Research Article

Endothelial Nitric Oxide Synthase (NOS3) +894 G>T Associates with Physical Activity and Muscle Performance among Young Adults

Margaux A. Guidry,1 Matthew A. Kostek,1 Theodore J. Angelopoulos,2 Priscilla M. Clarkson,3 Paul M. Gordon,4 Niall M. Moyna,5 Paul S. Visich,6 Robert F. Zoeller,7 Paul D. Thompson,8 Joseph M. Devaney,9 Heather Gordish-Dressman,9 Eric P. Hoffman,9 and Linda S. Pescatello 1

1 Department of Kinesiology & Human Performance Laboratory, University of Connecticut, Storrs, CT 06269, USA
2 Department of Health Professions, Center for Lifestyle Medicine, University of Central Florida, Orlando, FL 32816, USA
3 Department of Kinesiology, University of Massachusetts, Amherst, MA 01003, USA
4 Department of Physical Medicine and Rehabilitation, University of Michigan, Ann Arbor, MI 48109, USA
5 School of Health and Human Performance, Centre for Preventive Medicine, Dublin City University, Dublin, Dublin 9, Ireland
6 School of Health Sciences, Exercise Science Division, Central Michigan University, Mt. Pleasant, MI 48859, USA
7 Department of Exercise Science and Health Promotion, Florida Atlantic University, Boca Raton, FL 33431, USA
8 School of Health and Human Performance, Centre for Preventive Medicine, Dublin City University, Dublin, Dublin 9, Ireland
9 Center for Genetic Medicine Research, Children's National Medical Center, Washington, DC 20010, USA

Correspondence should be addressed to Margaux A. Guidry, margaux.guidry@gmail.com

Received 4 September 2012; Accepted 5 October 2012

Academic Editors: D. Guidolin, T. Malinski, C. Maziere, and C.-C. Wu

Copyright © 2012 Margaux A. Guidry et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Objective. We examined the influence of missense polymorphism, endothelial nitric oxide synthase (NOS3) +894 G>T (rs1799983), on habitual physical activity (PA) and the muscle strength response to resistance training (RT). Methods. Men (n = 354) and women (n = 424; 24.3 ± 8.0 yr) were genotyped. Subjects reported hr/wk in vigorous and light intensity PA and sitting on the Paffenbarger PA questionnaire. One repetition maximum assessed muscle strength. Multivariable and repeated measures ANCOVA tested differences among NOS3 +894 TT and PA and RT phenotypes by gender. Results. hr/wk in vigorous intensity PA (5.5 ± 1.7 versus 8.3 ± 0.4; P = 0.019), more hr/wk in light intensity PA (42.1 ± 2.4 versus 35.8 ± 0.7; P = 0.011), and less hr/wk sitting (37.6 ± 2.8 versus 45.8 ± 0.9; P = 0.006) than those with the G allele. Women with NOS3 +894 TT gained more absolute (4.4 ± 0.3 versus 3.7 ± 0.8 kg; P = 0.013) and relative (78.3 ± 5.8 versus 61.9 ± 1.8%; P = 0.007) strength than those with the G allele. Conclusions. NOS3 +894 G>T associated with PA among men and women and the muscle strength response to RT among women only. Our findings indicate the need for prospective studies examining the influence of NOS3 variants on PA and the muscle response to RT as well as elucidating underlying mechanistic pathways for the associations observed.

1. Introduction

The endothelial nitric oxide synthase gene (NOS3) is located on chromosome 7 (7q36) and encodes NOS3, the rate limiting enzyme for nitric oxide (NO) production [1]. NO is the most potent vasodilator produced by the endothelium, increases in response to physical activity (PA) induced shear stress, and is modulated by genetic predispositions to NOS3 expression [1]. In addition to being a potent vasodilator, NO is involved in the control of skeletal muscle function [2], skeletal muscle glucose uptake during exercise [2], and mitochondrial ATP production [2], all of which can modulate muscle strength. NO is also produced in the cerebral circulation affecting neuronal activity including the
release of dopamine [3]. Therefore, NO mediated actions can also influence behavior and cognition as well as voluntary movement and motivation [4].

