Published in final edited form as:

Gene. 2012 November 15; 510(1): 66–70. doi:10.1016/j.gene.2012.08.020.

Leptin and Leptin Receptor Genetic Variants Associate with Habitual Physical Activity and the Arm Body Composition Response to Resistance Training

S Walsh¹, CJ Haddad², MA Kostek², TJ Angelopoulos³, PM Clarkson⁴, PM Gordon⁵, NM Moyna⁶, PS Visich⁷, RF Zoeller⁸, RL Seip⁹, S Bilbie⁹, PD Thompson⁹, J Devaney¹⁰, H Gordish-Dressman¹⁰, EP Hoffman¹⁰, Thomas B. Price¹¹, and LS Pescatello²

¹Department of Physical Education and Human Performance, Central Connecticut State University, New Britain, CT, 06050

²Department of Kinesiology, University of Connecticut, Storrs, CT, 06269

³Department of Health Professions and Center for Lifestyle Medicine, University of Central Florida, Orlando, FL, 32826

⁴Department of Exercise Science, Totman Building, University of Massachusetts, Amherst, MA, 01003

⁵Department of Physical Medicine and Rehabilitation, School of Medicine, University of Michigan, Ann Arbor, MI 48108

⁶Department of Sport Science and Health, Dublin City University, Dublin, Ireland, 7008802

⁷Exercise & Sport Performance, University of New England, Biddeford, ME, 04005

⁸Department of Exercise Science and Health Promotion, Florida Atlantic University, Davie, FL 33314

⁹Division of Cardiology, Henry Low Heart Center, Hartford Hospital, Hartford, CT, Hartford, CT 06102

¹⁰Research Center for Genetic Medicine, Children's National Medical Center, Washington, DC, 20010

¹¹Health Sciences, University of Bridgeport, Bridgeport, CT 06604

Abstract

PURPOSE—We investigated the influence of *Leptin* (*LEP*) and *leptin receptor* (*LEPR*) SNPs on habitual physical activity (PA) and body composition response to a unilateral, upper body resistance training (RT) program.

METHODS—European-derived American volunteers (men=111, women=131, 23.4±5.4 yr, 24.4±4.6 kg·m⁻²) were genotyped for *LEP* 19 G>A (rs2167270), and *LEPR* 326 A>G

© 2012 Elsevier B.V. All rights reserved.

Correspondence to: Sean Walsh, PhD, Associate Professor, Department of Physical Education and Human Performance, School of Education and Professional Studies, Central Connecticut State University, 1615 Stanley Street, New Britain, CT 06050-4010, Tel (860) 832-2164, Fax (860) 832-2159, walshse@ccsu.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

(rs1137100), 668 A>G (rs1137101), 3057 G>A (rs1805096), and 1968 G>C (rs8179183). They completed the Paffenbarger PA Questionnaire. Arm muscle and subcutaneous fat volumes were measured before and after 12wk of supervised RT with MRI. Multivariate and repeated measures ANCOVA tested differences among phenotypes by genotype and gender with age and body mass index as covariates.

RESULTS—Adults with the *LEP* 19 GG genotype reported more kcal/wk in vigorous intensity PA (1273.3 ± 176.8 , $p=0.017$) and sports/recreation (1922.8 ± 226.0 , $p<0.04$) than A allele carriers (718.0 ± 147.2 , 1328.6 ± 188.2 , respectively). Those with the *LEP* 19 GG genotype spent more hr/wk in light intensity PA (39.7 ± 1.6) than A allele carriers (35.0 ± 1.4 , $p=0.03$). In response to RT, adults with the *LEPR* 668 G allele gained greater arm muscle volume (67687.05 ± 3186.7 vs. 52321.87 ± 5125.05 mm³, $p=0.01$) and subcutaneous fat volume (10599.89 ± 3683.57 vs. -5224.73 ± 5923.98 mm³, $p=0.02$) than adults with the *LEPR* 668 AA genotype, respectively.

CONCLUSION—*LEP* 19 G>A and *LEPR* 668 A>G associated with habitual PA and the body composition response to RT. These *LEP* and *LEPR* SNPs are located in coding exons likely influencing *LEP* and *LEPR* function. Further investigation is needed to confirm our findings and establish mechanisms for *LEP* and *LEPR* genotype and PA and body composition associations we observed.

Keywords

exercise; genomics; polymorphism

1.1 Introduction

Leptin (LEP) is a hormone secreted mainly from adipose tissue that plays a role in regulating energy intake by its inhibitory effects on food intake and increases in energy expenditure by stimulating metabolic rate and physical activity (PA) to maintain energy balance (Lenard and Berthoud 2008). The biologic activities of LEP on target tissues are carried out through selective binding to its receptor (LEPR) (Paracchini et al 2005). LEPR exists in two isoforms: the long form (Ob-Rb) and short form receptors (Ob-Ra, c, d). It is a member of the class I cytokine receptor family that is expressed in the hypothalamus (Considine et al 1996) and peripheral tissues including skeletal muscle (Ceddia et al 2001). LEP acts as an afferent signal in a negative feedback loop by binding to LEPR regulating the size of adipose tissue (Sahu 2004).

