (166) reported that transgenic mice overexpressing constitutively active calcineurin or NFAT3 develop cardiac hypertrophy. Other investigators have reported increased calcineurin activity in hearts of patients with different forms of hypertrophy including: iodiopathic cardiomyopathy (92), aortic stenosis, and hypertrophic obstructive cardiomyopathy (214).

The role of calcineurin in skeletal muscle is not as clear as its role in cardiac muscle. There have been several reports which have suggested that calcineurin may play a role in skeletal muscle hypertrophy (54, 55, 163, 172, 240, 257), while results from other studies have suggested that calcineurin is involved in skeletal muscle fiber-type conversion (39, 165, 174, 188, 241, 257). Still others have reported that calcineurin plays a role in myogenic differentiation (50, 73, 74). In a transgenic mice study, Talmadge et al. (257) reported that calcineurin activation can influence skeletal muscle phenotype (fiber-type), and that the specific influence of calcineurin activation on the phenotypic and mass characteristics of a muscle, is dependent upon the original phenotypic state of

the muscle. Therefore, calcineurin appears to play some role in influencing skeletal muscle phenotypes (mass and fiber type).

Several in vivo studies have supported a role for calcineurin activation in promoting skeletal muscle growth. For example, Bigard et al. (23) reported that inhibition of calcineurin with cyclosporine A (CsA) significantly reduced the growth of both the slow/type I soleus muscle and fast/type II plantaris muscle in normal, ambulatory rats (23). CsA also slowed the growth of mouse plantaris muscle during overload hypertrophy (54) and reduced or prevented soleus and plantaris growth after a period of unloading and atrophy (163). Similarly, overexpression of a muscle-specific, constitutively active calcineurin caused an increase in soleus muscle, but produced a decrease in plantaris muscle mass in ambulatory mice (257). Also Dunn et al. (55) showed in mice that overload-induced hypertrophy and fast-to-slow contractile protein transitions were prevented in muscle fibers expressing a peptide which bound calcium/calmodulin complexes and inhibited their signaling to calmodulin-dependent enzymes such as calcineurin.

In contrast to these results, some investigators have presented findings against a role for calcineurin activation in promoting muscle growth. Serrano et al. (241) reported that growth in soleus muscle fibers that were regenerating after injection with toxin was not affected by the calcineurin activity inhibitors, CsA or FK506 (241). Other studies reported that expression of a muscle-specific, constitutively active calcineurin had no effect on muscle fiber size or mass in soleus or plantaris muscles (174), whereas, null-mutant mice for the CnAα isoform showed an increase in fiber number in soleus muscle, but no change in fiber size or number in plantaris muscle (187). To some extent, the

apparent conflict in results as far as calcineurin's role in promoting muscle growth may be due to differences in dosing with calcineurin inhibitors (both amount as well as length of dosing), where relatively small doses are ineffective at inhibiting muscle growth, as discussed in a review article (160). Similar explanations concerning calcineurin dose dependency may underlie differences in findings on calcineurin-overexpressing animals. Other factors which may explain the discrepancy in results are differences in gender, species, or even strain of animals tested, as well as differences in muscle type studied and differences in the mechanism regulating the increase in muscle size depending on the specific type (hypertrophy, maintenance, regeneration) or stimulus for muscle growth.

In a another study concerning the role of calcineurin in muscle growth, researchers generated and analyzed null mutants and muscle-targeted, conditional mutants for specific isoforms (188). One line targeted the ß-isoform of CnA and produced a reduction of ~ 50% in total calcineurin activity in muscle. In a second line, a conditional, muscle-specific null mutation of *PPP3R1* (*PPP3R1*1-LoxP(fl/fl)-MLC-cre mice) produced a > 80% reduction in muscle calcineurin activity. Somatic deletion of CnAβ resulted in a significant reduction in fiber number and muscle mass relative to wild-type mice. However, for *PPP3R1*1-LoxP(fl/fl)-MLC-cre mice there were no differences in fiber number and muscle mass relative to wild-type mice. This difference may be explained by the fact that CsA treatments would affect calcineurin activity in all muscle cells at all stages of development, whereas activity of calcineurin in *PPP3R1*1-LoxP(fl/fl)-MLC-cre mice would be affected only in cells that express myosin light chain 1f. Because myosin light chain 1f expression is initiated after early stages of myogenic cell proliferation and differentiation (148), early myogenic cells in the conditional

mutants would be expected to express wild-type levels of calcineurin. Alternatively, CnAβ mutants would be calcineurin deficient throughout myogenesis, which would lead to a reduction in myogenic cells, and ultimately to a reduction in the number of muscle fibers, based on evidence suggesting that calcineurin promotes myogenic cell proliferation and early differentiation (73, 74).

Parsons et al. (188) reported that activation of muscle calcineurin may contribute to muscle fiber growth in at least some muscles and under some experimental conditions. After IGF-1 treatments, both CnAβ-null mutants and wild-type mice showed similar increases in plantaris and soleus muscle mass. However, the significant increase in plantaris muscle caused by IGF-1 treatment of wild-type mice was not observed in *PPP3R1*1-LoxP(fl/fl)-MLC-cre mice, although soleus muscle mass increase did occur. This finding implicates the calcineurin that is expressed specifically in muscle in the adaptive response to IGF-1 stimulation. However, an explanation for the lack of a similar response in CnAβ mutants has yet to be established. However, the greater loss of calcineurin activity in *PPP3R1*1-LoxP(fl/fl)-MLC-cre mice than in CnAβ-null mutants suggests that the differences may reflect the magnitudes of calcineurin activity.

Further insight into the role of calcineurin on muscle growth during overload may be provided by comparisons of effects of different perturbations on calcineurin activity. Dunn et al. (54) reported that growth of plantaris muscle during overload by synergist ablation for 4 wk was reduced ~ 45% by CsA treatments, which decrease calcineurin activity by 65% (57). Similarly, CnAβ-null mutants in which calcineurin activity was reduced by ~50%, showed a 54% reduction in the increase in plantaris muscle mass during 6 wk of overload (188). However, plantaris muscle in *PPP3R1*1-LoxP(fl/fl)-

MLC-cre mice, in which there was a > 80% reduction in muscle calcineurin activity, experienced only a trend for a 21% reduction in muscle growth.

In addition to its possible role in influencing hypertrophy in response to overload, studies have suggested that calcineurin plays a role in skeletal muscle differentiation. Friday et al. (73) found that differentiation of skeletal muscle myoblasts was inhibited at the first (commitment) stage by treatment with either CsA or expression of CAIN, a physiological inhibitor of calcineurin. These authors concluded that myogenesis is initiated by a calcineurin-dependent pathway. Also Delling et al. (50) concluded from studies using both adenovirus-mediated gene transfer of activated calcineurin protein and calcineurin inhibitory peptide (CAIN) that the IGF-calcineurin-NFATc3 pathway enhances myogenic differentiation.

Still other investigators have provided results suggesting a role of calcineurin in activating slow type I muscle fiber gene programs (23, 39, 54, 241). In *PPP3R1*1-LoxP(fl/fl)-MLC-cre mice experiencing overload, fiber switching to a slower phenotype was impaired (188), and systemic null mutation of either calcineurin Aα or Aβ resulted in a reduction in the proportion of slow/type I fibers in healthy, ambulatory mice (187). Likewise, it has been reported that overexpression of calcineurin in skeletal muscle produces a shift toward a slower phenotype (174, 257). This calcineurin-activated switch to a slower phenotype may play an important role in the muscle phenotype responses to strength training in adults due to observations from several investigators, that the consequence of resistance training is a conversion of some fiber types from less to more metabolically efficient, such as from type II d/x to IIa (56, 106, 129, 251, 252). Thus, if

calcineurin does indeed play a role in fiber-type switching it could play a very important role in the muscle phenotype responses to strength training.

Although its exact role in skeletal muscle is unclear, calcineurin does appear to influence skeletal muscle phenotype response to muscle stimulation. Calcineurin may activate different classes of transcription factors and co-activators (MEF2, GATA) depending on the type of calcium signal (prolonged, low amplitude or high-amplitude) on the muscle cell (182) to produce different responses (hypertrophy, fiber-type switching, etc). One study has even shown that calcineurin may regulate satellite cell fusion during muscle fiber hypertrophy via the NFATc2 transcription factor (100).

Reports have suggested that calcineurin is linked with IGF-1 in a mechanical signaling pathway to influence skeletal muscle cell phenotypes (172, 240). Another report also suggested an IGF-calcineurin-NFATc3 link for influencing myogenic differentiation (50). Mechanical loading causes a rapid transient increase of IGF-1 release by muscle cells (190). The binding of IGF-1 to its receptor on muscle cells can subsequently stimulate L-type calcium channel activity to increase cytosolic calcium (48). Cytosolic calcium then binds to calmodulin, which then activates calcineurin. Activated calcineurin dephosphorylates NFAT or other transcription factors resulting in the translocation of transcription factors into the nucleus, where they bind to the transcription factor response elements to enhance the expression of specific genes to influence muscle phenotypes. *In vitro* studies in mice skeletal muscle cells showed that the IGF-1-induced hypertrophy of these cells could be prevented by inhibition of calcineurin activity (172, 240). Experimental manipulations that cause increased mechanical loads on muscle have been shown to produce increases in muscle mass that

can be attenuated by reductions in calcineurin activity (54, 163, 188). For example, calcineurin inhibition during rat muscle overload, caused by synergist ablation, significantly reduced the hypertrophic response of this muscle, and prevented the 20-fold increase in the number of slow, myosin heavy chain-I-expressing fibers (slow/type I fibers) that occurred in overloaded muscle, in which calcineurin was not inhibited (54).

Besides the IGF-1-calcineurin mechanical signaling pathway, there have been reports of other IGF-1-stimulated signaling pathways that may play a role in skeletal muscle hypertrophy, including the PI3K/Akt/mTOR pathway (186, 218, 241). Even though it is likely that there are multiple pathways involved in the IGF-1-mediated muscle phenotype response to ST, there appears to be sufficient evidence supporting an important role for an IGF-1-calcineurin mechanical signaling pathway in skeletal muscle phenotype responses to ST.

Calcineurin B promoter region 5-base pair insertion/deletion (I/D) polymorphism. There have been few reports on the influence of polymorphisms of the calcineurin gene and the genes encoding for its subunits on protein levels, activity level of calcineurin, and other phenotypes. For example, Poirier et al. (194) investigated the influence of calcineurin polymorphisms and polymorphisms of related genes on cardiac hypertrophy. These authors reported that the nuclear factor NFATC4 gene, activated by calcineurin, influenced the individual cardiac hypertrophic response. More specifically, a Gly/Ala substitution at position 160 of the NFATC4 protein (G160A) was associated with left ventricular mass and wall thickness (194). However, these authors did not report the influence of any calcineurin polymorphisms on cardiac hypertrophy response.