Candidate gene studies report NOS3 (−786 T>C, rs1800779 and +894 G>T, rs1799983) single nucleotide polymorphisms (SNPs) associate with health/fitness and exercise performance phenotypes. We have shown NOS3 −786 T>C is associated with resting blood pressure (BP) and the BP response to acute bouts of submaximal [5] and maximal aerobic exercise [6]. Others have reported NOS3 −786 T>C to be associated with resting forearm blood flow [7] and the parasympathetic modulation response to aerobic exercise training [8] as well as the differentiation of elite power from endurance athletes [9]. NOS3 +894 G>T has been found to be associated with the BP [10, 11], HR, and stroke volume responses to submaximal and maximal aerobic exercise [12], the nonexercising muscle vasodilation response to isometric handgrip exercise [13], and parasympathetic modulation response to submaximal aerobic exercise [8]. Lastly, NOS3 is one of the three most studied genes regarding the BP response to exercise training [14].

Collectively, these data indicate NOS3 SNPs are logical candidates to explore for associations with habitual PA and the muscle strength response to resistance training (RT). Thus, we examined the association of NOS3 −786 T>C and +894 G>T on habitual PA levels and the muscle strength response to RT among a subsample of healthy, European-derived American adults from the Functional Single Nucleotide Polymorphisms Associated with Human Muscle Size and Strength (FAMuSS) study [15]. We hypothesized that these two NOS3 SNPs would be associated with habitual PA levels and the muscle strength response to RT.

2. Materials and Methods

The FAMuSS study was conducted by the Exercise and Genetics Collaborative Research Group that was comprised of researchers from 10 university and hospital settings. The experimental design of FAMuSS has been described elsewhere [6, 15–21]. The institutional review boards from the 10 institutions involved with the study approved the study protocol and informed consent was obtained from all individuals prior to enrollment.

Potential study volunteers were recruited and screened at eight RT sites. Individuals who reported use of medications known to affect skeletal muscle function (i.e., corticosteroids, antihypertensive or antilipemic medications, anabolic steroids, diuretics, arthritis medications, Depo-Provera Contraceptive Injection, Clenbuterol, Rhinocort nasal inhaler, lithium, chronic use of nonsteroidal anti-inflammatory drugs) were excluded from consideration. Subjects were also excluded from participation if they had any previous chronic medical conditions such as diabetes mellitus, and any metal implants in the arms, eyes, head, brain, neck, or heart. Other exclusionary criteria included consuming on average ≥2 alcoholic drinks daily; use of dietary supplements reported to build muscle size/strength or to cause weight gain such as protein supplements, creatine, or androgenic precursors; and/or gained or lost >2.2 kg within 3 months of study participation.

2.1. Subjects. FAMuSS participants who satisfied the inclusion criteria and elected to participate in the study included 1219 individuals (509 males, 708 females). The Paffenbarger PA Questionnaire [22] was completed to assess the self-reported PA levels of FAMuSS participants. Study investigators obtained measurements of height and weight using a standard balance beam scale. FAMuSS participants who completed the Paffenbarger PA Questionnaire and were genotyped for NOS3 −786 T>C (n = 284, TT/TC n = 252, CC n = 32) and NOS3 +894 G>T (n = 479, GG/GT n = 435, TT n = 44) comprising the subsample for this study that totaled 844 men (n = 347) and women (n = 497).

2.2. Determination of Physical Activity Phenotypes. The Paffenbarger PA Questionnaire was used to estimate weekly PA over the last year prior to study enrollment. The Paffenbarger PA Questionnaire is a validated [23] eight-item instrument used to measure self-reported weekly duration and intensity of PA. Item eight provided data for this study and asked respondents to divide a typical weekday and weekend day into hours spent in five PA categories (vigorous, moderate, and light intensity; sitting; or sleeping) [22]. The PA phenotypes reported in this substudy were those that show statistically significant associations with the NOS3 genotypes and included hr/wk spent in vigorous and light intensity PA, and sitting.