Physical inactivity is a leading contributor to premature death and over 35 chronic diseases, including heart disease, diabetes mellitus, and obesity (Booth et al 2002). Despite overwhelming evidence of the many health benefits of physical activity, most people do not engage in the amount of PA necessary to achieve them (Lees and Booth 2004). Heritability studies show that genetic factors account for 20% to 70% of the variation in PA levels (Stubbe et al 2006), yet research examining the influence of genetic predispositions to be physically active, termed *activity genetics*, is scarce (Rankinen 2009; Rankinen et al 2010).

LEP activity is modulated by genetic variation. Hager et al. (Hager et al 1998) observed that a single A/G substitution at position 19, *LEP* 19 G>A (rs2167270), of the untranslated region of exon 1 effects LEP concentrations. Individuals homozygous for the *LEP* 19 G allele showed significantly lower LEP concentrations compared to those either heterozygous or homozygous for the A allele (Hager, Clement, Francke, Dina, Raison, Lahlou, Rich, Pelloux, Basdevant, Guy-Grand, North, and Froguel 1998). Several common polymorphisms of *LEPR* have also been identified to influence LEPR activity (Thompson et al 1997). *LEPR* 668 A>G (rs1137101) is located in exon 6, a putative LEP binding region. Chagnon et al. (Chagnon et al 1999) hypothesized that the single amino acid change of

glutamine to arginine could alter the binding capacity of LEPR to LEP. *LEPR* genetic variants have also been associated with PA and 24 hr energy expenditure in humans (Stefan et al 2002). Stefan et al. (Stefan, Vozarova, Del, Ossowski, Thompson, Hanson, Ravussin, and Tataranni 2002) observed Pima Indians that were homozygous for the *LEPR* 668 A allele had lower 24 hr energy expenditure and lower PA levels assessed within a respiratory chamber. Richert et al. (Richert et al 2007) found that boys 7 yr of age with the *LEPR* A668A genotype had lower self reported PA levels as determined by questionnaire than boys who were carriers of the G allele (Richert, Chevalley, Manen, Bonjour, Rizzoli, and Ferrari 2007).

Heritability estimates for body composition phenotypes range from 30% to 90% (Perusse et al 1996; Perusse et al 2005). LEP deficiency due to variation in the *LEPR* or *LEP* is associated with severe obesity in humans (Friedman and Halaas 1998; Sahu 2004). Investigators from the Quebec Family Study (Chagnon, Chung, Perusse, Chagnon, Leibel, and Bouchard 1999) observed three *LEPR* single nucleotide polymorphisms (SNPs) associated with body composition phenotypes, with the *LEPR* 668 A>G showing the strongest associations with fat free mass (Chagnon, Chung, Perusse, Chagnon, Leibel, and Bouchard 1999). Men who were carriers of the G allele with a body mass index < 27 kg/m² had 4 kg less fat free mass than non-carriers of the G allele.

Therefore the aims of this present study were to examine whether two biologically relevant candidate genes, *LEP* and *LEPR*, are associated with habitual PA levels and the body composition response to a 12 wk unilateral, upper arm RT among a large sample of healthy, young normal weight adults. We hypothesized that *LEP* and *LEPR* genetic variants would associate with habitual PA and differentially impact the body composition response to a RT.

2.1 MATERIAL & METHODS

This sub-study was from a larger project entitled, Functional Single Nucleotide Polymorphisms Associated with Human Muscle Size and Strength (FAMuSS), conducted by the Exercise and Genetics Collaborative Research Group (Thompson et al 2004). Study protocol and informed consent were approved by the institutional review boards from the 10 sites involved with FAMuSS.

2.2 Subjects

Study participants were healthy European-derived American men and women 18 to 39 yr. Individuals did not qualify for participation if they self-reported a history of RT during the prior year, use of protein supplements during the prior 3 months, or alcohol consumption (>14 drinks/wk).

2.3 Physical activity measurements

A sub sample of FAMuSS subjects (n=560) completed the Paffenbarger Physical Activity Questionnaire (PPAQ) (Paffenbarger, Jr. et al 1995) during their initial visit. The PPAQ consisted of eight questions that quantified leisure-time PA levels. Questions 4 through 7 assessed leisure time exercise habits including sports and recreational activities. Question 8 asked subjects to divide a typical weekday and weekend day into hours spent in five intensity PA categories so that the total hours from each of the five categories totaled 24 hr. We considered all activities with a MET value >6 as vigorous intensity, MET value of 3–6 as moderate intensity, and MET value <3 as low intensity (Pate et al 1995). We then derived these PA phenotypes: Distance walked (mi/wk), PA index (kcal/wk), energy expended (EE) in vigorous and moderate intensity PA (kcal/wk), and sports and recreation (kcal/wk) as described previously (Ainsworth et al 1993; Paffenbarger, Jr., Wing, and Hyde 1995).