We are aware of only one report on any polymorphisms in genes encoding for calcineurin or its subunits, which was for a polymorphism in the gene encoding for the regulatory subunit of calcineurin, calcineurin B (258). The gene that encodes for calcineurin B is located on human chromosome 2p16-p15 (281). This gene encodes for calcineurin B in all tissues except the testis, and it is highly conserved at the level of both protein and DNA sequences in eukaryotes.

Tang et al. (258) identified and investigated the influence of the 5-base pair (bp) insertion/deletion (I/D) polymorphism in the promoter region of the calcineurin B (*PPP3R1*) gene on traditional left ventricular hypertrophy and inappropriately high left ventricular mass in severe hypertensive Caucasian and African American men and women. These authors reported that this polymorphism influenced inappropriately high left ventricular mass in severe hypertensives, with those individuals possessing a D allele at increased risk for developing inappropriately high left ventricular mass. This 5-bp deletion is predicted to eliminate a consensus Nkx-2 transcription binding sight and disrupt an AseI restriction site (258). These authors suggest that the Nkx-2 transcriptional binding site serves as an important binding site for a repressor or inhibitor of *PPP3R1* transcription, and the 5-bp deletion in this region removes the inhibition and consequently promotes the expression of *PPP3R1*, leading to increased calcineurin activity. Due to the influence that this polymorphism may have on hypertrophy in cardiac muscle, and the fact that cardiac and skeletal muscle share common hypertrophic pathways (182), it is possible that this polymorphism may influence hypertrophic responses to mechanical overload in skeletal muscle as well. However, we are unaware

of any previous cross-sectional or strength training reports on the influence of calcineurin gene polymorphisms on skeletal muscle phenotypes.

In conclusion, loss of muscle mass and function due to sarcopenia may result in loss of independence, disability, and even mortality in the elderly. ST has been shown to be the most effective intervention in the prevention and treatment of sarcopenia, however, significant inter-individual variability exists in the muscle phenotype response to ST, suggesting a genetic influence. A small number of candidate genes have been identified which appear to influence muscle phenotype responses to ST, including *IGF1*. However, IGF-1 is linked with several downstream proteins that influence muscle hypertrophy. At present, no studies have reported the influence of more than one gene, which is part of a pathway of genes involved in muscle hypertrophy, on muscle response to ST. Therefore, the need exists to investigate gene polymorphisms linked in a common pathway to better understand genetic influences on muscle phenotype responses to ST, in order to better identify appropriate interventions for individuals in the prevention and treatment of sarcopenia.

REFERENCES

1. **Adams GR and McCue SA**. Localized infusion of IGF-I results in skeletal muscle hypertrophy in rats. *J Appl Physiol* 81: 2509-2516, 1998.
2. **Agarwal AK, Giachetti G, Lavery G, Nikkila H, Palermo M, Ricketts M, McTernan C, Bianchi G, Manunta P, Strazzullo P, Mantero F, White PC and Stewart PM**. CA-Repeat polymorphism in intron 1 of HSD11B2: effects on gene expression and salt sensitivity. *Hypertension* 36: 187-194, 2000.
3. **Alexander NB, Schulz AB and Warwick DN**. Rising from chair: effects of age and functional ability on performance mechanics. *J Gerontol Med Sci* 46: M91-M98, 1991.
4. **Alway SE, Degens H, Lowe DA and Krishnamurthy G**. Increased myogenic repressor Id mRNA and protein levels in hindlimb muscles of aged rats. *Am J Physiol Regul Integr Comp Physiol* 282: R411-R422, 2002.
5. **Andersen JL, Terzis G and Kryger A**. Increase in the degree of coexpression of myosin heavy chain isoforms in skeletal muscle fibers in the very old. *Muscle Nerve* 22: 449-454, 1999.
6. **Aniansson A, Grimby G and Hedberg M**. Compensatory muscle fiber hypertrophy in elderly men. *J Appl Physiol* 73: 812-816, 1992.
7. **Aniansson A, Hedberg M, Henning GB and Grimby G**. Muscle morphology, enzymatic activity, and muscle strength in elderly men: a follow-up study. *Muscle Nerve* 9: 585-591, 1986.

8. **Aniansson A, Sperling L, Rundgren A and Lehnberg E**. Muscle function in 75-year-old men and women. A longitudinal study. *Scand J Rehabil Med Suppl* 9: 92-102, 1983.
9. **Aniansson A, Zetterberg C, Hadberg M and Henriksson K**. Impaired muscle function with aging. A background factor in the incidence of fractures of the proximal end of the femur. *Clinical Orthopedic Related Resistant* 191: 193-200, 1984.
10. **Arden NK and Spector TD**. Genetic influences on muscle strength, lean body mass, and bone mineral density: a twin study. *J Bone Mineral Res* 12: 2076-2081, 1997.
11. **Baker J, Liu JP, Robertson EJ and Efstratiadis A**. Role of insulin-like growth factors in embryonic and postnatal growth. *Cell* 75: 73-82, 1993.
12. **Balagopal P, Rooyackers OE, Adey DB, Ades PA and Nair KS**. Effects of aging on in vivo synthesis of skeletal muscle myosin heavy-chain and sarcoplasmic protein in humans. *Am J Physiol* 273: E790-E800, 1997.
13. **Ballard FJ and Francis GL**. Effects of anabolic agents on protein breakdown in L6 myoblasts. *Biochem J* 210: 243-249, 1983.
14. **Bamman MM, Shipp JR, Jiang J, Gower BA, Hunter GR, Goodman A, McLafferty CLJr and Urban RJ**. Mechanical load increases muscle IGF-I and androgen receptor mRNA concentrations in humans. *Am J Physiol Endocrinol Metab* 280: E383-E390, 2001.
15. **Barjot C, Navarro M, Cotten ML, Garandel V, Bernardi H and Bacou F**. Rabbit slow and fast skeletal muscle-derived satellite myoblast phenotypes do not

involve constitutive differences in the components of the insulin-like growth factor system. *J Cell Physiol* 169: 227-234, 1996.

16. **Bartke A, Coschigano K, Kopchick J, Chandrashekar V, Mattison J, Kinney B and Hauck S**. Genes that prolong life: relationships of growth hormone and growth to aging and life span. *J Gerontol A Biol Sci Med Sci* 56: B340-B349, 2001.
17. **Barton-Davis ER, Shoturma D, I, Musaro A, Rosenthal N and Sweeney HL**. Viral mediated espression of insulin-like growth factor I blocks the age-related loss of skeletal muscle function. *Proc Natl Acad Sci USA* 95: 15603-15607, 1998.
18. **Bassey EJ, Fiatarone MA, O'Neill EF, Kelly M and Evans WJ**. Leg extensor power and functional performance in very old men and women. *Clinical Science* 82: 321-327, 1992.
19. **Bassey EJ and Harries UJ**. Normal values for handgrip strength in 920 men and women aged over 65 years, and longitudinal changes over 4 years in 620 survivors. *Clin Soc (Lond)* 84: 331-337, 1993.
20. **Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, Garry PJ and Lindeman RD**. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 147: M755-M763, 1998.
21. **Baxter RC and Martin JL**. Radioimmunoassay of growth hormone-dependent insulinlike growth factor binding protein in human plasma. *J Clin Invest* 78: 1504-1512, 1986.
22. **Baxter RC, Martin JL and Beniac VA**. High molecular weight insulin-like growth factor binding protein complex. *J Biol Chem* 264: 11843-11848, 1989.

23. **Bigard X, Sanchez H, Zoll J, Mateo P, Rousseau V, Veksler V and Ventura-Clapeir R**. Calcineurin co-regulates contractile and metabolic components of slow muscle phenotype. *J Biol Chem* 275: 19653-19660, 2000.

24. **Blackman MR, Sorkin JD, Munzer T, Bellantoni MF, Busby-Whitehead J, Stevens TE, Jayme J, O'Connor KG, Christmas C, Tobin JD, Stewart KJ, Cottrell E, St.Clair C, Pabst KM and Harman SM**. Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. *JAMA* 288: 2282-2292, 2002.

25. **Bloesch D, Schutz Y, Breitenstein E, Jequier E and Felber JP**. Thermogenic response to an oral glucose load in men: comparison between young and elderly subjects. *J Am Coll Nutr* 7: 471-483, 1988.

26. **Borges O**. Isometric and isokinetic knee extension and flexion torque in men and women aged 20-70. *Scand J Rehabil Med* 21: 45-53, 1989.

27. **Bouchard C, Perusse L, Leblanc C, Tremblay A and Theriault G**. Inheritance of the amount and distribution of human body fat. *Int J Obes* 12: 205-215, 1988.

28. **Brissenden JE, Ullrich A and Francke U**. Human chromosomal mapping of genes for insulin-like growth factors I and II and epidermal growth factor. *Nature* 310: 781-784, 1984.

29. **Brown A, McCartney N and Sale D**. Positive adaptation to weight-lifting in the elderly. *J Appl Physiol* 69: 1725-1733, 1990.

30. **Brown M and Holloszy JO**. Effects of walking, jogging, and cycling on strength, flexibility, speed, and balance of 60- to 72-year olds. *Aging (Milano)* 5: 427-434, 1993.

31. **Brown WF**. A method for estimating the number of motor units in thenar muscles and the changes in motor unit counting with ageing. *J Neurol Neurosurg Psychiatry* 35: 845-852, 1972.

32. **Buckbinder L, Talbott R, Velasco-Miguel S, Takenaka I, Faha B, Seizinger BR and Kley N**. Induction of the growth inhibitor IGF-binding protein 3 by p53. *Nature* 377: 646-649, 1995.

33. **Campbell WW, Crim MC, Dallal GE, Young VR and Evans WJ**. Increased protein requirements in elderly people: new data and retrospective reassessments. *Am J Clin Nutr* 60: 501-509, 1994.

34. **Campbell WW, Joseph LJ, Davey SL, Cyr-Campbell D, Anderson RA and Evans WJ**. Effects of resistance training and chromium picolinate on body composition and skeletal muscle in older men. *J Appl Physiol* 86: 29-39, 1999.

35. **Cappon J, Brasel JA, Mohan S and Cooper DM**. Effect of brief exercise on circulating insulin-like growth factor I. *J Appl Physiol* 76: 2490-2496, 1994.

36. **Carmelli D and Reed T**. Stability and change in genetic and environmental influences on hand-grip strength in older male twins. *J Appl Physiol* 89: 1879-1883, 2000.

