Individual Responsiveness to Exercise-Induced Fat Loss and Improvement of Metabolic Profile in Young Women is Associated with Polymorphisms of Adrenergic Receptor Genes

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Abstract
The effectiveness of physical exercise on fat loss and improvement of aerobic capacity varies considerably between individuals. A strong linkage exists between common allelic variants of the adrenergic receptor genes and weight gain, as well as changes in body composition. Therefore we aimed to check if body composition and metabolic variables were modulated by the ADRB2 (Gly16Arg and Glu227Gln), ADRB3 (Trp64Arg) and ADR A2A (rs553668 G/A) gene polymorphisms in 163 Polish sedentary women (age 19-24; body mass index (BMI) 21.7 ± 0.2 kg/m²) involved in a 12-week aerobic training program. Only 74.8% of participants lost fat mass. On average, participants lost 5.8 (10.4)% of their relative fat mass with training (range: +28.3 to -63.6%). The improvement of VO₂max was significantly greater in participants who could lose their fat mass compared to women who were unsuccessful in fat loss (4.5 (5.6)% vs. 1.5 (3.8)%; p = 0.0045). The carriers of a low number (0-3) of obesity-related risk alleles (ADRB2 Gly16, ADRB2 Gly227, ADR A2A rs553668 G) were more successful in fat mass loss compared to the carriers of a high number (5-6) of risk alleles (7.7 (9.8) vs 4.0 (9.4)%; p = 0.0362). The presented results support the assumption that variation within adrenergic receptor genes contributes to interindividual changes of body composition in response to physical exercise.

Key words: ADRB2, ADRB3, ADR A2A, polygenic, obesity, fat, HDL.

Introduction
Unhealthy lifestyle habits like lack of physical activity and excessive energy intake may result in overweight and obesity (Rank et al., 2012). The latter is one of the major and growing health problems of the XXI century. The presence of the elevated adipose tissue (increased adiposity) increases the likelihood of various medical conditions, such as hypertension, coronary heart disease, type 2 diabetes mellitus, and certain types of cancer (Masuo and Lambert, 2011). Thus, it is at least partly preventable by developing healthy diet and regular physical exercises that, in consequence, could help participants stay at a healthy weight (Greenway, 2015). However, a wide range of inter-individual variability in weight gain and changes in body composition induced by physical exercises and diets is seen in human populations which indicates the role of non-environmental factors such as genetic modifiers (Bouchard, 2008; Eynon et al., 2013; Garenc et al., 2003; Leonska-Duniec et al., 2016; Masuo et al., 2001; Wolfarth et al., 2005).

Various epidemiological and clinical studies indicate that strong linkage exists between common allelic variants of the adrenergic receptor genes and weight gain as well as changes in body composition (Bea et al., 2010; Masuo et al., 2005a; Phares et al., 2004; Szendrei et al., 2016). These adrenergic receptors (ADRs) encoded by the ADR (α-adrenergic receptors - inhibitory) and ADRB (β-adrenergic receptors - stimulatory) genes are part of the sympathetic nervous system and exert their actions via coupling with the catecholamines. Because catecholamines are important regulators of lipolysis and energy expenditure during both energy restriction as well as exercise, it is clearly understandable that sympathetic nerve activation may play a role in modifying weight gain and changes in body composition. Reduced energy expenditure and lowered resting metabolic rate are predictive of overweight and obesity (Ahles and Engelhardt, 2014; O’Dell et al., 2015).

Recent studies have shown that allelic variation in the ADRs family exists, with the single nucleotide polymorphisms (SNPs) as the most common genetic polymorphisms (Green et al., 1993; Ikegami et al., 1996). Genetic diversity of the ADRs influence receptor expression, activity, and agonist regulation, in consequence contribute to the variable changes in body composition as well as weight gain and obesity (Hellstrom et al., 1999; Large et al., 1997). Within the β-adrenergic receptor family genes, the ADRB2 and the ADRB3 are of particular interest. β2-adrenergic receptors (β2-ADRs) encoded by the ADRB2 gene are the dominant lipolytic receptors in white adipose tissue and skeletal muscle (Enoksson et al., 2000; Hagstrom-Toft et al., 1998). β2-ADRs are also expressed throughout the smooth muscles of the cardiovascular and respiratory tracts and in the heart. Therefore, they play a pivotal role in the
metabolic and musculoskeletal systems, promoting gluco-
genogenesis and glycogenolysis in the liver and skeletal
muscles. They also influence insulin secretion and regulate
energy expenditure through lipid mobilization from white
adipose tissue (Brodde, 2008; Sarpeshkar and Bentley,
2010).

Gly16Arg (rs1042713,46G>A, G285A) and
Glu27Gln (rs1042714, 79G>C, G318C) are the most com-
a mon investigated polymorphisms of the ADRB2 gene
(Gjesing et al., 2009; Masuo and Lambert, 2011; Me-
irhaeghe et al., 2000; Petrone et al., 2006; Szendrei et al.,
2016). Studies of agonist stimulation in cultured cells re-
vealed that neither Gly16Arg nor Glu27Gln affected the
function of the β2-ADRs in terms of ligand binding or ad-
enylyl cyclase activity. However, transfected cells express-
ing the Gly16 variant of the receptor were shown to have
greater reduction in numbers or undergo significantly en-
hanced agonist-promoted downregulation when compared
to Arg16. In contrast to Gly16, the Glu27 receptor form
appears to be resistant to downregulation when compared
to Gln27 variant (Green et al., 1994; 1995).

