Gene 510 (2012) 66–70

Contents lists available at SciVerse ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Leptin and leptin receptor genetic variants associate with habitual physical activity and the arm body composition response to resistance training

S. Walsh [a,*], C.J. Haddad [b], M.A. Kostek [b], T.J. Angelopoulos [c], P.M. Clarkson [d], P.M. Gordon [e], N.M. Moyna [f], P.S. Visich [g], R.F. Zoeller [h], R.L. Seip [i], S. Bilbie [i], P.D. Thompson [i], J. Devaney [j], H. Gordish-Dressman [j], E.P. Hoffman [j], Thomas B. Price [k], L.S. Pescatello [b]

[a] Department of Physical Education and Human Performance, Central Connecticut State University, New Britain, CT 06050, USA
[b] Department of Kinesiology, University of Connecticut, Storrs, CT 06269, USA
[c] Department of Health Professions and Center for Lifestyle Medicine, University of Central Florida, Orlando, FL 32826, USA
[d] Department of Exercise Science, Totman Building, University of Massachusetts, Amherst, MA 01003, USA
[e] Department of Physical Medicine and Rehabilitation, School of Medicine, University of Michigan, Ann Arbor, MI 48108, USA
[f] Department of Sport Science and Health, Dublin City University, Dublin, 7008802, Ireland
[g] Exercise & Sport Performance, University of New England, Biddeford, ME, 04005, USA
[h] Department of Exercise Science and Health Promotion, Florida Atlantic University, Davie, FL 33314, USA
[i] Division of Cardiology, Henry Low Heart Center, Hartford Hospital, Hartford, CT, Hartford, CT 06102, USA
[j] Research Center for Genetic Medicine, Children's National Medical Center, Washington, DC 20010, USA
[k] Health Sciences, University of Bridgeport, Bridgeport, CT 06604, USA

ARTICLE INFO

Article history:
Accepted 15 August 2012
Available online 5 September 2012

Keywords:
Exercise
Genomics
Polymorphism

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 (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 12 wk 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 h/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 (67,687.05 ± 3186.7 vs. 52,321.87 ± 5125.05 mm^3, $p = 0.01$) and subcutaneous fat volume (10,599.89 ± 3683.57 vs. −5224.73 ± 5923.98 mm^3, $p = 0.02$) 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.

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

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.

* Corresponding author at: 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, USA. Tel.: +1 860 832 2164; fax: +1 860 832 2159.
E-mail address: walshse@ccsu.edu (S. Walsh).

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http://dx.doi.org/10.1016/j.gene.2012.08.020

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. (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 et al., 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. (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 h energy expenditure in humans (Stefan et al., 2002). Stefan et al. (2002) observed that Pima Indians who were homozygous for the *LEPR* 668 A allele had lower 24 h energy expenditure and lower PA levels assessed within in a respiratory chamber. 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 et al., 2007).

Heritability estimates for body composition phenotypes range from 30% to 90% (Perusse et al., 1996, 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 et al., 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 et al., 1999). Men who were carriers of the G allele with a body mass index <27 kg/m^2 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. Material and 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.

2.1. 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).

2.2. Physical activity measurements

A sub sample of FAMuSS subjects (n = 560) completed the Paffenbarger Physical Activity Questionnaire (PPAQ) (Paffenbarger 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 h. 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 et al., 1995). Additional PA phenotypes included: time (h/wk) spent in vigorous, moderate, light intensity PA, and sitting (Paffenbarger et al., 1993).

2.3. 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.

2.4. 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.

2.5. Magnetic resonance imaging (MRI)

Cross-sectional area (CSA) of the biceps brachii was determined bilaterally using MRI with 1.5 T systems and described in detail elsewhere (Kostek et al., 2007; Walsh et al., 2009). MRI was done pre-RT and within 48–96 h 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°