37. **Chagnon YC, Rice T, Perusse L, Borecki IB, Ho-Kim MA, Lacaille M, Pare C, Bouchard L, Gagnon J, Leon AS, Skinner JS, Wilmore JH, Rao DC and Bouchard C**. Genomic scan for genes affecting body composition before and after training in Caucasians from HERITAGE. *J Appl Physiol* 90: 1777-1787, 2001.

38. **Chakravarthy M, V, Abraha TW, Schwartz RJ, Fiorotto ML and Booth FW**. Insulin-like growth factor-I extends in vitro replicative life span of skeletal muscle satellite cells by enhancing G1/S cell cycle progression via the activation of phosphatidylinositol 3'-kinase/Akt pathway. *J Biol Chem* 275: 35942-35952, 2000.

39. **Chin ER, Olson EN, Richardson JA, Yang Q, Humphries C, Shelton JM, Wu H, Zhu W, Bassel-Duby R and Williams RS**. A calcineurin-dependent transcriptional pathway controls skeletal muscle fiber type. *Genes Dev* 2499-2509, 1998.

40. **Chiou ST and Chang WC**. Insulin-like growth factor I stimulates transcription of the c-jun proto-oncogene in Balb/C 3T3 cells. *Biochem Biophys Res Commun* 183: 524-531, 1992.

41. **Clarkson PM, Devaney JM, Gordish-Dressman H, Thompson PD, Hubal MJ, Urso M, Price TB, Angelopoulos TJ, Gordon PM, Moyna NM, Pescatello LS, Visich PS, Zoeller RF, Seip RL and Hoffman EP**. ACTN3 genotype is associated with increases in muscle strength in response to resistance training in women. *J Appl Physiol* 99: 154-163, 2005.

42. **Coleman M, DeMayo F, Yin K, Lee H, Geske R, Montgomery C and Schwartz R**. Myogenic vector expression of insulin-like growth factor I stimulates muscle cell differentiation and myofiber hypertrophy in transgenic mice. *J Biol Chem* 270: 12109-12116, 1995.

43. **Connelly DM, Rice CL, Roos MR and Vandervoort AA**. Motor unit firing rates and contractile properties in tibialis anterior of young and old men. *J Appl Physiol* 87: 843-852, 1999.

44. **Crabtree GR**. Generic signals and specific outcomes: signaling through Ca2+, calcineurin, and NF-AT. *Cell* 96: 611-614, 1999.

45. **D'Ercole AJ, Applewhite GT and Underwood LE**. Evidence that somatomedin is synthesized by multiple tissues in the fetus. *Dev Biol* 75: 315-328, 1980.

46. **Daughaday WH, Hall K, Raben MS, Salmon WDJr, van den Brande JL and van Wyk JJ**. Somatomedin: proposed designation for sulphation factor. *Nature* 235: 107, 1972.

47. **Deal C, Ma J, Wilkin F, Paquette J, Rozen F, Ge B, Hudson T, Stampfer M and Pollak M**. Novel promoter polymorphism in insulin-like growth factor-binding protein-3: correlation with serum levels and interaction with known regulators. *J Clin Endocrinol Metab* 86: 1274-1280, 2001.

48. **Delbono O, Renganathan M and Messi ML**. Regulation of mouse skeletal muscle L-type Ca2+ channel by activation of the insulin-like growth factor-1 receptor. *J Neurosci* 17: 6918-6928, 1997.

49. **DeLellis K, Ingles S, Kolonel L, McKean-Cowdin R, Henderson B, Stanczyk F and Probst-Hensch NM**. IGF1 genotype, mean plasma level and breast cancer risk in the Hawaii/Los Angeles multiethnic cohort. *Br J Cancer* 88: 277-282, 2003.

50. **Delling U, Tureckova J, Lim HW, De Windt LJ, Rotwein P and Molkentin JD**. A calcineurin-NFATc3-dependent pathway regulates skeletal muscle

differentiation and slow myosin heavy-chain expression. *Molecular and Cellular Biology* 20: 6600-6611, 2000.

51. **Desypris G and Parry DJ**. Relative efficacy of slow and fast alpha-motoneurons to reinnervate mouse soleus muscle. *Am J Physiol* 258: C62-C70, 1990.
52. **Doherty TJ, Vandervoort AA, Taylor AW and Brown WF**. Effects of motor unit losses on strength in older men and women. *J Appl Physiol* 74: 868-874, 1993.
53. **Duclos MJ, Wilkie RS and Goddard C**. Stimulation of DNA synthesis in chicken muscle satellite cells by insulin and insulin-like growth factors: evidence for exclusive mediation by a type-I insulin-like growth factor receptor. *J Endocrinol* 128: 35-42, 1991.
54. **Dunn SE, Burns JL and Michel RN**. Calcineurin is required for skeletal muscle hypertrophy. *J Biol Chem* 274: 21908-21912, 1999.
55. **Dunn SE, Chin ER and Michel RN**. Matching of calcineurin activity to upstream effectors is critical for skeletal muscle growth. *J Cell Biol* 151: 663-672, 2000.
56. **Dunn SE and Michel RN**. Coordinated expression of myosin heavy chain isoforms and metabolic enzymes within overloaded rat muscle fibers. *Am J Physiol* 273: C371-C383, 1997.
57. **Dunn SE, Simard AR, Prud'homme RA and Michel RN**. Calcineurin and skeletal muscle growth. *Nat Cell Biol* 4: E46, 2002.
58. **Ehrenborg E, Larsson C, Stern I, Janson M, Powell DR and Luthman H**. Contiguous localization of the genes encoding human insulin-like growth factor

binding proteins 1 (IGBP1) and 3 (IGBP3) on chromosome 7. *Genomics* 12: 497-502, 1992.

59. **Eliakim A, Moromisato M, Moromisato D, Brasel JA, Roberts CTJr and Cooper DM**. Increase in muscle IGF-I protein but not IGF-I mRNA after 5 days of endurance training in young rats. *Am J Physiol* 273: R1557-R1561, 1997.
60. **Eliakim A, Oh Y and Cooper DM**. Effect of single wrist exercise on fibroblast growth factor-2, insulin-like growth factor, and growth hormone. *Am J Physiol Regul Integr Comp Physiol* 279: R548-R553, 2000.
61. **Era P, Lyyra AL, Viitasalo JT and Heikkinen E**. Determinants of isometric muscle strength in men of different ages. *Eur J Appl Physiol Occup Physiol* 64: 84-91, 1992.
62. **Ewton DZ, Falen SL and Florini JR**. The type II insulin-like growth factor (IGF) receptor has low afffinity for IGF-I analogs: pleiotypic actions of IGFs on myoblasts are apparently mediated by the type I receptor. *Endocrinology* 120: 115-123, 1987.
63. **Ferry RJJ, Cerri RW and Cohen P**. Insulin-like growth factor binding proteins: new proteins, new functions. *Horm Res* 51: 53-67, 1999.
64. **Fiatarone Singh MA, Ding M, Manfredi TJ, Solares GS, O'Neill EF, Clements KM, Ryan ND, Kehayias JJ, Fielding RA and Evans WJ**. Insulin-like growth factor I in skeletal muscle after weight-lifting exercise in frail elders. *American Journal of Physiology* 277: E135-E143, 1999.
65. **Fiatarone M, Marks E, Ryan N, Meredith C, Lipsitz L and Evans W**. High-intensity strength training in nonagenarians. *JAMA* 263: 3029-3034, 1990.

66. **Florini JR and Ewton DZ**. Insulin acts as a somatomedin analog in stimulating myoblast growth in serum-free medium. *In Vitro* 17: 763-768, 1981.

67. **Florini JR, Ewton DZ and Coolican SA**. Growth hormone and insulin-like growth factor system in myogenesis. *Endocr Rev* 17: 481-517, 1996.

68. **Foldvari M, Clark M, Laviolette LC, Bernstein MA, Kaliton D, Casteneda C, Pu CT, Hausdorff JM, Fielding RA and Singh MA**. Association of muscle power with functional status in community-dwelling elderly women. *J Gerontol A Biol Sci Med Sci* 55: M192-M199, 2000.

69. **Folland J, Leach B, Little T, Hawker K, Myerson S, Montgomery H and Jones D**. Angiotensin-converting enzyme genotype affects the response of human skeletal muscle to functional overload. *Exp Physiol* 85: 575-579, 2000.

70. **Foulstone EJ, Savage PB, Crown AL, Holly JM and Stewart CE**. Role of insulin-like growth factor binding protein-3 (IGFBP-3) in the differentiation of primary human adult skeletal myoblasts. *J Cell Physiol* 195: 70-79, 2003.

71. **Frayling TM, Hattersley AT, McCarthy A, Holly J, Mitchell SM, Gloyn AL, Owen K, Davies D, Smith GD and Ben-Shlomo Y**. A putative functional polymorphism in the IGF-I gene: association studies with type 2 diabetes, adult height, glucose tolerance, and fetal growth in U.K population. *Diabetes* 51: 2313-2316, 2002.

72. **Frederiksen H, Gaist D, Petersen HC, Hjelmborg J, McGue M, Vaupel JW and Christensen K**. Hand grip strength: a phenotype suitable for identifying genetic variants affecting mid- and late-life physical functioning. *Genet Epidemiol* 23: 110-122, 2002.

73. **Friday BB, Horsley V and Pavlath GK**. Calcineurin activity is required for the initiation of skeletal muscle differentiation. *J Cell Biol* 149: 657-665, 2000.

74. **Friday BB, Mitchell PO, Kegley KM and Pavlath GK**. Calcineurin initiates skeletal muscle differentiation by activating MEF2 and MyoD. *Differentiation* 71: 217-227, 2003.

75. **Frontera WR, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ and Roubenoff R**. Aging of skeletal muscle: a 12-yr longitudinal study. *J Appl Physiol* 88: 1321-1326, 2000.

76. **Frontera WR, Hughes VA, Lutz KJ and Evans WJ**. A cross-sectional study of muscle strength and mass in 45- to 78-yr-old men and women. *J Appl Physiol* 71: 644-650, 1991.

77. **Frontera WR, Meredith CN, O'Reilly KP, Knuttgen HG and Evans WJ**. Strength conditioning in older men: skeletal muscle hypertrophy and improved function. *J Appl Physiol* 64: 1038-1044, 1988.

78. **Frontera WR, Suh D, Krivickas LS, Hughes VA, Goldstein R and Roubenoff R**. Skeletal muscle fiber quality in older men and women. *Am J Physiol Cell Physiol* 279: C611-C618, 2000.

79. **Fujita Y, Nakamura Y, Hiraoka J, Kobayashi K, Sakata K, Nagai M and Yanagawa H**. Physical-strength tests and mortality among visitors to health-promotion centers in Japan. *J Clin Epidemiol* 48: 1349-1359, 1995.