Numerous studies have investigated the impact of
these polymorphic variants on changes in body composi-
tion, weight gain and obesity, as well as physical activity
and athletic performance and conflicting results have been
obtained (Ahmetov et al., 2016; Leońska-Duniec et al.,
2016). In some studies it was found, that subjects carrying
the Gly16 or Glu27 alone or both had increased risk of obe-
sity (Gonzalez Sanchez et al., 2003; Lange et al., 2005;
Large et al., 1997; Masuo et al., 2005a; Kawaguchi et al.,
2006). Specifically, it was observed that Glu27 polymor-
phism interacts with physical activity influencing obesity
risk among female subjects (Corbalan et al., 2002). Some
research groups on the contrary, reported that the Gln27 is
the risk allele (Meirhaeghe et al., 2000; Pereira et al.,
2003). However, others found no relationship between
Gly16Arg and Gln27Glu polymorphisms and obesity-rela-
ted phenotypes (Bea et al., 2010; Echwald et al., 1998;
Gjesing et al., 2009; Kortner et al., 1999; Rosado et al.,
2015).

The β3-adrenergic receptors (β3-ADRs) that are en-
coded in human by ADRB3 gene are mainly expressed in
adipose tissue and differ from the β2-ADRs in terms of a
sequence cause the retention of lipids in adipocytes. It
appears to be resistant to downregulation when compared
to Arg16. In contrast to Gly16, the Glu27 receptor form

As opposed to ADRB genes, there is less information about relationship between polymorphisms in
ADRA genes and changes in body composition as well as
weight gain and obesity-related phenotypes. However
there are evidences that polymorphisms of the ADRB2B
and the ADRA2A genes could be involved (Bea et al., 2010;
Phares et al., 2004). Specifically, it was observed that the
A allele of the G1780A (rs553668) polymorphism local-
ized in the 3’UTR of the ADRA2A gene is associated with
obesity and type 2 diabetes, as well as body mass index
(BMI) and percentage of body fat (Lima et al., 2007; Lang-
berg et al., 2013).

Considering the aforementioned facts we have de-
cided to check if body mass and body composition, as well
as metabolic variables observed in physically active partic-
pants will be modulated by the ADRB2, ADRB3 and
ADRA2A gene polymorphisms. To test this hypothesis, we
have performed a genetic association study that aimed to
detect a correlation between the Gly16Arg and Glu27Gln
of the ADRB2 gene, Trp64Arg of the ADRB3 gene as well
as G1780A of the ADRA2A gene polymorphisms and se-
lected body composition measurements as well as obesity-
related metabolic traits in response to a 12-week aerobic
training program.

Methods

Ethics statement
All the procedures followed in the study were approved by
the Ethics Committee of the Regional Medical Chamber in
Szczecin (Approval number 09/KB/IV/2011) and were
conducted ethically according to the principles of the
World Medical Association Declaration of Helsinki and
ethical standards in sport and exercise science research.
The experimental procedures were conducted in accord-
ance with the set of guiding principles for reporting the re-
sults of genetic association studies defined by the Strength-
ening the Reporting of Genetic Association studies
(STREGA) Statement (Little et al., 2009).

Participants
One hundred and sixty three Polish European Caucasian women mean age 21 ± 1 years (range 19–24) met the inclusion criteria and were included in the study. None of these individuals had engaged in regular physical activity in the previous 6 months. They had no history of any metabolic, cardiovascular diseases or previous musculoskeletal injuries. Participants were nonsmokers and refrained from taking any medications or supplements known to affect metabolism. Prior to the start of the training phase, participants were included into a dietary program and on the basis of individual dietary plan they were asked to keep a balanced diet, of approximately 2000 kcal a day. The participants were asked to keep a food diary every day. Weekly consultations were held on which the quality and quantity of meals were analyzed and, if necessary, minor adjustments were made.

**Physical exercise training protocol**

The training stage was preceded by a week-long familiarization stage, when the examined women exercised 3 times a week, at an intensity of about 50% of their maximum heart rate (HRmax) (Zarębska et al., 2016). After the week-long familiarization stage, the main training started. Each training unit consisted of a warm-up routine (10 min), the main aerobic routine (43 min), and cool-down phase (stretching and breathing exercise for 7 min). The main aerobic routine was a combination of 2 alternating styles – low and high impact. Music of variable rhythm intensity (tempo) was incorporated into both styles. A 12-week program of low-high impact aerobics was divided as follows: (i) 3 weeks (9 training units), 60 min each, at about 50%–60% of HRmax, tempo 135–140 beats per minute (BPM), (ii) 3 weeks (9 training units), 60 min each, at 60%–70% of HRmax, tempo 140–152 BPM, (iii) 3 weeks (9 training units), 60 min with the intensity of 65%–75% of HRmax, tempo 145–158 BPM, and (iv) 3 weeks (9 training units), 60 min with an intensity of 65%–80% of HRmax, tempo 145–160 BPM. All 36 training units were administered and supervised by the same instructor.

**Body composition measurements**

All participants were measured for selected body mass and body composition variables before and after the completion of a 12-week training period. Body composition tests took place after fasting for at least 8 hours. Body mass and body composition were assessed with the bioimpedance method using a Tanita TBF 300M electronic scale (Arlington Heights, Illinois, USA). Body mass and body composition measurements taken with the use of the Tanita electronic scale are as follows: total body mass (kg), fat free mass (FFM, kg), fat mass (kg), fat mass percentage (FM, %), BMI (kg/m²), tissue impedance (Ohm), total body water (TBW, kg) and basal metabolic rate (BMR, kJ or kcal).