Additional PA phenotypes included: Time (hr/wk) spent in vigorous, moderate, light intensity PA, and sitting (Paffenbarger, Jr. et al 1993).

2.4 Anthropometric measurements

Body weight and height were measured and recorded pre- and post-RT. Body weight was determined using a standard balance beam scale (Model 338 Eye-Level Physician Scale, Detectoscale, Webb City, MO) following the removal of shoes and heavy clothing. Body height was recorded in inches. Body mass index (kg m^{-2}) was then calculated.

2.5 Resistance training program

All subjects participated in a 12 wk, 2 d/wk upper arm, unilateral RT program. All training was performed on the non-dominant arm. RT sessions were supervised and lasted approximately 45–60 min. Each RT session began with a warm-up consisting of two sets of 12 repetitions of the biceps preacher curl and seated overhead triceps extension. Five exercises were done in the following order: biceps preacher curl, seated overhead triceps extension, biceps concentration curl, triceps kickback, and standing biceps curl. Initial training weight was set at 65% one repetition maximum (1RM). There was a 2 min rest period between each set. RT was periodized to maximize muscle strength gains. Visits one to eight required three sets of 12 repetitions at 65–75% 1RM; visits nine to 18, three sets of eight repetitions at 75–82% 1RM; and visits 19 to 24, three sets of six repetitions at 83–90% 1RM.

2.6 Magnetic resonance imaging (MRI)

Cross-sectional area (CSA) of the biceps brachii was determined bilaterally using MRI with 1.5T systems and described in detail elsewhere (Kostek et al 2007; Walsh et al 2009). MRI was done pre-RT and within 48–96 hr of the final RT session. Prior to imaging, maximum arm circumference or point of measurement was ascertained and marked with a radiographic bead (Beekley Spots; Beekley Corp., Bristol, CT). The point of measurement was visually determined with a subject's arm abducted 90° at the shoulder joint, palm supinated and open, and elbow flexed at 90°. The subject was then instructed to maximally flex the biceps muscles. The point of measurement was located, the skin marked, and the tip of a radiographic bead aligned and placed on the mark. The same investigator measured the point of measurement pre- and post-RT.

The MRI involved imaging a 24 cm length of the upper arm using 15 axial slices. Subjects were laid supine on the imaging bed, with the arm aligned to the isocenter of the magnet. The hand was placed in the anatomical position and affixed with tape to the scanner bed surface. Coronal and sagittal scout images were generated to locate the long axis of the humerus and to align the 8th axial slice with the point of measurement. With the point of measurement as the center point, 15 spoiled gradient images were taken [time to echo (TE) = 1.9 ms, time to repeat (TR) = 200 ms, flow artifact suppression, 30° flip angle]. Axial imaging began at the superior portion of the arm and proceeded distally toward the elbow joint. Each image slice was 16 mm thick with a 0 mm inter-slice gap, 256 x 192 matrix resolution, 22 cm x 22 cm field of view, and number of experiments (NEX) = 6. MRI data from all investigational sites were submitted to the central imaging facility at Yale University via Magneto Optical Disk or CD-ROM for further analysis. Images were analyzed using a custom designed program created to function within Matlab (The Math Works, Inc., Natick, MA). The 8th slice was the location analyzed for biceps CSA pre- and post-RT. Subcutaneous fat and muscle volumetric measurements of the arm were calculated using the following equations, where $C = 0.01$ (conversion from pixels to squared centimeters) and $\text{trained} = \text{slice thickness (1.6 cm)}$:

$$\begin{aligned}\text{Subcutaneous fat volume (mL)} &= \sum(\text{arm} - \text{lean}) \times C \times \text{trained} \\ \text{Muscle volume (mL)} &= \sum(\text{lean} - \text{bone}) \times C \times \text{trained}\end{aligned}$$

2.7 Genotyping methods

Genotyping was done to identify *LEP* and *LEPR* genotypes using TaqMan allele discrimination assays that employed the 5' nuclease activity of Taq polymerase to detect a fluorescent reporter signal generated during the PCR reaction. We genotyped the following SNPs: *LEP* 19 G>A (rs2167270), and *LEPR* 326 A>G (rs1137100), 668 A>G (rs1137101), 3057 G>A (rs1805096), and 1968 G>C (rs8179183). Alleles were detected simultaneously using allele-specific oligonucleotides labeled with different fluorophores, and genotypes determined by the ratio of the two fluorophores used. Allele-specific PCR reactions for each single nucleotide polymorphism (SNP) included 10 ng genomic DNA, 900 nM forward and reverse PCR primers, 200 nM fluorescent allele discrimination probes and TaqMan® Universal PCR Master Mix, No AmpErase® UNG (Applied Biosystems, Foster City, CA, USA) in a final volume of 25 l. The PCR profile was 10 min at 95 °C (denaturation), and 44 cycles of 15 s at 92°C and 1 min at an annealing temperature of 60 °C. Reactions were set up using a MWG robot, and fluorescence ratios and allele calling done using an ABI 7900. For quality control, negative controls (water blanks) and duplicate samples covering 5% of the total number of samples analyzed (100% agreement) were included in the analysis.