80. **Gallagher D, Visser M, De Meersman RE, Sepulveda D, Baumgartner RN, Pierson RN, Harris T and Heymsfield SB**. Appendicular skeletal muscle mass: effects of age, gender, and ethnicity. *J Appl Physiol* 83: 229-239, 1997.

81. **Geusens P, Vandevyver C, Vanhoof J, Cassiman JJ, Boonen S and Raus J**. Quadriceps and grip strength are related to vitamin D receptor genotype in elderly nonobese women. *J Bone Miner Res* 12: 2082-2088, 1997.

82. **Giorgino F and Smith RJ**. Dexamethasone enhances insulin-like growth factor-I effects on skeletal muscle cell proliferation. Role of specific intracellular signaling pathways. *J Clin Invest* 96: 1473-1483, 1995.

83. **Green H, Morikawa M and Nixon T**. A dual effector theory of growth-hormone action. *Differentiation* 29: 195-198, 1985.

84. **Grimby G, Aniansson A, Hedberg M, Henning G, Granguard U and Kvist H**. Training can improve muscle strength and endurance in 78- to 84-yr-old men. *J Appl Physiol* 73: 2517-2523, 1992.

85. **Grundberg E, Brandstrom H, Ribom EL, Ljunggren O, Mallmin H and Kindmark A**. Genetic variation in the human vitamin D receptor is associated with muscle strength, fat mass and body weight in Swedish women. *Eur J Endocrinol* 150: 323-328, 2004.

86. **Gucev ZS, Oh Y, Kelley KM and Rosenfeld RG**. Insulin-like growth factor binding protein 3 mediates retinoic acid- and transforming growth factor beta2-induced growth inhibition in human breast cancer cells. *Cancer Res* 56: 1545-1550, 1996.

87. **Hakkinen K and Hakkinen A**. Neuromuscular adaptations during intensive strength training in middle-aged and elderly males and females. *Electromyogr Clin Neurophysiol* 35: 137-147, 1995.

88. **Hakkinen K and Komi P, V**. Changes in neuromuscular performance in voluntary and reflex contraction during strength training in man. *Int J Sports Med* 4: 282-288, 1983.

89. **Hameed M, Harridge SD and Goldspink G**. Sarcopenia and hypertrophy: a role for insulin-like growth factor-1 in aged muscle? *Exerc Sport Sci Rev* 30: 15-19, 2002.

90. **Hameed M, Lange KH, Andersen JL, Schjerling P, Kjaer M and Harridge SD**. The effect of recombinant human growth hormone and resistance training on IGF-I mRNA expression in the muscles of elderly men. *J Physiol* 555: 231-240, 2004.

91. **Hameed M, Orrell RW, Cobbold M, Goldspink G and Harridge SD**. Expression of IGF-I splice variants in young and old human skeletal muscle after high resistance exercise. *J Physiol* 547: 247-254, 2003.

92. **Haq S, Choukroun G, Lim H, Tymitz KM, del Monte F, Gwathmey J, Grazette L, Michael A, Hajjar R, Force T and Molkentin JD**. Differential activation of signal transduction pathways in human hearts with hypertrophy versus advanced heart failure. *Circulation* 103: 670-677, 2001.

93. **Harman SM, Metter EJ, Tobin JD, Pearson J and Blackman MR**. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab* 86: 724-731, 2001.

94. **Harrela M, Koistinen H, Kaprio J, Lehtovirta M, Tuomilehto J, Eriksson J, Toivanen L, Koskenvuo M, Leinonen P, Koistinen R and Seppala M**. Genetic

and environmental components of interindividual variation in circulating levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3. *J Clin Invest* 98: 2612-2615, 1996.

95. **Hasten DL, Pak-Loduca J, Obert KA and Yarasheski KE**. Resistance exercise acutely increases MHC and mixed muscle protein synthesis rates in 78-84 and 23-32 yr olds. *Am J Physiol Endocrinol Metab* 278: E620-E626, 2000.
96. **Hasty P, Bradley A, Morris JH, Edmonson DG, Venuti JM, Olson EN and Klein WH**. Muscle deficiency and neonatal death in mice with a targeted mutation in the myogenin gene. *Nature* 364: 501-506, 1993.
97. **Hendrix LJ, Carter MW and Scott DT**. Covariance analyses with heterogeneity of slopes in fixed models. *Biometrics* 38: 641-650, 1982.
98. **Hill M and Goldspink G**. Expression and splicing of the insulin-like growth factor gene in rodent muscle is associated with muscle satellite (stem) cell activation following local tissue damage. *J Physiol* 549: 409-418, 2003.
99. **Hong Y, Pedersen NL, Brismar K, Hall K and de Faire U**. Quantitative genetic analyses of insulin-like growth factor I (IGF-I), IGF-binding protein-1, and insulin levels in middle-aged and elderly twins. *J Clin Endocrinol Metab* 81: 1791-1797, 1996.
100. **Horsley V, Friday BB, Matteson S, Kegley KM, Gephart J and Pavlath GK**. Regulation of the growth of multinucleated muscle cells by an NFATC2-dependent pathway. *J Cell Biol* 153: 329-338, 2001.
101. **Hurley BF, Redmond RA, Pratley RE, Treuth MS, Rogers MA and Goldberg AP**. Effects of strength training on muscle hypertrophy and muscle cell disruption in older men. *Int J Sports Med* 16: 378-384, 1995.

102. **Hurley M, V, Rees J and Newham DJ**. Quadriceps function, proprioceptive acuity and functional performance in healthy young, middle-aged and elderly subjects. *Age Ageing* 27: 55-62, 1998.

103. **Huygens W, Thomis MA, Peeters MW, Vlietinck RF and Beunen GP**. Determinants and upper-limit heritabilities of skeletal muscle mass and strength. *Can J Appl Phys* 29: 186-200, 2004.

104. **Huynh H, Yang X and Pollak M**. Estradiol and antiestrogens regulate a growth inhibitory insulin-like growth factor binding protein 3 autocrine loop in human breast cancer cells. *J Biol Chem* 271: 1016-1021, 1996.

105. **Iannuzzi-Sucich M, Prestwood KM and Kenny AM**. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. *J Gerontol A Biol Sci Med Sci* 57: M772-M777, 2002.

106. **Ianuzzo CD, Hamilton N and Li B**. Competitive control of myosin expression: hypertrophy vs. hyperthyroidism. *J Appl Physiol* 70: 2328-2330, 1991.

107. **Ivey FM, Roth SM, Ferrell RE, Tracy BL, Lemmer JT, Hurlbut DE, Martel GF, Siegel EL, Fozard JL, Metter EJ, Fleg JL and Hurley BF**. The effects of age, gender, and myostatin genotype on the hypertrophic response to strength training and detraining. *J Gerontol A Biol Sci Med Sci* 55: M641-M648, 2000.

108. **Ivey FM, Tracy BL, Lemmer JT, NessAiver M, Metter EJ, Fozard JL and Hurley B**. Effects of strength training and detraining on muscle quality: age and gender comparisons. *Journal of Gerontology: Biological Sciences* 55A: B152-B157, 2000.

109. **Jakobi JM and Rice CL**. Voluntary muscle activation varies with age and muscle group. *J Appl Physiol* 93: 457-462, 2002.

110. **Jernstrom H, Chu W, Vesprini D, Tao Y, Majeed N, Deal C, Pollak M and Narod SA**. Genetic factors related to racial variation in plasma levels of insulin-like growth factor-1: implications for premenopausal breast cancer risk. *Molecular Genetics and Metabolism* 72: 144-154, 2001.

111. **Jernstrom H, Deal C, Wilkin F, Chu W, Tao Y, Majeed N, Hudson T, Narod SA and Pollak M**. Genetic and nongenetic factors associated with variation of plasma levels of insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 in healthy premenopausal women. *Cancer Epidemiol Biomarkers Prev* 10: 377-384, 2001.

112. **Jones B and Klissouras V**. Genetic variation in the strength-velocity relation of human muscle. In: Sport and Human Genetics, edited by Malina RM and Bouchard C. Champaign, IL: Human Kinetics, 1986, p. 155-163.

113. **Jones J, I and Clemmons DR**. Insulin-like growth factors and their binding proteins: biological actions. *Endocr Rev* 16: 3-34, 1995.

114. **Jozsi AC, Campbell WW, Joseph L, Davey SL and Evans WJ**. Changes in power with resistance training in older and younger men and women. *J Gerontol A Biol Sci Med Sci* 54: M591-M596, 1999.

115. **Juul A, Dalgaard P, Blum WF, Bang P, Hall K, Michaelsen KF, Muller J and Skakkebaek NE**. Serum levels of insulin-like growth factor (IGF)-binding protein-3 (IGFBP-3) in healthy infants, children, and adolescents: the relation to

IGF-I, IGF-II, IGFBP-1, IGFBP-2, age, sex, body mass index, and pubertal maturation. *J Clin Endocrinol Metab* 80: 2534-2542, 1995.

116. **Juul A, Moller S, Mosfeldt-Laursen E, Rasmussen MH, Scheike T, Pedersen SA, Kastrup KW, Yu H, Mistry J, Rasmussen S, Muller J, Henriksen J and Skakkebaek NE**. The acid-labile subunit of human ternary insulin-like growth factor binding protein complex in serum: hepatosplanchnic release, diurnal variation, circulating concentrations in healthy subjects, and diagnostic use in patients with growth hormone deficiency. *J Clin Endocrinol Metab* 83: 4408-4415, 1998.

117. **Kaklamani VG, Linos A, Kaklamani E, Markaki I and Mantzoros C**. Age, sex, and smoking are predictors of circulating insulin-like growth factor 1 and insulin-like growth factor-binding protein 3. *J Clin Oncol* 813-817, 1999.

118. **Kallman DA, Plato CC and Tobin JD**. The role of muscle loss in the age-related decline of grip-strength: cross-sectional and longitudinal perspectives. *J Gerontol* 45: M82-M88, 1990.

119. **Kao PC, Mathey APJr and Lang CA**. Insulin-like growth factor-I comparisons in healthy twin children. *J Clin Endocrinol Metab* 78: 310-312, 1994.

120. **Kato I, Eastham J, Li B, Smith M and Yu H**. Genotype-phenotype analysis for the polymorphic CA repeat in the insulin-like growth factor-I (IGF-I) gene. *Genet Epidemiol* 18: 203-209, 2003.

121. **Kauffman TL**. Strength training effect in young and aged women. *Archives Physician Medical Rehabilitation* 66: 223-226, 1985.

122. **Kawakami Y, Abe T, Kuno SY and Fukunaga T**. Training-induced changes in muscle architecture and specific tension. *Eur J Appl Physiol Occup Physiol* 72: 37-43, 1995.