**Biochemical and hematological analyses**

Fasting blood samples were obtained in the morning from the elbow vein. Blood samples from each participant were collected in 2 tubes. Biochemical and hematological analyses were performed before the start of the aerobic fitness training programme and repeated at the 12th week of this training programme (after the 36th training unit). The analyses were performed immediately after the blood collection. Complete blood count, including white blood cells (WBC), red blood cells (RBC), hemoglobin (HGB), hematocrit (HTC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and total platelet level (PLT) were obtained using Sysmex K-4500 Haematology Analyzer (TOA SYMEX, Kobe, Japan). All biochemical analyses were conducted using Random Access Automatic Biochemical Analyzer for Clinical Chemistry and Turbidimetry A15 (BIO- SYSTEMS S.A., Barcelona, Spain). Blood plasma was used to determine lipid profile: triglycerides (Tg), cholesterol (Chol), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) concentrations. Plasma Tg and Chol concentrations were determined using diagnostic colorimetric enzymatic method according to the manufacturer’s protocol (BioMaxima S.A., Lublin, Poland). HDL plasma concentration was determined using human anti-ß-lipoprotein antibody and colorimetric enzymatic method according to the manufacturer’s protocol (BioMaxima S.A.). Plasma concentrations of LDL were determined using a direct method according to the manufacturer’s protocol (PZ Cormay S.A., Lomianki, Poland). All analysis procedures were verified with the use of multiparametric control serum (BIOLABO S.A.S, Maizy, France), as well as control serum of normal level (BionormL) and high level (BioPathL) lipid profiles (BioMaxima S.A.).

**VO₂max measurement**

Subjects performed a continuous graded exercise test on an electronically braked cycle ergometer (VIAsprint™ 150P Bicycle, CareFusion Germany GmbH, Hoechberg, Germany) with an automatically calibrated volume sensor and a breath-by-breath gas analyzer (Oxycon Pro, Erich JAEGER GmbH, Hoechberg, Germany) to determine their maximal oxygen uptake (VO₂max) before and after the completion of a 12-week training period. The device was calibrated in accordance with the manufacturer’s instructions. The test began by 5 min continuous pedaling, with a frequency of 60 revolutions per minute (RPM) and a relative load of 1.2 W/kg. After this phase, the workload was systematically increased by 15 watts every minute until voluntary exhaustion. The effort was interrupted when pedaling frequency declined by 10%, that is, when the pedalling frequency fell below 54 RPM. All of the participants reached RER greater than 1.0. The highest value of oxygen uptake was considered to be VO₂max.

**Genetic analyses**

The buccal cells donated by the subjects were collected in Resuspension Solution (GenElute Mammalian Genomic DNA Miniprep Kit; Sigma, Steinheim, Germany) with the use of sterile foam-tipped applicators (Puritan, Guilford, Maine, USA). DNA was extracted from the buccal cells using a GenElute Mammalian Genomic DNA Miniprep Kit (Sigma) according to the manufacturer’s protocol. Obtained concentration of genomic DNA was 30–50 ng/1 μl. All samples were genotyped in duplicate using allelic dis-
crimination assays with TaqMan® probes (Applied Biosystems, Carlsbad, California, USA) on CFX96 Touch™ Real-Time PCR Detection System (Bio-Rad, Hercules, California, USA). Freshly purified/sterile water was used as a negative control for PCR. To discriminate the ADRB2 Gly16Arg and Glu27Gln, ADRB3 Trp64Arg as well as ADR2A G1780A alleles, TaqMan® Pre-Designed SNP Genotyping Assays were used (assay IDs: C____2084764_20, C____2084765_20, C____2215549_20 and C____996424_20, respectively), including appropriate primers and fluorescently labelled (FAM and VIC) MGB™ probes to detect the alleles.

Statistical analyses

Hardy-Weinberg equilibrium was tested by comparing the observed genotype frequencies with the expected ones using the Chi-square test with one degree of freedom in Microsoft EXCEL. Training responses were expressed as percentage change from baseline. The percentage changes were compared across genotypes using either parametric (t-test or one-way ANOVA) or non-parametric (Mann-Whitney or Kruskal-Wallis) tests for normally and non-normally distributed data, respectively. Spearman’s (non-parametric) correlations were used to assess the relationships between different phenotypes. Differences in phenotypes between groups were analysed using unpaired t tests. Power was calculated using non-central chi-square distribution (pchipq function in R, https://cran.r-project.org) assuming alpha 0.05 and a variance explained of 0.01, 0.05, and 0.10 by additive effects at the marker of interest. The power for a stated sample size (n = 163) was 24.8%, 81.5% and 98.1% for variances of 0.01, 0.05 and 0.10, respectively. Normality of the distribution was evaluated using the Kolmogorov-Smirnov test. The association of ADRB2 haplotypes with training responses was analysed using haplo.stats package for R. The regression of percentage change of body composition parameters, lipids and glucose on ADRB2 haplotypes was conducted using haplo.glm function assuming the additive model and minimum haplotype frequency of 5%.

Power for a stated sample size (n = 163) was calculated for a given set of haplotypes, their population frequencies and a specified genetic effect size (additive model of haplotype effects) in terms of a regression model R squared value (a haplo.power.qt function of the haplo.stats package). The power for the R squared values 1%, 5% and 10% were 18.9%, 74.1% and 97.3%, respectively. Linear regression coefficients corresponding to R squared 1%, 5% and 10% were 0.14, 0.32, 0.45, respectively.