2.8 Statistical analysis

Descriptive statistics were performed on all variables. All SNPs were in Hardy-Weinberg Equilibrium determined by χ^2 . The correlation coefficient method found that no SNPs were in linkage disequilibrium. Multivariate and repeated measures ANCOVA tested differences among PA and body composition phenotypes (i.e., subcutaneous fat volume and muscle volume) by *LEP* and *LEPR* genotype and gender, with age and body mass index as covariates. The phenotypes observed in the current study did not differ among *LEP* A19A and G19A genotype groups as well as among *LEPR* G668G and G668A genotype groups so these genotypes were combined and statistical analyses repeated on two genotype groups for each SNP using a dominant model, i.e., GG and GA/AA. All statistical analyses were performed with SPSS 15.0 for Windows with $p < 0.05$ established as the level of statistical significance. A Bonferroni-correction was applied to account for multiple statistical testing. All data are reported as mean $\pm$ SEM. Data for SNPs where significant findings were observed are reported.

3.1 RESULTS

3.2 Subjects Characteristics

The study sample ($n = 560$) had a mean age of 23.4 ± 5.4 yr and a BMI of 24.4 ± 4.6 kg/m². Age, weight, height, and BMI was greater in subjects homozygous for the *LEPR* 668 A allele versus those carrying the *LEPR* 668 G allele ($p < 0.05$) (Table 1). No significant differences were observed for any physical characteristics by *LEP* 19 G>A, and *LEPR* 326 A>G (rs1137100) and 1968 G>C (rs8179183) genotypes (data not shown).

3.3 Physical Activity Phenotypes

Adults with the *LEP* 19 GG genotype reported more kcal/wk in vigorous intensity PA ($p = 0.017$) and sports/recreation, ($p = 0.04$) than A allele carriers (Table 2). Those with the *LEP* 19 GG genotype spent more hr/wk in light intensity PA than A allele carriers ($p = 0.03$) (Table 2). No significant associations were observed among PA phenotypes and *LEPR* 326

A>G (rs1137100), 668 A>G (rs1137101), 3057 G>A (rs1805096), and 1968 G>C (rs8179183) genotypes (data not shown).

3.4 Resistance Training

Biceps cross-sectional area—Carriers of the *LEPR* 668 G allele (n=166) gained greater absolute arm (p=0.007) and muscle CSA (p=0.007) (Table 3). In addition carriers of the *LEPR* 668 G allele gained more absolute subcutaneous fat CSA, while adults with the *LEPR* 668 AA genotype (n=62) lost subcutaneous fat CSA in the trained arm (p=0.002) (Table 3). No significant associations were observed among biceps CSA phenotypes and *LEP* 19 G>A, and *LEPR* 326 A>G (rs1137100), 3057 G>A (rs1805096), and 1968 G>C (rs8179183) genotypes (data not shown).

Biceps muscle and fat volume—Adults with the *LEPR* 668 G allele gained more arm muscle volume (p=0.01) and subcutaneous fat volume (p=0.02) than adults with the *LEPR* 668 AA genotype (Table 4). Adults with the *LEPR* 668 G also displayed relative gains in subcutaneous fat volume, while adults with the *LEPR* 668 AA genotype displayed decreases in subcutaneous fat volume (p=0.003) (Table 4). No significant associations were observed among biceps muscle and fat volume phenotypes and *LEP* 19 G>A, and *LEPR* 326 A>G (rs1137100), 3057 G>A (rs1805096), and 1968 G>C (rs8179183) genotypes (data not shown).

4.1 DISCUSSION

The present study examined the influence of genetic variation in two biologically relevant candidate genes, *LEP* and *LEPR*, on habitual PA levels and the body composition response to a 12 wk unilateral, upper arm RT among a large sample of healthy, young normal weight adults. Important new findings were subjects homozygous for the *LEP* 19 G allele expended more energy in vigorous intensity PA (~555 kcal/wk) and sports and recreation (~594 kcal/wk), and spent more time in light intensity PA (~5 hr/wk) than carriers of the A allele. A difference in ~555 kcal/wk in vigorous intensity PA between *LEP* 19 G>A genotype groups may have significant health implications. Vigorous intensity PA is now an integral part of the updated physical activity recommendations for Americans (Haskell et al 2007; US Department of Health and Human Services 2008). The American College of Sports Medicine/American Heart Association update recommends participation in aerobic PA above minimum recommended amounts (at least 30 min of moderate intensity) because it provides additional health benefits, and results in greater gains in physical fitness and reductions in risk for premature chronic health conditions and mortality related to physical inactivity (Haskell, Lee, Pate, Powell, Blair, Franklin, Macera, Heath, Thompson, and Bauman 2007). Individuals homozygous for the *LEP* 19 G allele may be receiving additional health benefits as result of expending more energy in vigorous intensity PA due to their genetic predispositions than carriers of the A allele.