123. **Keen DA, Yue GH and Enoka RM**. Training-related enhancement in the control of motor output in the elderly. *J Appl Physiol* 77: 2648-2658, 1994.

124. **Kent-Braun JA, Ng A, V and Young K**. Skeletal muscle contractile and noncontractile components in young and older women and men. *J Appl Physiol* 88: 662-668, 2000.

125. **Kim JG, Roh KR and Lee JY**. The relationship among serum insulin-like growth factor-I, insulin-like growth factor-I gene polymorphism, and bone mineral density in postmenopausal women in Korea. *Am J Obstet Gynecol* 186: 345-350, 2002.

126. **Klein CS, Rice CL and Marsh GD**. Normalized force, activation, and coactivation in the arm muscles of young and old men. *J Appl Physiol* 91: 1341-1349, 2001.

127. **Kostek MC, Delmonico MJ, Reichel JB, Roth SM, Douglass L, Ferrell RE and Hurley BF**. Muscle strength response to strength training is influenced by insulin-like growth factor 1 (IGF-1) genotype in older adults. *J Appl Physiol* 98: 2147-2154, 2005.

128. **Kraemer WJ, Hakkinen K, Newton RU, Nindl BC, Volek JS, McCormick M, Gotshalk LA, Gordon SE, Fleck SJ, Campbell WW, Putukian M and Evans WJ**. Effects of heavy-resistance training on hormonal response patterns in younger vs. older men. *J Appl Physiol* 87: 982-992, 1999.

129. **Kraemer WJ, Patton JF, Gordon SE, Harman EA, Deschenes MR, Reynolds K, Newton RU, Triplett NT and Dziados JE**. Compatibility of high-intensity strength and endurance training on hormonal and skeletal muscle adaptations. *J Appl Physiol* 78: 976-989, 1995.

130. **Kubo K, Kanehisa H, Azuma K, Ishizu M, Kuno SY, Okada M and Fukunaga T**. Muscle architectural characteristics in young and elderly men and women. *Int J Sports Med* 24: 125-130, 2003.

131. **Kwon IS, Oldaker S, Schrager M, Talbot LA, Fozard JL and Metter EJ**. Relationship between muscle strength and the itme taken to complete a standardized walk-turn-walk test. *J Gerontol A Biol Sci Med Sci* 56: B398-B404, 2001.

132. **Larsson L, Grimby G and Karlsson J**. Muscle strength and speed of movement in relation to age and muscle morphology. *J Appl Physiol* 46: 451-456, 1979.

133. **Laukkanen P, Keikkinen E and Kauppinen M**. Muscle strength and mobility as predictors of survival in 75-84-year-old people. *Age Ageing* 24: 468-473, 1995.

134. **Lauretani F, Russo CR, Bandinelli S, Bartali B, Cavazzini C, Di Iorio A, Corsi AM, Rantanen T, Guralnik JM and Ferrucci L**. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. *J Appl Physiol* 95: 1851-1860, 2003.

135. **Lemmer JT, Hurlbut DE, Martel GF, Tracy BL, Ivey FM and Metter EJ**. Age and gender responses to strength training and detraining. *Med Sci Sports Exerc* 32: 1505-1512, 2000.

136. **LeRoith D, Werner H, Beitner-Johnson D and Roberts CTJr**. Molecular and cellular aspects of the insulin-like growth factor I receptor. *Endocr Rev* 16: 143-163, 1995.

137. **Lexell J, Downham DY, Larsson Y, Bruhn E and Morsing B**. Heavy-resistance training in older Scandinavian men and women: short- and long-term effects on arm and leg muscles. *Med Sci Sports Exerc* 5: 329-341, 1995.

138. **Lexell J, Taylor CC and Sjostrom M**. What is the cause of ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. *J Neurol Sci* 84: 275-294, 1988.

139. **Lexell J, Taylor CC and Sjostrom M**. Analysis of sampling errors in biopsy techniques using data from whole muscle cross-sections. *J Appl Physiol* 59: 1228-1235, 1985.

140. **Li CH, Yamashiro D, Gospodarowicz D, Kalplan SL and Van Vliet G**. Total synthesis of insulin-like growth factor I (somatomedin C). *Proc Natl Acad Sci USA* 80: 2216-2220, 1983.

141. **Lindle RS, Metter EJ, Lynch NA, Fleg JL, Fozard JL, Tobin J, Roy TA and Hurley BF**. Age and gender comparisons of muscle strength in 654 women and men aged 20-93 yr. *J Appl Physiol* 83: 1581-1587, 1997.

142. **Lipsitz LA, Nakajima I, Gagnon M, Hirayama T, Connelly CM, Izumo H and Hirayama T**. Muscle strength and fall rates among residents of Japanese and American nursing homes: an International Cross-Cultural Study. *J Am Geriatr Soc* 42: 953-959, 1994.

143. **Liu JP, Baker J, Perkins AS, Robertson EJ and Efstratiadis A**. Mice carrying null mutations of the genes encoding insulin-like growth factor I (Igf-1) and type 1 IGF receptor (Igf1r). *Cell* 75: 59-72, 1993.

144. **Lord SR, Ward JA, Williams P and Anstey K**. Physiological factors associated with falls in older community-dwelling women. *J Am Geriatr Soc* 42: 1110-1117, 1994.

145. **Lowe WLJr, Lasky SR, LeRoith D and Roberts CTJr**. Distribution and regulation of rat insulin-like growth factor I messenger ribonucleic acids encoding alternative carboxy terminal E-peptides: evidence for differential processing and regulation in liver. *Mol Endocrinol* 2: 528-535, 1988.

146. **Lowe WLJr, Schaffner AE, Roberts CTJr and LeRoith D**. Developmental regulation of somatomedin gene expression in the brain is region specific. *Mol Endocrinol* 1: 181-187, 1987.

147. **Lynch NA, Metter EJ, Lindle RS, Fozard JL, Tobin JD, Roy TA, Fleg JL and Hurley BF**. Muscle quality. I. Age-associated differences between arm and leg muscle groups. *J Appl Physiol* 86: 188-194, 1999.

148. **Lyons GE, Ontell M, Cox R, Sassoon D and Buckingham M**. The expression of myosin genes in developing skeletal muscle in the mouse embryo. *J Cell Biol* 111: 1465-1476, 1990.

149. **Macaluso A and De Vito G**. Muscle strength, power, and adaptations to resistance training in older people. *Eur J Appl Physiol* 91: 450-472, 2004.

150. **Marcell TJ**. Sarcopenia: causes, consequences, and preventions. *J Gerontol A Biol Sci Med Sci* 58: M911-M916, 2003.

151. **Martin JL, Coverley JA, Pattison ST and Baxter RC**. Insulin-like growth factor-binding protein-3 production by MCF-7 breast cancer cells: stimulation by retinoic acid and cyclic adenosine monophosphate and differential effects of estradiol. *Endocrinology* 136: 1219-1226, 1995.

152. **Matsumoto A**. Andropause: clinical implications of the decline in serum testosterone levels with aging in men. *J Gerontol* 57: M76-M99, 2002.

153. **McKoy G, Ashley W, Mander J, Yang SY, Williams N, Russell B and Goldspink G**. Expression of insulin growth factor-1 splice variants and structural genes in rabbit skeletal muscle induced by stretch and stimulation. *J Physiol* 516: 583-592, 1999.

154. **Melton LJ, III, Khosla S, Crowson CS, O'Connor MK, O'Fallon WM and Riggs BL**. Epidemiology of sarcopenia. *J Am Geriatr Soc* 48: 625-630, 2000.

155. **Merrill GF, Florini JR and Dulak NC**. Effects of multiplication stimulating activity (MSA) on AIB transport into myoblast and myotube cultures. *J Cell Physiol* 93: 173-182, 1977.

156. **Messi ML and Delbono O**. Target-derived trophic effect on skeletal muscle innervation in senescent mice. *J Neurosci* 23: 1351-1359, 2003.

157. **Metter EJ, Conwit R, Tobin J and Fozard JL**. Age-associated loss of power and strength in the upper extremities in women and men. *J Gerontol A Biol Sci Med Sci* 52: B267-B276, 1997.

158. **Metter EJ, Talbot LA, Schrager M and Conwit R**. Skeletal muscle strength as a predictor of all-cause mortality in healthy men. *J Gerontol A Biol Sci Med Sci* 57: B359-B365, 2002.

159. **Metter EJ, Talbot LA, Schrager M and Conwit R**. Arm-cranking muscle power and arm isometric muscle strength are independent predictors of all-cause mortality in men. *J Appl Physiol* 96: 814-821, 2004.

160. **Michel RN, Dunn SE and Chin ER**. Calcineurin and skeletal muscle growth. *Proc Nutr Soc* 63: 341-349, 2004.

161. **Miller MD, Crotty M, Giles LC, Bannerman E, Whitehead C, Cobiac L, Daniels LA and Andrews G**. Corrected arm muscle area: an independent predictor of long-term mortality in community-dwelling older adults? *J Am Geriatr Soc* 50: 1272-1277, 2002.

162. **Missmer SA, Haiman CA, Hunter DJ, Willett WC, Colditz GA, Speizer FE, Pollak MN and Hankinson SE**. A sequence repeat in the insulin-like growth factor-1 gene and risk of breast cancer. *Int J Cancer* 100: 332-336, 2002.

163. **Mitchell PO, Mills ST and Pavlath GK**. Calcineurin differentially regulates maintenance and growth of phenotypically distinct muscles. *Am J Physiol Cell Physiol* 282: C984-C992, 2002.

164. **Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D and Ross R**. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol* 85: 115-122, 1998.

165. **Miyazaki M, Hitomi Y, Kizaki T, Ohno H, Haga S and Takemasa T**. Contribution of the calcineurin signaling pathway to overload-induced skeletal muscle fiber-type transition. *J Physiol and Pharmacol* 55: 751-764, 2004.

166. **Molkentin JD, Lu JR, Antos CL, Markham B, Richardson J, Robbins J, Grant SR and Olson EN**. A calcineurin-dependent transcriptional pathway for cardiac hypertrophy. *Cell* 93: 215-228, 1998.

167. **Morley JE**. Decreased food intake with aging. *J Gerontol* 56: S81-S88, 2001.

168. **Morton CC, Byers MG, Nakai H, Bell G, I and Shows TB**. Human genes for insulin-like growth factors I and II and epidermal growth factor are located on 12q22----q24.1, 11p15, and 4q25----q27, respectively. *Cytogenet Cell Genet* 41: 245-249, 1984.

169. **Murgia M, Serrano A L, Calabria E, Pallafacchina G, Lomo T and Schiaffino S**. Ras is involved in nerve-activity-dependent regulation of muscle genes. *Nat Cell Biol* 2: 142-147, 2000.