Gene-gene interactions among ADRB2, ADRB3 and ADR2A polymorphisms were analysed using non-parametric model-free method of reducing genotype combinations called multifactor dimensionality reduction (MDR) using he MDR software package (version 3.0.2, http://sourceforge.net) (Gui et al., 2013; Ritchie et al., 2001). The 10-fold cross-validation training scores, cross-validation testing scores (the t-test statistic for the unequal variance computed by comparing phenotype between high- and low-level genotypes for the ten pooled testing sets), as well as cross validation consistency (CVC, the number of times the same model was chosen in the training set) were determined. P values for interactions were calculated using permutation tests. Single-locus analyses were carried out in STATISTICA data analysis software system, version 12 (StatSoft, Inc. 2014, www.statsoft.com).

Results

Individual variability in the change of relative fat mass and BMI are shown in Figures 1-2. Only 74.8% of participants could lose their relative fat mass in response to a 12-week aerobic training program, which was not dependent on their initial relative fat mass (p = 0.744) or BMI (p = 0.988). On average, participants lost 5.8 (10.4)% of their relative fat mass with training (range: +28.3 to -63.6%). The improvement of VO2max was significantly greater in women who could lose their fat mass compared to women who were unsuccessful in fat loss (4.5 (5.6)% vs. 1.5 (3.8)%; p = 0.0045). The efficiency of fat loss was inversely correlated with the improvement of VO2max in response to a 12-week aerobic training (r = – 0.37; p < 0.0001).

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Individual variability in the BMI change (%) in response to a 12-week aerobic training of 163 women.
All investigated polymorphisms conformed to Hardy-Weinberg expectations ($\chi^2 = 0.92$, p = 0.337; $\chi^2 = 2.36$, p = 0.124; $\chi^2 = 2.31$, p = 0.129; $\chi^2 = 0.17$, p = 0.680, for Gly16Arg, Glu27Gln of the ADRB2, Trp64Arg of the ADRB3 and G1780A of the ADRA2A, respectively. Owing to the low number of the ADRB3 Arg64/Arg64 (n = 3) and ADRA2A AA (n = 2) homozygotes, they were pooled together with corresponding heterozygous genotypes. There were no differences in percentage changes across genotypes for any of the analysed polymorphisms (Tables 1-4).

However, polygenic analysis has shown that the carriers of a low number (0-3) of obesity-related risk alleles (ADRB2 Gly16, ADRB2 Glu27, ADRB2 Arg64/Arg64 (n = 3) and ADRA2A AA (n = 2) homozygotes, they were pooled together with corresponding heterozygous genotypes. There were no differences in percentage changes across genotypes for any of the analysed polymorphisms (Tables 1-4).

Table 1. The ADRB2 Gly16Arg genotypes and response to training (% change from baseline).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Gly16/Gly16 (n=73)</th>
<th>Gly16/Arg16 (n=68)</th>
<th>Arg16/Arg16 (n=22)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>body mass (kg)</td>
<td>-0.86±2.52</td>
<td>-1.42±2.51</td>
<td>-1.67±2.16</td>
<td>0.259</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.54±2.25</td>
<td>-1.40±2.42</td>
<td>-1.48±1.74</td>
<td>0.051</td>
</tr>
<tr>
<td>BMR</td>
<td>-0.33 (-0.82, 0.19)</td>
<td>-0.43 (-0.82, 0.0)</td>
<td>-0.55 (-0.79, -0.13)</td>
<td>0.214†</td>
</tr>
<tr>
<td>%FM</td>
<td>-3.80 (-7.14, 2.73)</td>
<td>-5.45 (-9.53, -1.77)</td>
<td>-6.94 (-10.98, -0.29)</td>
<td>0.088†</td>
</tr>
<tr>
<td>FFM</td>
<td>0.63 (-0.65, 1.36)</td>
<td>1.07 (-0.33, 2.29)</td>
<td>1.27 (-0.70, 2.06)</td>
<td>0.524†</td>
</tr>
<tr>
<td>TBW</td>
<td>0.61 (-0.58, 1.67)</td>
<td>0.77 (-0.92, 2.35)</td>
<td>1.51 (-0.63, 2.24)</td>
<td>0.813†</td>
</tr>
<tr>
<td>TC</td>
<td>0.10±12.30</td>
<td>-0.64±11.67</td>
<td>0.54±14.67</td>
<td>0.904</td>
</tr>
<tr>
<td>TGL</td>
<td>10.06±40.55</td>
<td>8.25±35.40</td>
<td>20.73±40.06</td>
<td>0.410</td>
</tr>
<tr>
<td>HDL</td>
<td>-4.58±17.06</td>
<td>-5.40±18.41</td>
<td>-5.29±15.92</td>
<td>0.959</td>
</tr>
<tr>
<td>LDL</td>
<td>4.89±20.89</td>
<td>4.06±20.54</td>
<td>3.20±22.59</td>
<td>0.938</td>
</tr>
<tr>
<td>glucose</td>
<td>-4.55 (-11.25, 2.86)</td>
<td>-2.74 (-9.97, 4.98)</td>
<td>-0.69 (-6.10, 2.50)</td>
<td>0.512†</td>
</tr>
</tbody>
</table>

Mean ± SD or median with interquartile range (in brackets), † Kruskal-Wallis test; BMI – body mass index; BMR – basal metabolic rate; %FM – fat mass percentage; FFM – fat free mass; TBW – total body water; TC – total cholesterol; TGL – triglycerides; HDL – high density lipoprotein, LDL – low density lipoprotein