LEP has been shown to increase spontaneous PA (11) and *LEP* mediated increases in cocaine- and amphetamine-regulated transcript increases PA levels (Kristensen et al 1998). *LEP* administration also activates the sympathetic nervous system (Tang-Christensen et al 1999) and measurements of spontaneous PA in humans have been found to be related with sympathetic nervous system activity (Snitker et al 1997). Collectively, these findings suggest that differential circulating levels of *LEP* due to genetic variation may impact *LEP* mediated increases in cocaine- and amphetamine-regulated transcript and/or stimulation of sympathetic nervous system activity resulting in higher or lower PA levels that we observed in the current study. A limitation of the current study is that we do not have measures of circulating *LEP* concentrations. Thus, this hypothesis should be tested in future work attempting to replicate our findings.

Stefan et al. (Stefan, Vozarova, Del, Ossowski, Thompson, Hanson, Ravussin, and Tataranni 2002) and Richert et al (Richert, Chevalley, Manen, Bonjour, Rizzoli, and Ferrari 2007) observed genotype associations with PA levels in the *LEPR* 668 A>G while we did not. One explanation for these differences may be the result of different populations and measurement tools for the phenotypes of interest. Stefan et al. (Stefan, Vozarova, Del, Ossowski, Thompson, Hanson, Ravussin, and Tataranni 2002) examined a very genetically homogenous population in the Pima Indians and used a respiratory chamber to assess 24 hr energy expenditure and PA levels. Richert et al. (Richert, Chevalley, Manen, Bonjour, Rizzoli, and Ferrari 2007) studied boys 7 yr of age and determined PA levels by a self-report PA questionnaire. In contrast, our study population consisted of young healthy adults, and we used a self-report PA questionnaire. As result of these methodological differences, it is difficult to explain reasons for the different *LEPR* 668 A>G and PA findings among these studies.

The present study is one of few to examine the influence that genetic variation has on the body composition response to a RT program. Our new and noteworthy findings are adults with the *LEPR* 668 G allele not only gained greater muscle volume than adults with the *LEPR* 668 AA genotype but also greater subcutaneous fat volume, resulting in a 4.6% increase in subcutaneous fat. In comparison adults with the *LEPR* 668 AA genotype lost subcutaneous fat, displaying a 2% decrease in comparison to baseline values as a result of RT. Quinton et al. (Quinton et al 2001) found *LEPR* 668 A>G, which changes an amino acid and therefore potentially protein structure and function, associated with an impaired signaling capacity. *LEPR* 668 A>G has been associated with differences in body composition by others (Chagnon, Chung, Perusse, Chagnon, Leibel, and Bouchard 1999). Quinton et al. (19) concluded that variations in *LEPR* function associated with genotype are important factors in the regulation of adiposity (Quinton, Lee, Ross, Eastell, and Blakemore 2001).

We speculate that impaired signaling capacity of *LEPR*, as result of genotype, may explain the differences observed in the current study regarding the subcutaneous fat response to RT. Our research group has observed that a missense mutation in the *SH2b1* gene (rs7498665) resulted in women with the rare allele gaining more subcutaneous fat than women with two copies of the common allele (Orkunoglu-Suer et al 2010). Similarly, another FAMuSS study from our research consortium reported *PPARα* L162V associated with the subcutaneous fat response to RT, with men carrying the rare allele gained considerably greater adiposity following unilateral resistance arm (Uthurralt et al 2007). Our previous reports (Orkunoglu-Suer et al 2011; Uthurralt, Gordish-Dressman, Bradbury, Tesi-Rocha, Devaney, Harmon, Reeves, Brandoli, Hansen, Seip, Thompson, Price, Angelopoulos, Clarkson, Moyna, Pescatello, Visich, Zoeller, Gordon, and Hoffman 2007) in combination with the present findings suggest that an interaction may exist between genetic profile and the body composition response to RT. Individuals who RT, with a certain genetic profile, may lead to poorer body composition response outcomes and limited localized exercise may trigger an increase in adiposity.

5.1 CONCLUSION

The present results adds *LEP* 19 G>A to a growing list of SNPs that have been identified as making contributions to the inter-individual variation in habitual PA levels and *LEPR* 668 A>G as influencing the body composition response to RT. Genetic factors influencing PA levels are now viewed as “the core” of the transdisciplinary model of exercise behavior. Therefore exercise genomics may provide an exciting new avenue that may add additional strategies in treating physical inactivity (Angela D.Bryan et al 2010). Elucidation of the genetic component of the body composition response to RT may be an important step

toward development of novel and safe therapeutic strategies for reducing subcutaneous fat by developing individualized RT exercise prescriptions designed to maximize body composition changes. Potential mechanisms for these findings are unclear; therefore, further research is warranted to ascertain the physiologic pathways by which *LEP* 19 G>A differentially associates with habitual PA levels and *LEPR* 668 A>G with the body composition response to RT.

Acknowledgments

We thank the students and technicians at the participating institutions for their time and effort along with the subjects for their participation and commitment to the project.