2.3. One Repetition Maximum Strength Testing (1RM). The dynamic strength of the elbow flexor muscles was assessed in both arms before and after 12 wk of resistance training (RT) by 1RM on a standard preacher curl bench (Yukon International Inc., Cleveland, OH) using Powerblock dumbbells (Powerblocks, Intellibell, Inc., Owatonna, MN) in increments of 1.1 and 2.2 kg. If a weight increase was needed in between the powerblock increments, a 0.6 kg increment was added using Platemates (Benoit Built Inc., Boothbay Harbor, ME). Each subject performed two warm up sets with increasing weight. Subjects were verbally instructed to perform one full range of motion with 100% of the estimated maximum weight extending the elbow to 180° and curling the weight back up to the shoulder. The arm not being tested rested on the lap with the hand in a pronated position. If the lift was successful, a 3 min rest was taken and the weight increased slightly; if the lift was unsuccessful, a 3 min rest was taken and the weight decreased slightly. The procedure was repeated until subjects failed to complete a full range of motion lift. Weights were chosen so that the 1RM could be determined in three to five attempts. Maximum weight lifted was recorded in kg as the greatest amount of weight successfully lifted one time. Study investigators gave verbal encouragement to each subject during each 1RM attempt. The same study investigator administered pre- and post-RT 1RM test for a given subject.

2.4. Resistance Training Program. Subjects underwent 12 wk of gradually progressive, supervised RT of their nondominant arm twice per wk with sessions separated by a minimum
of 48 hr. Each RT session began with a warm up consisting of two sets of 12 repetitions of the biceps preacher curl and overhead triceps extension. After a 3 min rest, subjects performed three sets of 12 repetitions at 65 to 75% of baseline 1RM for each of the following five exercises: biceps preacher curl, biceps concentration curl, standing biceps curl, overhead triceps extension, and triceps kickback. All exercises were performed using dumbbells (Powerblocks, Intellbell, Inc., Owatonna, MN). The speed of each repetition was a total of 4 s, 2 s for the concentric and 2 s for the eccentric phase. A 2 min rest followed each set. At week five, the number of repetitions was decreased to eight and then to six at week 10. Thus, the exercise intensity at weeks five and 10 increased to 75 to 82% 1RM and 83 to 90% 1RM, respectively. Training sessions lasted 45 to 60 min. Muscle strength phenotypes included baseline muscle strength (kg) and the change in absolute (kg) and relative (%) muscle strength phenotypes included baseline muscle strength (kg) and the change in absolute (kg) and relative (%) muscle strength.

2.5. DNA Extraction and Genotyping. A sample of whole blood was obtained from each subject, refrigerated, and the change in absolute (kg) and relative (%) muscle strength phenotypes included baseline muscle strength (kg) and the change in absolute (kg) and relative (%) muscle strength. DNA was extracted using the Puregene Whole Blood DNA Isolation kit (Gentra Systems, Inc, MN). TaqMan Allelic Discrimination assays were pre-designed by ABI (Foster City, CA, USA). The two NOS3 SNP assays were designed to detect both alleles during the PCR reaction using allele-specific oligonucleotides each labeled with a different fluorophore (VIC and FAM). The PCR profile contained 20 ng genomic DNA, 900 nM forward and reverse primers, 200 nM fluorescent allele discrimination probes (FAM and VIC-labeled), and 5 μL TaqMan Genotyping Master Mix (ABI) in a final volume of 10 μL. 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. The resultant PCR products were analyzed using an ABI 7900HT system and the two alleles are called using SDS 2.3 software and checked manually. NOS3 SNPs that were genotyped were −786 T>C (n = 308, TT n = 128, TC n = 147, CC n = 33) and +894 G>T (n = 393, GG n = 195, GT n = 165, TT n = 33).

2.6. Statistical Analyses. Descriptive statistics were calculated on all study variables. Hardy Weinberg Equilibrium (HWE) was determined for each SNP using $\chi^2$. Linkage disequilibrium (LD) was assessed using the $r^2$ measured between each pair of SNPs. NOS3 −786 T>C ($P = 0.29$) and +894 G>T ($P = 0.98$) did not deviate from HWE. Multivariable ANCOVA tested associations among NO3 genotypes and PA phenotypes. Repeated measures ANCOVA tested associations among NO3 genotypes and the muscle strength response phenotypes to RT. These analyses included gender as a between factor and age, body mass index (BMI), and BP as covariates. If significant main effects were found, post hoc analyses were performed with a Bonferroni adjustment for multiple comparisons. The NOS3 genotype comparisons which emerged as significantly associated with the PA and muscle strength phenotypes were recessive models for NOS3 −786 TT/TC ($n = 252$) versus CC ($n = 32$) and NOS3 +894 GG/GT ($n = 479$) and TT ($n = 44$). Alpha level was $P < 0.05$, and analyses were performed using SPSS 14.0 for Windows.