Table 2. The ADRB2 Glu27Gln genotypes and response to training (% change from baseline).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Glu27/Glu27 (n=38)</th>
<th>Glu27/Gln27 (n=71)</th>
<th>Gln27/Gln27 (n=54)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>body mass (kg)</td>
<td>-0.98±2.85</td>
<td>-1.10±2.38</td>
<td>-1.50±2.32</td>
<td>0.545</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.59±2.32</td>
<td>-1.03±2.44</td>
<td>-1.33±2.05</td>
<td>0.310</td>
</tr>
<tr>
<td>BMR</td>
<td>-0.24 (-0.99, 0.20)</td>
<td>-0.42 (-0.83, 0.07)</td>
<td>-0.47 (-0.79, -0.12)</td>
<td>0.450†</td>
</tr>
<tr>
<td>%FM</td>
<td>-3.31 (-7.04, 0.98)</td>
<td>-4.33 (-8.33, -0.82)</td>
<td>-6.09 (-10.71, -0.29)</td>
<td>0.412†</td>
</tr>
<tr>
<td>FFM</td>
<td>0.77 (-0.42, 1.93)</td>
<td>0.64 (-0.88, 1.92)</td>
<td>1.15 (-0.69, 2.18)</td>
<td>0.955†</td>
</tr>
<tr>
<td>TBW</td>
<td>0.60 (-0.31, 1.73)</td>
<td>0.67 (-0.90, 2.06)</td>
<td>1.19 (-0.63, 2.29)</td>
<td>0.967†</td>
</tr>
<tr>
<td>TC</td>
<td>-1.35±11.02</td>
<td>1.94±12.49</td>
<td>-2.05±12.75</td>
<td>0.159</td>
</tr>
<tr>
<td>TGL</td>
<td>3.69±35.67</td>
<td>14.07±40.31</td>
<td>11.34±37.67</td>
<td>0.404</td>
</tr>
<tr>
<td>HDL</td>
<td>-4.11±16.60</td>
<td>-6.35±19.13</td>
<td>-3.90±15.65</td>
<td>0.693</td>
</tr>
<tr>
<td>LDL</td>
<td>3.71±18.83</td>
<td>7.48±21.30</td>
<td>0.59±21.33</td>
<td>0.184</td>
</tr>
<tr>
<td>glucose</td>
<td>-5.26 (-11.27, 3.95)</td>
<td>-2.70 (-9.64, 4.35)</td>
<td>-2.62 (-9.41, 3.23)</td>
<td>0.787†</td>
</tr>
</tbody>
</table>

Mean ± SD or median with interquartile range (in brackets), † Kruskal-Wallis test; BMI – body mass index; BMR – basal metabolic rate; %FM – fat mass percentage; FFM – fat free mass; TBW – total body water; TC – total cholesterol; TGL – triglycerides; HDL – high density lipoprotein, LDL – low density lipoprotein
Table 3. The \textit{ADRB3} Trp64Arg genotypes and response to training (% change from baseline).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Trp64/Trp64 (n=136)</th>
<th>Arg64/Arg64+Trp64/Arg64 (n=27)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>body mass (kg)</td>
<td>-1.14±2.45</td>
<td>-1.56±2.62</td>
<td>0.416</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.99±2.35</td>
<td>-1.23±2.02</td>
<td>0.620</td>
</tr>
<tr>
<td>BMR</td>
<td>-0.42 (-0.83, 0.04)</td>
<td>-0.39 (-0.80, 0.23)</td>
<td>0.551†</td>
</tr>
<tr>
<td>%FM</td>
<td>-4.34 (-9.03, 0.0)</td>
<td>-5.08 (-7.04, -0.82)</td>
<td>0.986†</td>
</tr>
<tr>
<td>FFM</td>
<td>0.65 (-0.67, 2.13)</td>
<td>1.08 (-0.44, 1.71)</td>
<td>0.915†</td>
</tr>
<tr>
<td>TBW</td>
<td>0.74 (-0.63, 2.32)</td>
<td>1.11 (-0.60, 1.67)</td>
<td>0.787†</td>
</tr>
<tr>
<td>TC</td>
<td>0.08±12.51</td>
<td>-1.28±11.44</td>
<td>0.603</td>
</tr>
<tr>
<td>TGL</td>
<td>11.46±39.36</td>
<td>7.14±33.44</td>
<td>0.594</td>
</tr>
<tr>
<td>HDL</td>
<td>-6.10±17.58</td>
<td>0.44±15.61</td>
<td>0.074</td>
</tr>
<tr>
<td>LDL</td>
<td>5.13±21.10</td>
<td>0.21±19.40</td>
<td>0.263</td>
</tr>
<tr>
<td>glucose</td>
<td>-2.84 (-9.61, 3.82)</td>
<td>-2.95 (-11.25, 4.29)</td>
<td>0.844†</td>
</tr>
</tbody>
</table>

Mean ± SD or median with interquartile range (in brackets); † Mann-Whitney test; BMI – body mass index; BMR – basal metabolic rate; %FM – fat mass percentage; FFM – fat free mass; TBW – total body water; TC – total cholesterol; TGL – triglycerides; HDL – high density lipoprotein, LDL – low density lipoprotein.

Table 4. The \textit{ADRA2A} G1780A genotypes and response to training (% change from baseline).