Abbreviations

LEP	Leptin
PA	physical activity
LEPR	Leptin Receptor
SNPs	single nucleotide polymorphisms
FAMuSS	Functional Single Nucleotide Polymorphisms Associated with Human Muscle Size and Strength
RT	Resistance Training
PPAQ	Paffenbarger Physical Activity Questionnaire
EE	energy expended
1RM	one repetition maximum
MRI	Magnetic resonance imaging
CSA	Cross-sectional area

References

- Ainsworth BE, Leon AS, Richardson MT, Jacobs DR, Paffenbarger RS Jr. Accuracy of the College Alumni Physical Activity Questionnaire. *J Clin Epidemiol*. 1993; 46:1403–1411. [PubMed: 8263567]
- Bryan, Angela D.; Magnan, Renee E.; Nilsson, Renea; Marcus, Bess H.; Tompkins, Sara Anne; Hutchinson, Kent E. The big picture of individual differences in physical activity behavior change: A transdisciplinary approach. *Psychology of Sport and Exercise*. 2010; 12:20–26. [PubMed: 21278837]
- Booth FW, Chakravarthy MV, Gordon SE, Spangenburg EE. Waging war on physical inactivity: using modern molecular ammunition against an ancient enemy. *J Appl Physiol*. 2002; 93:3–30. [PubMed: 12070181]
- Ceddia RB, William WN Jr, Curi R. The response of skeletal muscle to leptin. *Front Biosci*. 2001; 6:D90–D97. [PubMed: 11145919]
- Chagnon YC, Chung WK, Perusse L, Chagnon M, Leibel RL, Bouchard C. Linkages and associations between the leptin receptor (*LEPR*) gene and human body composition in the Quebec Family Study. *Int J Obes Relat Metab Disord*. 1999; 23:278–286. [PubMed: 10193873]
- Considine RV, Considine EL, Williams CJ, Hyde TM, Caro JF. The hypothalamic leptin receptor in humans: identification of incidental sequence polymorphisms and absence of the db/db mouse and fa/fa rat mutations. *Diabetes*. 1996; 45:992–994. [PubMed: 8666155]
- Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. *Nature*. 1998; 395:763–770. [PubMed: 9796811]

- Hager J, Clement K, Francke S, Dina C, Raison J, Lahlou N, Rich N, Pelloux V, Basdevant A, Guy-Grand B, North M, Froguel P. A polymorphism in the 5' untranslated region of the human ob gene is associated with low leptin levels. *Int J Obes Relat Metab Disord*. 1998; 22:200–205. [PubMed: 9539186]
- Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc*. 2007; 39:1423–1434. [PubMed: 17762377]
- Kostek MA, Pescatello LS, Seip RL, Angelopoulos TJ, Clarkson PM, Gordon PM, Moyna NM, Visich PS, Zoeller RF, Thompson PD, Hoffman EP, Price TB. Subcutaneous fat alterations resulting from an upper-body resistance training program. *Med Sci Sports Exerc*. 2007; 39:1177–1185. [PubMed: 17596787]
- Kristensen P, Judge ME, Thim L, Ribel U, Christjansen KN, Wulff BS, Clausen JT, Jensen PB, Madsen OD, Vrang N, Larsen PJ, Hastrup S. Hypothalamic CART is a new anorectic peptide regulated by leptin. *Nature*. 1998; 393:72–76. [PubMed: 9590691]
- Lees SJ, Booth FW. Sedentary death syndrome. *Can J Appl Physiol*. 2004; 29:447–460. [PubMed: 15317985]
- Lenard NR, Berthoud HR. Central and peripheral regulation of food intake and physical activity: pathways and genes. *Obesity* (Silver Spring). 2008; 16(Suppl 3):S11–S22. [PubMed: 19190620]
- Orkunoglu-Suer, FE.; Harmon, BT.; Gordish-Dressman, H.; Clarkson, PM.; Thompson, PD.; Angelopoulos, TJ.; Gordon, PM.; Hubal, MJ.; Moyna, NM.; Pescatello, LS.; Visich, PS.; Zoeller, RF.; Hoffman, EP.; Devaney, JM. *Obesity*. Silver. Spring; 2010. MC4R Variant Is Associated With BMI but Not Response to Resistance Training in Young Females.
- Orkunoglu-Suer FE, Harmon BT, Gordish-Dressman H, Clarkson PM, Thompson PD, Angelopoulos TJ, Gordon PM, Hubal MJ, Moyna NM, Pescatello LS, Visich PS, Zoeller RF, Hoffman EP, Devaney JM. MC4R Variant Is Associated With BMI but Not Response to Resistance Training in Young Females. *Obesity* (Silver Spring). 2011; 19:662–666. [PubMed: 20725061]
- Paffenbarger RS Jr, Blair SN, Lee IM, Hyde RT. Measurement of physical activity to assess health effects in free-living populations. *Med Sci Sports Exerc*. 1993; 25:60–70. [PubMed: 8423758]
- Paffenbarger RS Jr, Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. 1978. *Am J Epidemiol*. 1995; 142:889–903. [PubMed: 7572969]
- Paracchini V, Pedotti P, Taioli E. Genetics of leptin and obesity: a HuGE review. *Am J Epidemiol*. 2005; 162:101–114. [PubMed: 15972940]
- Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, Buchner D, Ettinger W, Heath GW, King AC. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA*. 1995; 273:402–407. [PubMed: 7823386]
- Perusse L, Despres JP, Lemieux S, Rice T, Rao DC, Bouchard C. Familial aggregation of abdominal visceral fat level: results from the Quebec family study. *Metabolism*. 1996; 45:378–382. [PubMed: 8606647]
- Perusse L, Rankinen T, Zuberi A, Chagnon YC, Weisnagel SJ, Argyropoulos G, Walts B, Snyder EE, Bouchard C. The human obesity gene map: the 2004 update. *Obes Res*. 2005; 13:381–490. [PubMed: 15833932]
- Quinton ND, Lee AJ, Ross RJ, Eastell R, Blakemore AI. A single nucleotide polymorphism (SNP) in the leptin receptor is associated with BMI, fat mass and leptin levels in postmenopausal Caucasian women. *Hum Genet*. 2001; 108:233–236. [PubMed: 11354636]
- Rankinen, T. Genetics and Physical Activity Level. In: Bouchard, C.; Katzmarzyk, P., editors. *Physical Activity and Obesity*. 2009. p. 73-75.
- Rankinen T, Roth SM, Bray MS, Loos R, Perusse L, Wolfarth B, Hagberg JM, Bouchard C. Advances in exercise, fitness, and performance genomics. *Med Sci Sports Exerc*. 2010; 42:835–846. [PubMed: 20400881]
- Richert L, Chevalley T, Manen D, Bonjour JP, Rizzoli R, Ferrari S. Bone mass in prepubertal boys is associated with a Gln223Arg amino acid substitution in the leptin receptor. *J Clin Endocrinol Metab*. 2007; 92:4380–4386. [PubMed: 17785359]