170. **Murphy WR, Daughaday WH and Hartnett C**. The effect of hypophysectomy and growth hormone on the incorporation of labeled sulfate into tibial epiphyseal and nasal cartilage of the rat. *J Lab Clin Med* 47: 715-722, 1956.

171. **Musaro A, McCullagh K, Paul A, Houghton L, Dobrowonly G, Molinaro M, Barton ER, Sweeney HL and Rosenthal N**. Localized Igf-1 transgene expression sustains hypertrophy and regeneration in senescent skeletal muscle. *Nature Genetics* 27: 195-200, 2001.

172. **Musaro A, McCullagh KJ, Naya FJ, Olson EN and Rosenthal N**. IGF-1 induces skeletal muscle myocyte hypertrophy through calcineurin in association with GATA-2 and NF-ATc1. *Nature* 400: 581-585, 1999.

173. **Nair KS**. Muscle protein turnover: methodological issues and the effect of aging. *J Gerontol A Biol Sci Med Sci* 50 Spec No: 107-112, 1995.

174. **Naya FJ, Mercer B, Shelton J, Richardson JA, Williams RS and Olson EN**. Stimulation of slow skeletal muscle fiber gene expression by calcineurin *in vivo*. *J Biol Chem* 275: 4545-4548, 2000.

175. **Newman AB, Haggerty CL, Goodpaster B, Harris T, Kritchevsky S, Nevitt M, Miles TP and Visser M**. Strength and muscle quality in a well-functioning cohort of older adults: the Health, Aging and Body Composition Study. *J Am Geriatr Soc* 51: 323-330, 2003.

176. **Nguyen T, V, Howard GM, Kelly PJ and Eisman JA**. Bone mass, lean mass, and fat mass: same genes or same environments? *Am J Epidemiol* 147: 3-16, 1998.

177. **Nickerson T and Huynh H**. Vitamin D analogue EB1089-induced prostate regression is associated with increased gene expression of insulin-like growth factor binding proteins. *J Endocrinol* 160: 223-229, 1999.

178. **Nickerson T and Pollak M**. Bicalutamide (Casodex)-induced prostate regression involves increased expression of genes encoding insulin-like growth factor binding proteins. *Urology* 54: 1120-1125, 1999.

179. **Nicklas BJ, Ryan AJ, Trueth MM, Harman SM, Blackman MR and Hurley BF**. Testosterone, growth hormone and IGF-1 responses to acute and chronic resistive training in men aged 55-70 years. *Int J Sports Med* 16: 445-450, 1995.

180. **Nindl BC, Kraemer WJ, Marx JO, Arciero PJ, Dohi K, Kellogg MD and Loomis GA**. Overnight responses of the circulating IGF-I system after acute, heavy-resistance exercise. *J Appl Physiol* 90: 1319-1326, 2001.

181. **Oh Y, Muller HL, Ng L and Rosenfeld RG**. Transforming growth factor-beta-induced cell growth inhibition in human breast cancer cells is mediated through insulin-like growth factor-binding protein-3 action. *J Biol Chem* 270: 13589-13592, 1995.

182. **Olson EN and Williams RS**. Remodeling muscles with calcineurin. *Bioassays* 22: 510-519, 2000.

183. **Ong J, Yamashita S and Melmed S**. Insulin-like growth factor I induces c-fos messenger ribonucleic acid in L6 rat skeletal muscle cells. *Endocrinology* 120: 353-357, 1987.

184. **Overend TJ, Cunningham DA, Paterson DH and Lefcoe MS**. Thigh composition in young and elderly men determined by computed tomography. *Clin Physiol* 12: 629-640, 1992.

185. **Owino V, Yang SY and Goldspink G**. Age-related loss of skeletal muscle function and the inability to express the autocrine form of insulin-like growth factor-1 (MGF) in response to mechanical overload. *FEBS Lett* 505: 259-263, 2001.

186. **Pallafacchina G, Calabria E, Serrano AL, Kalhovde JM and Schiaffino S**. A protein kinase B-dependent and rapamycin-sensitive pathway controls skeletal muscle growth but not fiber type specification. *Proc Natl Acad Sci USA* 99: 9213-9218, 2002.

187. **Parsons S, Wilkens BJ, Bueno OF and Molkentin JD**. Altered skeletal muscle phenotypes in calcineurin Aalpha and Abeta gene-targeted mice. *Mol Cell Biol* 23: 4331-4343, 2003.

188. **Parsons SA, Millay DP, Wilkins BJ, Bueno OF, Tsika GL, Neilsen JR, Liberatore CM, Yutzey KE, Crabtree GR, Tsika RW and Molkentin JD**. Genetic loss of calcineurin blocks mechanical overload-induced skeletal muscle fiber type switching but not hypertrophy. *J Biol Chem* 279: 26192-26200, 2004.

189. **Pendergast DR, Fisher NM and Calkins E**. Cardiovascular, neuromuscular, and metabolic alterations with age leading to frailty. *J Gerontol* 48: 61-67, 1993.

190. **Perrone CE, Fenwick-Smith D and Vandenburgh H H**. Collagen and stretch modulate autocrine secretion of insulin-like growth factor-1 and insulin-like growth factor binding proteins from differentiated skeletal muscle cells. *J Biol Chem* 270: 2099-2106, 1995.

191. **Phillips SK, Rook KM, Siddle NC, Bruce SA and Woledge RC**. Muscle weakness in women occurs at an earlier age than in men, but strength is preserved by hormone replacement therapy. *Clin Sci (Lond)* 84: 95-98, 1993.

192. **Platz EA, Pollak MN, Rimm EB, Majeed N, Tao Y, Willett WC and Giovannucci E**. Racial variation in insulin-like factor-1 and binding protein-3 concentrations in middle-aged men. *Cancer Epidemiol Biomarkers Prev* 8: 1107-1110, 1999.

193. **Ploutz-Snyder LL, Manini T, Ploutz-Snyder RJ and Wolf DA**. Functionally relevant thresholds of quadriceps femoris strength. *J Gerontol A Biol Sci Med Sci* 57: B144-B152, 2002.

194. **Poirier O, Nicaud VM, McDonagh T, Dargie HJ, Desnos M, Dorent R, Roizes G, Schwartz K, Tiret L, Komajda M and Cambien F**. Polymorphisms of genes

of the cardiac calcineurin pathway and cardiac hypertrophy. *Eur J Hum Genet 2003* 11: 659-664, 2003.

195. **Pollock ML, Franklin BA, Balady GJ, Chaitman BL, Fleg JL, Fletcher B, Limacher M, Pina IL, Stein RA, Williams M and Bazzarre T**. Resistance Exercise in Individuals With and Without Cardiovascular Disease; Benefits, Rationale, Safety, and Prescription, An Advisory From the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association. *American Heart Association* 101: 828-833, 2000.

196. **Porter MM, Vandervoort AA and Lexell J**. Aging of human muscle: structure, function, and adaptability. *Scand J Med Sci Sports* 5: 129-142, 1995.

197. **Powell-Braxton L, Hollingshead P, Warburton C, Dowd M, Pitts-Meek S, Dalton D, Gillett N and Stewart TA**. IGF-I is required for normal embryonic growth in mice. *Genes Dev* 7: 2609-2617, 1993.

198. **Psilander N, Damsgaard R and Pilegaard H**. Resistance exercise alters MRF and IGF-I mRNA content in human skeletal muscle. *J Appl Physiol* 95: 1038-1044, 2003.

199. **Quinn LS, Ehsan M, Steinmetz B and Kaleko M**. Ligand-dependent inhibition of myoblast differentiation by overexpression of the type-1 insulin-like growth factor receptor. *J Cell Physiol* 156: 453-461, 1993.

200. **Quinn LS, Steinmetz B, Maas A, Ong L and Kaleko M**. Type-1 insulin-like growth factor receptor overexpression produces dual effects on myoblast proliferation and differentiation. *J Cell Physiol* 159: 387-398, 1994.

201. **Rabinovsky ED, Gelir E, Gelir S, Lui H, Kattash M, DeMayo FJ, Shenaq SM and Schwartz RJ**. Targeted expression of IGF-1 transgene to skeletal muscle accelerates muscle and motor neuron regeneration. *FASEB* 17: 53-55, 2003.

202. **Randle PJ**. Plasma-insulin activity in hypopituitarism assayed by the rat-diaphragm method. *Lancet* 266: 809-810, 1954.

203. **Rantanen T, Era P and Heikkinen E**. Physical activity and the changes in maximal isometric strength in men and women from the age of 75 to 80 years. *J Am Geriatr Soc* 45: 1439-1445, 1997.

204. **Rantanen T, Guralnik JM, Sakari-Rantala R, Leveille S, Simonsick EM, Ling S and Fried LP**. Disability, physical activity, and muscle strength in older women: The women's health and aging study. *Archives Physician Medical Rehabilitation* 80: 130-135, 1999.

205. **Rantanen T, Harris T, Leveille SG, Visser M, Foley D, Masaki K and Guralnik JM**. Muscle strength and body mass index as long-term predictors of mortality in initially healthy men. *J Gerontol A Biol Sci Med Sci* 55: M168-M173, 2000.

206. **Rechler MM**. Insulin-like growth factor binding proteins. *Vitam Horm* 47: 1-114, 1993.

207. **Reed RL, Pearlmutter L, Yochum K, Meredith KE and Mooradian AD**. The relationship between muscle mass and muscle strength in the elderly. *J Am Geriatr Soc* 39: 555-561, 1991.

208. **Reed T, Fabsitz RR, Selby J, V and Carmelli D**. Genetic influences and grip strength norms in the NHLBI twins study males aged 59-69. *Ann Hum Biol* 18: 425-432, 1991.

209. **Reeves ND, Narici M, V and Maganaris CN**. Effect of resistance training on skeletal muscle-specific force in elderly humans. *J Appl Physiol* 96: 885-892, 2004.

210. **Ren Z, Cai Q, Shu XO, Cai H, Li C, Yu H, Gao Y and Zheng W**. Genetic polymorphisms in the IGFBP3 gene: association with breast cancer risk and blood IGFBP-3 protein levels among Chinese women. *Cancer Epidemiol Biomarkers Prev* 13: 1290-1295, 2004.

211. **Riechman SE, Balasekaran G, Roth SM and Ferrell RE**. Association of interleukin-15 and interleukin-15 receptor genetic variation with resistance exercise training responses. *J Appl Physiol* 97: 2214-2219, 2004.

212. **Rietveld I, Janssen JA, Hofman A, Pols HA, van Duijn CM and Lamberts SW**. A polymorphism in the IGF-1 gene influences the age-related decline in circulating total IGF-1 levels. *Eur J Endocrinol* 148: 171-175, 2003.