<table>
<thead>
<tr>
<th>Variables</th>
<th>GG (n=124)</th>
<th>AA+AG (n=39)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>body mass (kg)</td>
<td>-1.18±2.45</td>
<td>-1.30±2.59</td>
<td>0.796</td>
</tr>
<tr>
<td>BMI</td>
<td>-1.10±2.40</td>
<td>-0.80±1.92</td>
<td>0.470</td>
</tr>
<tr>
<td>BMR</td>
<td>-0.40 (-0.84, 0.08)</td>
<td>-0.48 (-0.79, 0.0)</td>
<td>0.782†</td>
</tr>
<tr>
<td>%FM</td>
<td>-4.44 (-8.65, -0.15)</td>
<td>-5.11 (-10.98, 0.0)</td>
<td>0.472†</td>
</tr>
<tr>
<td>FFM</td>
<td>0.64 (-0.57, 1.92)</td>
<td>1.08 (-0.93, 2.40)</td>
<td>0.547†</td>
</tr>
<tr>
<td>TBW</td>
<td>0.85 (-0.59, 2.11)</td>
<td>0.81 (-1.24, 2.29)</td>
<td>0.849†</td>
</tr>
<tr>
<td>TC</td>
<td>-0.51±12.10</td>
<td>0.99±13.08</td>
<td>0.599</td>
</tr>
<tr>
<td>TGL</td>
<td>11.08±38.44</td>
<td>9.67±38.68</td>
<td>0.841</td>
</tr>
<tr>
<td>HDL</td>
<td>-6.47±16.42</td>
<td>-0.39±19.71</td>
<td>0.057</td>
</tr>
<tr>
<td>LDL</td>
<td>4.33±20.64</td>
<td>4.27±21.79</td>
<td>0.987</td>
</tr>
<tr>
<td>glucose</td>
<td>-2.74 (-9.50, 4.32)</td>
<td>-3.95 (-11.59, 2.38)</td>
<td>0.610†</td>
</tr>
</tbody>
</table>

Mean ± SD or median with interquartile range (in brackets); † Mann-Whitney test; BMI – body mass index; BMR – basal metabolic rate; %FM – fat mass percentage; FFM – fat free mass; TBW – total body water; TC – total cholesterol; TGL – triglycerides; HDL – high density lipoprotein, LDL – low density lipoprotein.

Table 5. Regression of percentage change of body composition parameters, lipids and glucose on \textit{ADRB2} haplotypes.

<table>
<thead>
<tr>
<th>Haplotype/intercept</th>
<th>Intercept [Arg16; Gln27]</th>
<th>Intercept [Gly16; Gln27]</th>
<th>[Arg16; Gln27]</th>
<th>[Gly16; Gln27]</th>
</tr>
</thead>
<tbody>
<tr>
<td>body mass (kg)</td>
<td>-0.93 (-2.67) **</td>
<td>-0.43 (-1.49)</td>
<td>0.05 (0.13)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-0.65 (-2.04) *</td>
<td>-0.57 (-2.11) *</td>
<td>0.03 (0.08)</td>
<td></td>
</tr>
<tr>
<td>BMR</td>
<td>-0.28 (-1.15)</td>
<td>-0.36 (-1.71)</td>
<td>-0.16 (-0.60)</td>
<td></td>
</tr>
<tr>
<td>%FM</td>
<td>-4.70 (-3.23) ***</td>
<td>-1.86 (-1.51)</td>
<td>0.37 (0.24)</td>
<td></td>
</tr>
<tr>
<td>FFM</td>
<td>1.0 (2.50) *</td>
<td>0.12 (0.35)</td>
<td>-0.23 (-0.53)</td>
<td></td>
</tr>
<tr>
<td>TBW</td>
<td>1.01 (2.45) *</td>
<td>0.001 (0.005)</td>
<td>-0.04 (-0.10)</td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>0.58 (0.36)</td>
<td>-0.33 (-0.23)</td>
<td>-1.22 (-0.66)</td>
<td></td>
</tr>
<tr>
<td>TGL</td>
<td>7.18 (1.33)</td>
<td>3.92 (0.86)</td>
<td>2.12 (0.37)</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>-5.39 (-2.21) *</td>
<td>-0.18 (-0.09)</td>
<td>1.22 (0.47)</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>6.54 (2.24) *</td>
<td>-1.53 (-0.62)</td>
<td>-2.85 (-0.91)</td>
<td></td>
</tr>
<tr>
<td>glucose</td>
<td>-2.06 (-1.03) *</td>
<td>1.19 (0.70)</td>
<td>-2.34 (-1.09)</td>
<td></td>
</tr>
</tbody>
</table>

Regression coefficients and t statistic (in brackets); minimum frequency for a haplotype to be included 5%; the most common haplotype \[Gly16;Glu27\] (45.1%) was the reference haplotype; BMI – body mass index; BMR – basal metabolic rate; %FM – fat mass percentage; FFM – fat free mass; TBW – total body water; TC – total cholesterol; TGL – triglycerides; HDL – high density lipoprotein, LDL – low density lipoprotein.

Discussion

Our genetic association study was designed to test whether variation in the \textit{ADRB2}, \textit{ADRB3} and \textit{ADRA2A} genes can modulate changes in selected body mass, body composition and metabolic variables following 12 weeks of supervised aerobic exercise training in women. Despite the fact...
that there were no differences in percentage changes across genotypes for any of the analysed polymorphisms of the \textit{ADRB2} (Gly16Arg, Glu27Gln), \textit{ADRB3} (Trp64Arg) and \textit{ADRA2A} (G1780A), the polygenic analysis has shown that the carriers of a low number (0-3) of obesity-related risk alleles (\textit{ADRB2} Gly16, \textit{ADRB2} Glu27, \textit{ADRA2A} rs553668 G) were more successful in fat mass loss compared to the carriers of a high number (5-6) of risk alleles (7.7 (9.8)\% vs 4.0 (9.4)\%, \(p = 0.0362\)). Moreover, carriers of a high number (5-6) of risk alleles (7.7 (9.8)\%) were more successful in fat mass loss compared to the carriers of a low number (0-3) of obesity-related risk alleles (4.0 (9.4)\%, \(p = 0.0362\)).