- Sahu A. Minireview: A hypothalamic role in energy balance with special emphasis on leptin. *Endocrinology*. 2004; 145:2613–2620. [PubMed: 15044360]
- Snitker S, Pratley RE, Nicolson M, Tataranni PA, Ravussin E. Relationship between muscle sympathetic nerve activity and plasma leptin concentration. *Obes Res*. 1997; 5:338–340. [PubMed: 9285841]
- Stefan N, Vozarova B, Del PA, Ossowski V, Thompson DB, Hanson RL, Ravussin E, Tataranni PA. The Gln223Arg polymorphism of the leptin receptor in Pima Indians: influence on energy expenditure, physical activity and lipid metabolism. *Int J Obes Relat Metab Disord*. 2002; 26:1629–1632. [PubMed: 12461680]
- Stubbe JH, Boomsma DI, Vink JM, Cornes BK, Martin NG, Skytthe A, Kyvik KO, Rose RJ, Kujala UM, Kaprio J, Harris JR, Pedersen NL, Hunkin J, Spector TD, de Geus EJ. Genetic influences on exercise participation in 37, 051 twin pairs from seven countries. *PLoS One*. 2006; 1:e22. [PubMed: 17183649]
- Tang-Christensen M, Havel PJ, Jacobs RR, Larsen PJ, Cameron JL. Central administration of leptin inhibits food intake and activates the sympathetic nervous system in rhesus macaques. *J Clin Endocrinol Metab*. 1999; 84:711–717. [PubMed: 10022442]
- Thompson DB, Ravussin E, Bennett PH, Bogardus C. Structure and sequence variation at the human leptin receptor gene in lean and obese Pima Indians. *Hum Mol Genet*. 1997; 6:675–679. [PubMed: 9158141]
- Thompson PD, Moyna N, Seip R, Price T, Clarkson P, Angelopoulos T, Gordon P, Pescatello L, Visich P, Zoeller R, Devaney JM, Gordish H, Bilbie S, Hoffman EP. Functional polymorphisms associated with human muscle size and strength. *Med Sci Sports Exerc*. 2004; 36:1132–1139. [PubMed: 15235316]
- US Department of Health and Human Services. 2008 physical activity guidelines for Americans. 2008. <http://www.health.gov/PAGuidelines>
- Uthurralt J, Gordish-Dressman H, Bradbury M, Tesi-Rocha C, Devaney J, Harmon B, Reeves EK, Brandoli C, Hansen BC, Seip RL, Thompson PD, Price TB, Angelopoulos TJ, Clarkson PM, Moyna NM, Pescatello LS, Visich PS, Zoeller RF, Gordon PM, Hoffman EP. PPARalpha L162V underlies variation in serum triglycerides and subcutaneous fat volume in young males. *BMC Med Genet*. 2007; 8:55. [PubMed: 17705849]
- Walsh S, Kelsey BK, Angelopoulos TJ, Clarkson PM, Gordon PM, Moyna NM, Visich PS, Zoeller RF, Seip RL, Bilbie S, Thompson PD, Hoffman EP, Price TB, Devaney JM, Pescatello LS. CNTF 1357 G -> A polymorphism and the muscle strength response to resistance training. *J Appl Physiol*. 2009; 107:1235–1240. [PubMed: 19628720]

Highlights

- We examined genetic variation and its association with physical activity levels.
- Leptin and Leptin Receptor SNP's were the genetic variants examined.
- *LEP19* G>A associated with habitual physical activity.
- *LEPR* 668 A>G associated with the body composition response to resistance training.