213. **Rinderknecht E and Humbel RE**. The amino acid sequence of human insulin-like growth factor I amd its structural homology with proinsulin. *J Biol Chem* 253: 2769-2776, 1978.

214. **Ritter O, Hack S, Schuh K, Rothlein N, Perrot A, Osterziel KJ, Schulte HD and Neyses L**. Calcineurin in human heart hypertrophy. *Circulation* 105: 2265-2269, 2002.

215. **Rivadeneira F, Houwing-Duistermaat JJ, Vaessen N, Vergeer-Drop JM, Hofman A, Pols HA, van Duijn CM and Uitterlinden AG**. Association between an insulin-like growth factor I gene promoter polymorphism and bone mineral density in the elderly: the Rotterdam Study. *J Clin Endocrinol Metab* 88: 3878-3884, 2003.

216. **Roberts CTJr, Lasky SR, Lowe WL, Seaman WT and LeRoith D**. Molecular cloning of rat insulin-like growth factor I complementary deoxyribonucleic acids: differential messenger ribonucleic acid processing and regulation by growth hormone in extrahepatic tissues. *Mol Endocrinol* 1: 243-248, 1987.

217. **Roman W, Fleckenstein J, Stray-Gundersen J, Alway S, Peshock R and Gonyea W**. Adaptations in the elbow flexors of elderly males after heavy-resistance training. *J Appl Physiol* 74: 750-754, 1993.

218. **Rommel C, Bodine SC, Clarke BA, Rossman R, Nunez L, Stitt TN, Yancopoulos GD and Glass DJ**. Mediation of IGF-1-induced skeletal myotube hypertrophy by PI(3)K/Akt/mTOR and PI(3)K/Akt/GSK3 pathways. *Nature Cell Biol* 3: 1009-1013, 2001.

219. **Roos MR, Rice CL and Vandervoort AA**. Age-related changes in motor unit function. *Muscle Nerve* 20: 679-690, 1997.

220. **Rooyackers OE, Adey DB, Ades PA and Nair KS**. Effect of age on invivo rates of mitochndrial protein synthesis in human skeletal muscle. *Proc Natl Acad Sci USA* 93: 15364-15369, 1996.

221. **Rooyackers OE and Nair KS**. Hormonal regulation of human muscle protein metabolism. *Annu Rev Nutr* 17: 457-485, 1997.

222. **Rosen CJ, Kurland ES, Vereault D, Adler RA, Rackoff PJ, Craig WY, Witte S, Rogers J and Bilezikian JP**. Association between serum insulin growth factor-I (IGF-I) and a simple sequence repeat in IGF-1 gene: implications for genetic studies of bone mineral density. *J Clin Endocrinol Metab* 83: 2286-2290, 1998.

223. **Rosenberg I**. Epidemiologic and methodologic problems in determining nutritional-status of older persons-proceedings of a national conference held in Albuquerque, New Mexico, October 19-21, 1988 - summary comments. *Am J Clin Nutr* 50: 1231-1233, 1989.

224. **Roth SM, Ferrell RE and Hurley BF**. Strength training for the prevention and treatment of sarcopenia. *J Nutr Health Aging* 4: 143-155, 2000.

225. **Roth SM, Metter EJ, Lee MR, Hurley BF and Ferrell RE**. C174T polymorphism in the CNTF receptor gene is associated with fat-free mass in men and women. *J Appl Physiol* 95: 1425-1430, 2003.

226. **Roth SM, Schrager MA, Ferrell RE, Riechman SE, Metter EJ, Lynch NA, Lindle RS and Hurley BF**. CNTF genotype is associated with muscular strength and quality in humans across the adult age span. *J Appl Physiol* 90: 1205-1210, 2001.

227. **Roth SM, Schrager MA, Lee MR, Metter EJ, Hurley BF and Ferrell RE**. Interleukin-6 (IL6) genotype is associated with fat-free mass in men but not women. *J Gerontol A Biol Sci Med Sci* 58: B1085-B1088, 2003.

228. **Rothenburg S, Koch-Nolte F, Rich A and Haag F**. A polymorphic dinucleotide repeat in the rat nucleolin gene forms Z-DNA and inhibits promoter activity. *Proc Natl Acad Sci USA* 98: 8985-8990, 2001.

229. **Rotwein P, Pollock KM, Didier DK and Krivi GG**. Organization and sequence of the human insulin-like growth factor I gene. Alternative RNA processing produces two insulin-like growth factor I precursor peptides. *J Biol Chem* 261: 4828-4832, 1986.

230. **Roubenoff R, Harris T B, Abad LW, Wilson PW, Dallal GE and Dinarello CA**. Monocyte cytokine production in an elderly population: effect of age and inflammation. *J Gerontol A Biol Sci Med Sci* 53: M20-M26, 1998.

231. **Roubenoff R, Parise H, Payette HA, Abad LW, D'Agostino R, Jacques PF, Wilson PW, Dinarello CA and Harris TB**. Cytokines, insulin-like growth factor 1, sarcopenia, and mortality in very old community-dwelling men and women: the Framingham Heart Study. *Am J Med* 115: 429-435, 2003.

232. **Rozen F, Zhang J and Pollak M**. Antiproliferative action of tumor necrosis factor-alpha on MCF-7 breastcancer cells is associated with increased insulin-like growth factor binding protein-3 accumulation**.** *Int J Oncol* 865-869, 1998.

233. **Salmon WDJr and Daughaday WH**. A hormonally controlled serum factor which stimulates sulfate incorporation by cartilage in vitro. *J Lab Clin Med* 49: 825-836, 1957.

234. **Sauvage LRJ, Myklebust BM, Crow-Pan J, Novak S, Millington P, Hoffman MD, Hartz AJ and Rudman D**. A clinical trial of strengthening and aerobic

exercise to improve gait and balance in elderly male nursing home residents. *Am J Phys Med Rehabil* 333-342, 1992.

235. **Sayer AA, Sydall H, O'Dell S D, Chen XH, Briggs PJ, Briggs R, Day IN and Cooper C**. Polymorphism of the IGF2 gene, birth weight and grip strength in adult men. *Age Ageing* 31: 468-470, 2002.

236. **Schmid C, Steiner T and Froesch ER**. Preferential enhancement of myoblast differentiation by insulin-like growth factors (IGF I and IGF II) in primary cultures of chicken embryonic cells. *FEBS Lett* 161: 117-121, 1983.

237. **Schrager MA, Roth SM, Ferrell RE, Metter EJ, Russek-Cohen E, Lynch NA, Lindle RS and Hurley BF**. Insulin-like growth factor-2 genotype, fat-free mass, and muscle performance across the adult life span. *J Appl Physiol* 97: 2176-2183, 2004.

238. **Schuller AG, Groffen C, van Neck JW, Zwarthoff EC and Drop SL**. cDNA cloning and mRNA expression of the six mouse insulin-like growth factor binding proteins. *Mol Cell Endocrinol* 104: 57-66, 1994.

239. **Seeman EJ, Hopper N, Young C, Formica C, Goss P, Accili D and Tsalamandris C**. Do genetic factors explain associations between muscle strength, lean mass, and bone density? A twin study. *American Jounral of Physiology* 270: E320-E327, 1996.

240. **Semsarian C, Wu MJ, Ju YK, Marciniec T, Yeoh T, Aleen DG, Harvey RP and Graham RM**. Skeletal muscle hypertrophy is mediated by a Ca2+ -dependent calcineurin signaling pathway. *Nature* 400: 576-581, 1999.

241. **Serrano A L, Murgia M, Pallafacchina G, Calabria E, Coniglio P, Lomo T and Schiaffino S**. Calcineurin controls nerve activity-dependent specification of slow skeletal muscle fibers but not muscle growth. *Proc Natl Acad Sci USA* 98: 13108-13113, 2001.

242. **Short KR and Nair KS**. Mechanisms of sarcopenia and aging. *J Endocrinol Invest* 22: 95-105, 1999.

243. **Sinaki M, McPhee M, Hodgson S, Merritt J and Offord K**. Relationship between bone mineral density of spine and strength of back extensors in healthy postmenopausal women. *Clincal Protocol* 61: 116-122, 1986.

244. **Sipila S, Taaffe DR, Cheng S, Puolakka J, Toivanen J and Suominen H**. Effects of hormone replacement therapy and high-impact physical exercise on skeletal muscle in postmenopausal women: a randomized placebo-controlled study. *Clin Soc (Lond)* 101: 147-157, 2001.

245. **Sjogren K, Liu JL, Blad K, Skrtic S, Vidal O, Wallenius V, LeRoith D, Tornell J, Isaksson OG, Jansson JO and Ohlsson C**. Liver-derived insulin-like growth factor I (IGF-I) is the principal source of IGF-I in blood but is not required for postnatal body growth in mice. *Proc Natl Acad Sci USA* 96: 7088-7092, 1999.

246. **Slattery ML, Baumgartner KB, Byers T, Guiliano A, Sweeney C, Herrick J, Curtin K, Murtaugh M and Wolff R**. Genetic, anthropometric, and lifestyle factors associated with IGF-1 and IGFBP-3 levels in Hispanic and non-Hispanic white women. *Cancer Causes and Control* 16: 1147-1157, 2005.

247. **Smith PJ, Spurrell EL, Coakley J, Hinds CJ, Ross RJ, Krainer AR and Chew SL**. An exonic splicing enhancer in human IGF-I pre-mRNA mediates

recognition of alternative exon 5 by the serine-arginine protein splicing factor-2/alternative aplicing factor. *Endocrinology* 143: 146-154, 2002.

248. **Sowers MR, Crutchfield M, Richards K, Wilkin MK, Furniss A, Jannausch M, Zhang D and Gross M**. Sarcopenia is related to physical functioning and leg strength in middle-aged women. *J Gerontol A Biol Sci Med Sci* 60: 486-490, 2005.

249. **Spangenburg EE, Abraha T, Childs TE, Pattison JS and Booth FW**. Skeletal muscle IGF-binding protein-3 and -5 expressions are age, muscle, and load dependent. *Am J Physiol Endocrinol Metab* 284: E340-E350, 2003.

250. **Stackhouse SK, Dean JC, Lee SC and Binder-MacLeod SA**. Measurement of central activation failure of the quadriceps femoris in healthy adults. *Muscle Nerve* 23: 1706-1712, 2000.

251. **Staron RS, Karapondo DL, Kraemer WJ, Fry AC, Gordon SE, Falkel JE, Hagerman FC and Hikida RS**. Skeletal muscle adaptations during early phase of heavy-resistance training in men and women. *J Appl Physiol* 76: 1247-1255, 1994.