Moreover, carboxylic site have an influence on individual variation in responsiveness to exercise training (Jensen et al., 2009; Rankinen and Bouchard, 2012). The ADRs gene family members have been extensively studied in the obesity field because of their participation in the regulation of energy expenditure (Marti et al., 2008; Ochoa et al., 2004). Particularly, the role of the lipolytic receptors genes, \textit{ADRB2}, with its Gly16Arg and Glu27Gln polymorphisms, alone or in haplotype combination, in weight gain, obesity and changes in body composition have been investigated by many scientists. It has been shown that the Gly16 allele may influence the propensity to higher BMI, because the Gly16 allele is associated with lower receptor density, and in consequence reduced efficiency, when compared to Arg16 allele (Chou et al., 2012). A higher frequency of the Gly16 allele in men resistant to weight loss and those who regained body weight after successful initial weight loss at 6 months was noticed in a study of overweight men who participated in a 24-month weight loss programme consisting of a low-calorie diet and everyday aerobic exercise (Masuo et al., 2005b). Numerous studies have also focused on the second polymorphic site in the \textit{ADRB2} gene. Some studies showed that the Glu27 allele may limit \textit{ADRB2} downregulation and thus affect body weight (Kawaguchi et al., 2006; Lange et al., 2005). Corbalan et al. (2002) reported that women who were more active during their free time and were carriers of the Glu27 allele had higher body weight compared to non-carriers, suggesting that these women may be more resistant to losing weight.

In contrast, the study by Phares et al. (2004) and Szendrei et al. (2016) showed that Glu27 carriers had a tendency for a greater loss of percent total body fat, greater weight and BMI reductions compared with noncarriers. What is more, the study of Bea et al. (2010) showed gene x exercise interactions for \textit{ADRB2} Glu27Gln on change in lean soft tissue (LST). There was a significant LST gain with exercise of the Glu27 allele carriers compared to loss among controls and no intervention effect of the Glu27 allele carriers compared to loss among controls and no intervention effect of the Glu27 allele noncarriers (Bea et al., 2010).

In our study, we have observed only a tendency of association of Gly16Arg and Glu27Gln alone with changes of selected body mass and body composition variables. However, we found that the \textit{ADRB2} risk alleles (Gly16 and Glu27) in combination with another risk allele of the \textit{ADRA2A} gene (rs553668 G) were associated with significantly smaller change of fat mass following 12 weeks of supervised aerobic exercise training in women. The results of Jensen et al. (2009) were focused on analyzing the haplotype structure of the \textit{ADRB2} gene in Danish Caucasian subjects and association with BMI. The investigation clearly suggested that when multiple SNPs from a single gene were analyzed, unique interactions in specific haplotype pairs rather than individual SNPs may affect BMI.

### Table 6. Analysis of the two-way and three-way interactions between \textit{ADRB2}, \textit{ADRB3} and \textit{ADRA2A} genes using quantitative multifactor dimensionality reduction for body composition parameters, lipids and glucose.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Best model*</th>
<th>Cross-validation training score</th>
<th>Cross-validation testing score</th>
<th>CVC*</th>
<th>(p)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>body mass (kg)</td>
<td>Gly16Arg</td>
<td>1.57</td>
<td>0.61</td>
<td>9/10</td>
<td>0.557</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Gly16Arg</td>
<td>2.35</td>
<td>1.06</td>
<td>9/10</td>
<td>0.435</td>
</tr>
<tr>
<td>%FM (%)</td>
<td>Gly16Arg,G1780A</td>
<td>2.45</td>
<td>-0.75</td>
<td>6/10</td>
<td>0.875</td>
</tr>
<tr>
<td>FFMM (kg)</td>
<td>G1780A</td>
<td>1.18</td>
<td>-2.29</td>
<td>6/10</td>
<td>0.995</td>
</tr>
<tr>
<td>TBW (kg)</td>
<td>Gly16Arg, Glu27Gln, Trp64Arg</td>
<td>2.20</td>
<td>-1.86</td>
<td>6/10</td>
<td>0.986</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>Glu27Gln</td>
<td>1.81</td>
<td>1.91</td>
<td>10/10</td>
<td>0.213</td>
</tr>
<tr>
<td>TGL (mg/dL)</td>
<td>Glu27Gln</td>
<td>2.11</td>
<td>-1.56</td>
<td>6/10</td>
<td>0.969</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>Trp64Arg, G1780A</td>
<td>3.69</td>
<td>3.67</td>
<td>10/10</td>
<td>0.018</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>Glu27Gln</td>
<td>1.76</td>
<td>0.55</td>
<td>7/10</td>
<td>0.557</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>Gly16Arg,Glu27Gln, Trp64Arg</td>
<td>2.45</td>
<td>-1.25</td>
<td>9/10</td>
<td>0.960</td>
</tr>
</tbody>
</table>

* the best gene-gene interaction model was determined using cross-validation consistency (CVC) and cross-validation testing score; † permuted \(p\) value (1000 permutations)