TABLE 1

Mean Subject Characteristics by *LEPR* 668 A>G Genotype for Men and Women in the Resistance Training Cohort.

Variable	AA (N=62)	GG/GA (N=167)
Age (yr)	25.1 ± 0.7 *	23.1 ± 0.4
Weight (kg)	74.5 ± 1.8 *	69.4 ± 1.15
Height (cm)	172.4±0.4 *	169.8±0.2
BMI (kg m ⁻²)	25.1 ± 0.5 *	23.1 ± 0.9

Values are means ±SE. *LEPR*, Leptin Receptor; A, *LEPR* A⁶⁶⁸ allele; G, *LEPR* G⁶⁶⁸ allele; BMI, body mass index

* P < 0.05, AA vs GG/GA

Table 2

Energy Expended and Time Spent Engaging in Physical Activity Intensity Categories Among Adults by *LEP* 19 G>A Genotype.

Variable	GG (N= 103)	AA/GA (N=139)
Physical activity index (kcal/wk)	2961.9±246.8	2491.2±205.5
Vigorous intensity PA (kcal/wk)	1273.3±176.8	718.0±147.2 *
Moderate intensity PA (kcal/wk)	629.6±107.2	530.4±89.3
Sports and recreation (kcal/wk)	1922.8±226.0	1328.6±188.2 *
Light intensity PA (hr/wk)	39.7±1.6	35.0±1.4 *
Sitting (hr/wk)	40.8±1.9	43.8±1.6

Values are means ±SE. Covariates included age and body mass index. LEP, Leptin; A, LEP A¹⁹ allele; G, LEP G¹⁹ allele

* GG vs AA/GA, p<0.05

Table 3Cross-Sectional Area Changes in the Trained Arm in Response to RT by *LEPR* 668 A>G Genotype

Phenotype	AA N=62	GG/GA N=166
Baseline whole arm cross sectional area (cm ²)	6178.06 ± 90.6	6252.55±56.39
Post RT whole arm cross sectional area (cm ²)	6744.40±97.0	6996.97±60.91
Absolute change (cm ²)	566.33±55.1 *	744.42±34.25
Relative change (%)	9.9±0.96 *	12.2±0.59
Baseline whole muscle cross sectional area (cm ²)	5308.85±168.68	5413.44±104.88
Post RT whole muscle cross sectional area (cm ²)	5869.33±175.58	6138.85±109.17
Absolute change (cm ²)	560.48±51.2 *	725.39±31.84
Relative change (%)	12.17±1.05	14.17±0.65
Baseline subcutaneous fat cross sectional area (cm ²)	2262.04±82.39	2291.36±51.23
Post RT subcutaneous fat cross sectional area (cm ²)	2211.36±87.42	2380.40±54.36
Absolute change(cm ²)	-50.68±37.61 *	89.03±23.39
Relative change (%)	-1.95±1.86 *	4.82±1.16

Values are means ±SE. Covariates included BMI and age with *LEPR* genotype set as the fixed factor. *LEPR*, Leptin Receptor; A, *LEPR* A⁶⁶⁸ allele; G, *LEPR* G⁶⁶⁸ allele

* P < 0.05, AA vs GG/GA

Table 4Volume Changes in Trained Arm in Response to Resistance Training by *LEPR* 668 A>G Genotype

Phenotype	AA N=62	GG/GA N=122
Baseline whole arm volume (mm ³)	578037.66±8449.74	583481.81±5254.01
Post RT whole arm volume (mm ³)	630588.66±8917.96	651499.52±5545.24
Absolute change (mm ³)	52551.01±5070.75 *	68017.71±3153.02
Relative Change (%)	9.78±0.95 *	12.02±0.59
Baseline whole muscle volume (mm ³)	494808.01±15341.97	504493.84±9557.60
Post RT whole muscle volume (mm ³)	547205.86±15866.25	571038.04±9884.22
Absolute change (mm ³)	52321.87±5125.05 *	67687.05±3186.78
Relative Change (%)	12.09±1.05	13.94±0.65
Baseline subcutaneous fat volume (mm ³)	211364.22±7549.02	211894.23±4702.82
Post RT subcutaneous fat volume (mm ³)	206319.65±7937.28	219719.84±4944.70
Absolute change (mm ³)	-5224.73±5923.98 *	10599.89±3683.57
Relative Change (%)	-2.05±1.8 *	4.61±1.1

Values are means ±SE. Covariates included BMI and age with *LEPR* genotype set as the fixed factor. *LEPR*, Leptin Receptor; A, *LEPR* A⁶⁶⁸ allele; G, *LEPR* G⁶⁶⁸ allele

* P < 0.05, AA vs GG/GA