252. **Staron RS, Malicky ES, Leonardi MJ, Falkel JE, Hagerman FC and Dudley GA**. Muscle hypertrophy and fast fiber type conversions in heavy resistance-trained women. *Eur J Appl Physiol Occup Physiol* 60: 71-79, 1990.

253. **Steele-Perkins G, Turner J, Edman JC, Hari J, Pierce SB, Stover C, Rutter WJ and Roth RA**. Expression and characterization of a functional human insulin-like growth factor I receptor. *J Biol Chem* 263: 11486-11492, 1988.

254. **Stewart CE and Rotwein P**. Growth, differentiation, and survival: multiple physiological functions for insulin-like growth factors. *Physiol Rev* 76: 1005-1026, 1996.

255. **Sullivan DH, Wall PT, Bariola JR, Bopp MM and Frost YM**. Progressive resistance muscle strength training of hospitalized frail elderly. *Am J Phys Med Rehabil* 80: 503-509, 2001.

256. **Sun G, Gagnon J, Chagnon YC, Perusse L, Despres JP, Leon AS, Wilmore JH, Skinner JS, Borecki I, Rao DC and Bouchard C**. Association and linkage between an insulin-like growth factor gene polymorphism and fat free mass in the HERITAGE Family Study. *Int J Obes Relat Metab Disord* 23: 929-935, 1999.

257. **Talmadge RJ, Otis JS, Rittler MR, Garcia ND, Spencer SR, Lees SJ and Naya FJ**. Calcineurin activation influences muscle phenotype in a muscle-specific fashion. *BMC Cell Biology* 5: 1-12, 2004.

258. **Tang W, Arnett DK, Devereux RB, Panagiotou D, Province MA, Miller MB, de Simone G, Gu C and Ferrell RE**. Identification of a novel 5-base pair deletion in calcineurin B (PPP3R1) promoter region and its association with left ventricular hypertrophy. *Am Heart J* 150: 845-851, 2005.

259. **Thissen JP, Ketelslegers JM and Maiter D**. Use of insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 in the diagnosis of acromegaly and growth hormone deficiency in adults. *Growth Regul* 6: 222-229, 1996.

260. **Thomis MA, Beunen GP, Maes HH, Blimkie CJ, Leemputte M, V, Claessens AL, Marchal G, Willems E and Vlietinek RF**. Strength training: importance of genetic factors. *Med Sci Sports Exerc* 30: 724-731, 1998.

261. **Thomis MA, Beunen GP, Van Leemputte M, Maes HH, Blimkie CJ, Claessens AL, Marchal G, Willems E and Vlietinek RF**. Inheritance of static and dynamic arm strength and some of its determinants. *Acta Physiol Scand* 163: 59-71, 1998.

262. **Thomis MA, Van Leemputte M, Maes HH, Blimkie CJ, Claessens AL, Marchal G, Willems E, Vlietinck RF and Beunen GP**. Multivariate genetic analysis of maximal isometric muscle force at different elbow angles. *J Appl Physiol* 82: 959-967, 1997.

263. **Tiainen K, Sipila S, Alen M, Heikkinen E, Kaprio J, Koskenvuo M, Tolvanen A, Pajala S and Rantanen T**. Heritability of maximal isometric muscle strength in older female twins. *J Appl Physiol* 96: 173-180, 2004.

264. **Toogood AA and Shalet SM**. Ageing and growth hormone status. *Bailleres Clin Endocrinol Metab* 12: 281-296, 1998.

265. **Tracy BL, Ivey FM, Hurlbut D, Martel GF, Lemmer JT, Siegel EL, Metter EJ, Fozard JL, Fleg JL and Hurley BF**. Muscle quality. II. Effects of strength training in 65- to 75-yr-old men and women. *J Appl Physiol* 86: 195-201, 1999.

266. **Tracy BL, Ivey FM, Hurlbut D, Martel GF, Lemmer JT, Siegel EL, Metter EJ, Fozard JL, Fleg JL and Hurley BF**. Muscle quality. II. Effects of strength training in 65- to 75-yr-old men and women. *J Appl Physiol* 86: 195-201, 1998.

267. **Trappe S, Gallagher P, Harber M, Carrithers J, Fluckey J and Trappe T**. Single muscle fibre contractile properties in young and old men and women. *J Physiol* 552: 47-58, 2003.

268. **Trappe S, Williamson D and Godard M**. Maintenance of whole muscle strength and size following resistance training in older men. *J Gerontol A Biol Sci Med Sci* 57: B138-B143, 2002.

269. **Trappe S, Williamson D, Godard M, Porter D, Rowden G and Costill D**. Effect of resistance training on single muscle fiber contractile function in older men. *J Appl Physiol* 89: 143-152, 2000.

270. **Trappe TA, Lindquist DM and Carrithers JA**. Muscle-specific atrophy of the quadriceps femoris with aging. *J Appl Physiol* 90: 2070-2074, 2001.

271. **Tricoli J, V, Rall LB, Scott J, Bell G, I and Shows TB**. Localization of insulin-like growth factor genes to human chromosomes 11 and 12. *Nature* 310: 784-786, 1984.

272. **Tricoli J, V, Winter DL, Hanlon AL, Raysor SL, Watkins-Bruner D, Pinover WH and Hanks GE**. Racial differences in insulin-like growth factor binding protein-3 in men at increased risk of prostate cancer. *Urology* 54: 178-182, 1999.

273. **Vaessen N, Heutink P, Janssen JA, Witteman JC, Testers L, Hofman A, Lamberts SW, Oostra BA, Pols HA and van Duijn CM**. A polymorphism in the gene for IGF-I: functional properties and risk for type 2 diabetes and myocardial infarction. *Diabetes* 50: 637-642, 2001.

274. **Van Pottelbergh I, Goemaere S, Nuytunck L, De Paepe A and Kaufman JM**. Association of the type I collagen alpha1 Sp1 polymorphism, bone density and upper limb muscle strength in community-dwelling elderly men. *Osteoporos Int* 12: 895-901, 2001.

275. **Velasco B, Cacicedo L, Escalada J, Lopez-Fernandez J and Sanchez-Franco F**. Growth hormone gene expression and secretion in aging rats is age dependent and not age-associated weight increase related. *Endocrinology* 139: 1314-1320, 1998.

276. **Verbrugge LM and Jette AM**. The disablement process. *Soc Sci Med* 38: 1-14, 1994.

277. **Vermeulen A**. Androgen replacement therapy in the aging male - a critical evaluation. *J Clin Endocrinol Metab* 86: 2380-2390, 2001.

278. **Villafuerte BC, Zhang WN and Phillips LS**. Insulin and insulin-like growth factor-I regulate hepatic insulin-like growth factor binding protein-3 by different mechanisms. *Mol Endocrinol* 10: 622-630, 1996.

279. **Visser M, Kritchevsky SB, Goodpaster BH, Newman AB, Nevitt M, Stamm E and Harris T B**. Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the health, aging and body composition study. *J Am Geriatr Soc* 50: 897-904, 2002.

280. **Walsh S, Zmuda JM, Cauley JA, Shea PR, Metter EJ, Hurley BF, Ferrell RE and Roth SM**. Androgen receptor CAG repeat polymorphism is associated with fat-free mass in men. *J Appl Physiol* 98: 132-137, 2005.

281. **Wang MG, Yi H, Guerini D, Klee CB and McBride OW**. Calcineurin A alpha (PPP3CA), calcineurin A beta (PPP3CB) and calcineurin B (PPP3R1) are located on human chromosomes 4, 10q21-->q22 and 2p16-->p15 respectively. *Cytogenet Cell Genet* 72: 236-241, 1996.

282. **Wang MG, Yi H, Guerini D, Klee CB and McBride OW**. Calcineurin A alpha (PPP3CA), calcineurin A beta (PPP3CB) and calcineurin B (PPP3R1) are located on human chromosomes 4, 10q21-->q22 and 2p16-->p15 respectively. *Cytogenet Cell Genet* 72: 236-241, 2005.

283. **Weber JL and May PE**. Abundant class of human DNA polymorphisms which can be typed using the polymerase chain reaction. *Am J Hum Genet* 44: 388-396, 1989.

284. **Welle S, Totterman S and Thornton C**. Effect of age on muscle hypertrophy induced by resistance training. *J Gerontol A Biol Sci Med Sci* 51: M270-M275, 1996.

285. **Wilkins BJ and Molkentin JD**. Calcineurin and cardiac hypertrophy: where have we been? Where are we going? *J Physiol* 541: 1-8, 2002.

286. **Wolfson L, Judge J, Whipple R and King M**. Strength is a major factor in balance, gait, and the occurrence of falls. *J Gerontol A Biol Sci Med Sci* 50A: 64-67, 1995.

287. **Woods KA, Camacho-Hubner C, Savage MO and Clark AJ**. Intrauterine growth retardation and postnatal growth failure associated with deletion of the insulin-like growth factor I gene. *N Engl J Med* 335: 1363-1367, 1996.

288. **Yang S, Alnaqeeb M, Simpson H and Goldspink G**. Cloning and characterization of an IGF-1 isoform expressed in skeletal muscle subjected to stretch. *J Muscle Res Cell Motil* 17: 487-495, 1996.

289. **Yang SY and Goldspink G**. Different roles of the IGF-1Ec peptide (MGF) and mature IGF-1 in myoblast proliferation and differentiation. *FEBS Lett* 522: 156-160, 2002.

290. **Young A, Stokes M and Crowe M**. Size and strength of the quadriceps muscles of old and young women. *Eur J Clin Invest* 14: 282-287, 1984.

291. **Young A, Stokes M and Crowe M**. The size and strength of the quadriceps muscles of old and young men. *Clin Physiol* 5: 145-154, 1985.

292. **Yu H, Li BDL, Smith M, Shi R, Berkel HJ and Kato I**. Polymorphic CA repeats in the IGF-I gene and breast cancer. *Breast Cancer Res Treat* 70: 117-122, 2001.

293. **Yu H, Mistry J, Nicar MJ, Khosravi MJ, Diamandis A, van Doorn J and Juul A**. Insulin-like growth factors (IGF-I, free IGF-I and IGF-II) and insulin-like growth factor binding proteins (IGFBP-2, IGFBP-3, IGFBP-6, and ALS) in blood circulation. *J Clin Lab Anal* 166-172, 1999.

294. **Yu KT and Czech MP**. The type I insulin-like growth factor receptor mediates the rapid effects of multiplication-stimulating activity on membrane transport systems in rat soleus muscle. *J Biol Chem* 259: 3090-3095, 1984.

295. **Zdanowicz MM and Teichberg S**. Effects of insulin-like growth factor-1/binding protein-3 complex on muscle atrophy in rats. *Exp Bio Med* 228: 891-897, 2003.