![Figure 3. A two-way interaction between \textit{ADRB3} Trp64Arg and \textit{ADRA2A} G1780A for HDL change.](image)
Because the main role of catecholamines in human fat cells depends on the balance between lipolytic ADRB and antiligilipotic ADRA receptors activities, gene-gene interactions in genes involved in the reciprocal regulation of lipolysis is inevitable (Phares et al., 2004). Indeed, such polygenic interactions have been spotted by some researchers. It has been reported that interactive effect of the ADRB2 Glu12/Glu9 and the ADRB3 Trp64Arg polymorphisms on obesity-related phenotypes in healthy white women exist (Dionne et al., 2001). It is worth noting that when the Glu12/Glu9 ADRB2 polymorphism did not associate with obesity-related phenotypes alone, subjects that carried the Arg64 ADRB3 and Glu9 ADRB2 variants had 9.3 kg greater fat mass and 4.8% greater percent body fat compared with subjects carrying only the Arg64 ADRB3 variant. Phares et al. (2004) found that the combined effects of the Glu12/Glu9, ADRA2B, Trp64Arg ADRB3, and Gln27Glu ADRB2 gene polymorphisms and their gene-gene interactions contribute significantly to explaining interindividual variability in body fat responses to exercise training. However, ADRA2B and ADRB3 interaction was the most significant source of variation for change in total body fat, trunk fat, and fat mass.

In the current study, we also observed interaction between ADRs genes; specifically, ADRB3xADRA2A interaction was detected for HDL percentage change. Our study showed that only single heterozygotes (ADRB3 Trp64Arg/ADRA2A GG and ADRB3 Trp64Trp/ADRA2A AG) had an increase in HDL serum concentration in response to training; the double heterozygotes (ADRB3 Trp64Arg/ADRA2A AG) and double homozygotes (ADRB3 Trp64Trp/ADRA2A GG) exhibited a decrease in HDL serum concentration after completion of 12 weeks of supervised aerobic exercise training.

It is widely accepted that regular aerobic exercise increases HDL-Chol. It was showed that beneficial adaptations in lipoprotein profile is achieved with moderate training intensities below the anaerobic threshold and training above the anaerobic threshold has no or even negative effects on blood lipoprotein profiles (Aellen et al., 1993; Drygas et al., 2000). Meta-analysis by Kodama et al. (2007) showed that the minimum aerobic exercise volume for an increase in HDL level exist - minimal weekly exercise volume for HDL level increase was 900 kcal of energy expenditure or 120 minutes of exercise per week (Kodama et al., 2007). The intensity of our 12-week exercise program gradually increased from 50-60% HR_{max} to 65%-80% of HR_{max} in the last 3 weeks of the training programme and the weekly exercise volume was 180 minutes. Each training unit consisted of a warm-up, the main aerobic routine which was a combination of 2 alternating styles – low and high impact, and cool-down phase. Despite that, low-high impact aerobics in general refer to cardio with moderate training intensities zones, one may speculate that low- and high-impact workouts are at least partly similar to interval training with the high-intensity periods that are typically at or close to anaerobic exercise, while the recovery periods involve activity of lower intensity.

With respect to our findings, there is a reason for us to hypothesise that the subjects with combination of ADRB3Arg64 / ADRA2A G and ADRB3 Trp64 / ADRA2A A rather than ADRB3 Trp64 / ADRA2A G respond better to our physical exercise program in terms of larger increase in HDL. It seems that duration, intensity as well as exercise frequency of our physical exercise programme were appropriate stimuli for ADRB3 Arg64 / ADRA2A G and ADRB3 Trp64 / ADRA2A A carriers to increase the HDL level. On the other hand, the ADRB3 Trp64 / ADRA2A G rather than ADRB3 Arg64 / ADRA2A A carriers respond with lowered HDL serum concentration in response to our 12 weeks of supervised aerobic exercise training. Therefore, there is a reason to hypothesise that low- and high- aerobic exercise training is not suitable for ADRB3 Trp64 / ADRA2A G carriers in terms of lower HDL levels, and the observed effect can be explained by an increase in energy consumption and achieving an ‘energy expenditure threshold’ during physical effort (Gibala and McGee, 2008; Kostrzewa-Nowak et al., 2015). It is also, highly probable, that other, rhythmic and repeated, aerobic exercises with moderate training intensities below the anaerobic threshold such as bicycling, jogging, or swimming would be more appropriate for this group of participants.

Conclusion

In summary, our findings suggest that the carriers of a low number of obesity-related risk alleles were more successful in fat mass loss compared to the carriers of a high number of risk alleles, as well as ADRB3xADRA2A gene interaction modifies the effects of aerobic exercise training in women on HDL levels. However, when we consider all aforementioned facts, the impact of genetic markers on determination of obesity-related traits is still unclear. Thus, the true level and the nature of the genotype x physical activity interactions in the field of obesity-related traits deserves to be further investigated. One of the possible ways is using a composite score of genetic markers that have been identified in GWAS as an obesity risk SNPs in the gene x physical activity interaction analyses (Li et al., 2010). However, only a comprehensive understanding of the underlying genetic and epigenetic mechanisms will enable us to uncover the "missing heritability" of the obesity-related traits (Herrera et al., 2011, Rankinen and Bouchard, 2012).

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References


Bea, J.W., Lohman, T.G., Cussler, E.C., Going, S.B. and Thompson, P.A.


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Key points

- There is a wide range of individual variability in the change of relative fat mass and BMI in response to a 12-week aerobic training program.
- The efficiency of fat loss was inversely correlated with the improvement of VO2max in response to a 12-week aerobic training.
- The carriers of a low number of obesity-related risk alleles were more successful in fat mass loss compared to the carriers of a high number of risk alleles.

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