3. Results

3.1. Subject Characteristics. Subjects ($n = 844$) were European-derived American men ($n = 347$) and women ($n = 497$). Age, BMI, and BP (±SEM) did not differ by gender and NOS3 +894 G>T and −786 T>C genotypes (Table 1) ($P > 0.05$). Subjects were healthy, young, normal weight with normal BP.

3.2. Physical Activity. PA phenotypes and NOS3 genotype associations did not differ by gender so results are presented in Table 2 for the total sample. Adults with the NOS3 +894 TT genotype reported less time in vigorous intensity PA ($P = 0.019$), and sitting ($P = 0.006$), but more time in light intensity PA ($P = 0.011$) than adults with the G allele. These PA phenotypes did not differ by NOS3 −786 T>C genotypes (Table 2) ($P > 0.05$).

3.3. Dynamic Muscle Strength. Among the total sample, absolute ($P = 0.015$) and relative ($P = 0.039$) muscle strength increased pre- to post-RT. However, the muscle strength response was NOS3 genotype and gender dependent (gender × genotype, $P = 0.006$) so that results are presented separately for men and women in Table 3. Among men, those with the NOS3 +894 TT genotype had greater absolute ($P = 0.012$) and relative ($P = 0.009$) muscle strength gains pre- to post-RT than those with the G allele. Among men the change in muscle strength pre- to post-RT did not differ between NOS3 +894 G>T genotypes ($P > 0.05$). The change in absolute and relative muscle strength pre- to post-RT did not differ by NOS3 −786 T>C genotypes among men and women ($P > 0.05$).

4. Discussion

We investigated the influence of NOS3 +894 G>T and −786 T>C on habitual PA and the muscle strength response to RT among a large sample of healthy, European-derived American adults from FAMuSS [15]. We found that NOS3 +894 G>T associated with habitual PA and the muscle strength response to RT. Specifically, adults with the NOS3 +894 TT genotype spent 7–9 hr/wk more in lower intensity PA, 3–4 hr/wk less in vigorous intensity PA, and 8–10 hr/wk less sitting than adults that were carriers of the NOS3 +894 G allele. Women with the NOS3 +894 TT genotype gained ~20% more dynamic muscle strength than those with the G allele; whereas there were no genotype differences in the muscle strength response to RT among men. In addition, there were no differences among NOS3 −786 T>C genotypes and PA and muscle performance phenotypes. Thus, it appears NOS3 +894 G>T may habitually influence the
preference of light PA, vigorous PA and sitting and the strength gains in women that can result from an RT program.

These findings suggest NOS3 +894 G>T may be important to consider for a personalized approach to exercise prescription along with a growing number of genetic variants that have been reported to be associated with muscle performance [15, 24–27] and habitual PA [21, 28–32]. For example, when recommending exercise to adults for its overall health benefits, the NOS3 +894 G>T and PA intensity dependent genotype differences we found could be considered when counseling people to become more physically active due to what appears to be a genetic predisposition to prefer light over vigorous intensity PA among those with the TT genotype. Similarly, women with the TT genotype appeared to make greater muscle strength gains from an RT program and could be counseled to engage in an RT program for this purpose, while women with the G allele could be counseled to participate in an RT program for its overall health benefits. Nonetheless, a personalized approach to exercise prescription based upon genotype such as described with these examples remains a vision of the future rather than a reality of the present [33].

Interestingly, mice without the NOS3 gene (NOS3 knockout mice) were found to participate in lower levels of voluntary PA than the control mice with the NOS3 gene [34]. In turn, the NOS3 knockout mice displayed a less favorable cardiovascular risk factor profile than their genetic counterparts [34]. These data reinforce the notion that NOS3 is an important gene to further investigate for its associations with voluntary PA in humans. Whether certain NOS3 SNPs will confer a higher risk or conversely some protection from being physically inactive is important to enhance our understanding of the true role of exercise in the prevention of common chronic diseases.

NOS3 +894 G>T is a missense mutation in the exon 7. This 894 G/T substitution, which results in an aspartate rather than glutamate at position 298 in the NOS3 protein, is of potential functional relevance as it alters NOS3 localization at the endothelial caveolae [35] that leads to a reduced response to shear stress, impaired enzyme regulation, and reduced NO bioavailability [8, 35]. Tesaurro et al. [36] reported the NOS3 +894 T allele generates protein products with different susceptibility to cleavage, suggesting that this SNP has a functional effect on the NOS3 protein.

NO plays a role as a neurotransmitter in the brain by stimulating soluble guanylyl cyclase to form the second messenger molecule, cyclic guanosine monophosphate (cGMP). cGMP relaxes the blood vessels following exercise, increasing blood flow to muscles post exercise to facilitate glucose uptake [37]. In addition, glutamate-induced dopamine release is also mediated by NO [3]. Glutamate regulates the release of dopamine in several brain regions and has been implicated in the regulation of various behaviors and behavioral disorders [3]. Lightfoot [38] and others [39] have shown that genetic control of PA is centrally mediated, possibly through the actions of dopamine receptors. These combined observations provide insights into biologically plausible peripheral and central explanations for the associations we observed among NOS3 +894 G>T and PA and the muscle strength response to RT.

NOS3 +894 G>T modulates the hemodynamic response to aerobic [8, 12] and isometric [13] exercise. Hand et al. [12] reported that NOS3 +894 G>T genotype associations may have resulted from differences in exercise-induced NO

### Table 1: Physical characteristics (X ± SEM) among the total sample and by NOS3 +894 G>T and −786 T>C genotypes.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NOS3 +894 G&gt;T (rs1799983)</th>
<th>NOS3 −786 T&gt;C (rs1800779)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GG/CT</td>
<td>TT/TG</td>
</tr>
<tr>
<td>N</td>
<td>548</td>
<td>53</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>23.8 ± 0.3</td>
<td>23.3 ± 0.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9 ± 0.3</td>
<td>26.6 ± 1.0</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>115.6 ± 0.4</td>
<td>117.0 ± 1.4</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72.9 ± 0.3</td>
<td>74.1 ± 1.1</td>
</tr>
</tbody>
</table>

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure.

### Table 2: Time spent (X ± SEM, hr/wk) in vigorous and light intensity physical activity, and sitting among the total sample and by NOS3 +894 G>T and −786 T>C genotypes.

<table>
<thead>
<tr>
<th>Physical activity phenotypes (hr/wk)</th>
<th>NOS3 +894 G&gt;T (rs1799983)</th>
<th>NOS3 −786 T&gt;C (rs1800779)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total sample</td>
<td>GG/CT</td>
</tr>
<tr>
<td>N</td>
<td>479</td>
<td>435</td>
</tr>
<tr>
<td>Vigorous intensity PA</td>
<td>6.8 ± 0.6</td>
<td>8.3 ± 0.4</td>
</tr>
<tr>
<td>Light intensity PA</td>
<td>38.9 ± 1.2</td>
<td>35.8 ± 0.7</td>
</tr>
<tr>
<td>Sitting</td>
<td>41.7 ± 1.5</td>
<td>45.8 ± 0.9</td>
</tr>
</tbody>
</table>

Covariates included age and body mass index with gender and NOS3 genotype as between factors.

**P < 0.05, ***P ≤ 0.01, NOS3 +894 TT versus GG/CT (bolded).
production due to NOS3 +894 G>T genotype dependent increased or decreased NOS3 transcription. Silva et al. [8] proposed genetic variations in NOS3 +894 G>T explain part of the parasympathetic adaption to isometric handgrip training in humans, causing a lower production of NO during and after each exposure to exercise. Lower NO availability could blunt improvements in training (or phenotypes that rely on NO, such as BP) that would normally occur when normal/higher levels of NO are produced [8].

The literature is limited regarding investigating the influence of NOS3 and control of skeletal muscle or muscle strength from dynamic resistance exercise in humans. NO production during skeletal muscle contraction is essential for the regulation of glucose uptake during exercise [40]. In humans it has been established that NO is involved in the control of skeletal muscle function including force generation [2], and skeletal muscle glucose uptake during exercise [2], actions that could modulate muscle strength. Exercise-induced muscle contraction increases shear stress which releases NO and increases blood flow due to interactions among insulin and 1-arginine that enhances glucose skeletal muscle uptake [2]. Pellinger et al. [37] recently reported that the availability of glucose to skeletal muscle is enhanced by postexercise hyperemia, therefore it could be speculated that NOS3 expression may affect muscle strength due to the increased vasodilation postexercise when greater amounts of NO are present allowing greater availability of glucose to skeletal muscle providing insight for the associations we found between NOS3 +894 G>T and the dynamic muscle strength response to RT.

Previous studies have suggested that gender differences in NO production could be due to ovarian hormones (i.e., estrogens) [41]. Furthermore, whole-body production of NO is greater in healthy, premenopausal women than in men under ambulatory conditions [41]. Estrogen may influence NO production by activating estrogen receptor mediated genomic pathways and upregulation of NOS3 [38, 41]. Sex hormones have been postulated to also affect PA levels through the estrogen receptor pathway [38]. This evidence lends insight into possible explanations for the gender dependent effects we found among women but not men regarding NOS3 +894 T>G associations with the muscle strength response to RT.

Contrary to our findings with NOS3 +894 G>T, NOS3 −786 T>C was not associated with self-reported PA levels or the muscle strength response to RT. Consistent with our results, Hand et al. [12] did not find NOS3 −786 T>C associations with habitual PA level and the hemodynamic response during submaximal or maximal exercise. Nonetheless, it is unclear why we found associations among NOS3 +894 G>T but not with NOS3 −786 T>C genotypes and PA and muscle performance phenotypes. NOS3 +894 G>T is found in the coding region of chromosome 7, while NOS3 −786 T>C is found in the promoter region [42]. Increased levels of methylation in the promoter region of a gene can reduce transcription of that gene [43]. The expression of NOS3 is known to be sensitive to epigenetic mechanisms and the methylation of NOS3 has been found to inversely correlate with its transcriptional activity [44]. Rao et al. [45] and Cooper and Keaney [44] recently reported that the methyl-CpG-binding (MBD2) protein was found to sense DNA methylation and mediate transcriptional repression of NOS3, therefore silencing gene transcription and NOS3 mediated responses. Thus, it can be speculated that due to increased methylation in the promoter region, adults with NOS3 −786 T>C produced less NO due to transcriptional repression of the NOS3 gene resulting in the lack of associations we found with self-reported PA levels or the muscle strength response to RT. However, we did not measure NO, so that future studies should be designed to determine whether these suppositions are so.

This study has several limitations. Habitual PA is a complex behavior that is likely influenced by many genes other than NOS3 genetic variants through multiple pathways. This study was not designed to obtain mechanistic data. Additionally, PA data were collected via questionnaire, thus exposing the possibility of subject recall or social desirability bias. However, the Paffenbarger PA questionnaire has been widely validated in similar populations to the present study and is considered an accurate method of leisure time PA in adults [46].

This investigation is a subset of the FAMuSS study which is the largest study that has investigated candidate genes associated with muscle performance, and the first study to specifically investigate NOS3 variant associations with PA and muscle strength in humans [15]. Furthermore, FAMuSS

<table>
<thead>
<tr>
<th>Total Sample</th>
<th>NOS3 +894 G&gt;T</th>
<th>NOS3 −786 T&gt;C</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>601</td>
<td>544</td>
</tr>
<tr>
<td>Pre-RT (kg)</td>
<td>9.0 ± 0.7</td>
<td>9.6 ± 0.7</td>
</tr>
<tr>
<td>Absolute change (kg)</td>
<td>4.1 ± 0.1</td>
<td>4.6 ± 0.1</td>
</tr>
<tr>
<td>Relative change (%)</td>
<td>54.7 ± 2.2</td>
<td>39.5 ± 1.4</td>
</tr>
</tbody>
</table>

Covariates included age and body mass index with gender and NOS3 genotype as fixed factors.

*P ≤ 0.01, NOS3 +894 TT versus GG/GT (bolded).
meets the criteria outlined by Hagberg et al. [14, 47] that are necessary for conducting exercise genomics studies including a large sample size, a well-structured exercise intervention with stringent assessment of phenotypes, and quality control of genotyping.

In summary, NOS3 +894 T>G associated with PA and the muscle response to RT among a young, healthy large sample of European-derived American men and women. Our findings indicate the need for prospective studies examining the influence of NOS3 variants on PA and the muscle response to RT as well as elucidating underlying mechanistic pathways for the associations observed. Information gathered in future studies will help clinicians better understand genetic predispositions to PA patterns and why some people respond more readily to an RT program than others.

Acknowledgment

This paper was supported by NIH-NINDS R01 NS40606-02 and the University of Connecticut, Center for Health, Intervention, and Prevention.

References


Submit your manuscripts at
http://www.hindawi.com