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PPARγ2 C1431T genotype increases metabolic syndrome risk in young men with low cardiorespiratory fitness

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Sanada K, Iemitsu M, Murakami H, Tabata I, Yamamoto K, Gando Y, Suzuki K, Higuchi M, Miyachi M. PPARγ2 C1431T genotype increases metabolic syndrome risk in young men with low cardiorespiratory fitness. *Physiol Genomics* 43: 103–109, 2011. First published December 14, 2010; doi:10.1152/physiolgenomics.00129.2010.—The peroxisome proliferator-activated receptor gamma 2 (PPARγ2) genotypes are related to obesity and the metabolic syndrome (MetS). A low level of cardiorespiratory fitness is also a strong determining factor in the development of MetS. This cross-sectional study was performed to investigate the influence of the interaction between the PPARγ2 genotype and cardiorespiratory fitness on the risk of MetS. Healthy Japanese men (n = 211) and women (n = 505) participated in this study. All subjects were divided into 8 groups according to sex, fitness level (high and low fitness groups), and age (younger, age < 40 yr; middle-aged/older, age ≥ 40 yr). The PPARγ2 genotypes (Pro12Ala and C1431T) were analyzed by real-time PCR with Taq-Man probes. Two-way ANCOVA with adjustment for age as a covariate indicated that fitness and the CC genotype of C1431T in the PPARγ2 gene interacted to produce a significant effect on MetS risk in younger men and that the risk of MetS in the CC genotype group with low cardiorespiratory fitness was significantly higher than in the corresponding CT+TT genotypes or in the high fitness groups. There was no significant interaction between fitness and genotype in determining MetS risk in middle-aged/older men or in women in any group. With regard to the Pro12Ala genotype of the PPARγ2 gene, there were no significant differences in fitness or genotype effects nor were there any interactions between measurement variables. We concluded that the CC genotype of C1431T in the PPARγ2 gene together with low cardiorespiratory fitness may increase the risk of MetS in younger men (age < 40 yr), even with adjustment for age.

physical fitness; peroxisome proliferator-activated receptor gamma 2; health care research; maximal oxygen uptake; obesity gene

There has been a considerable increase in the number of studies reporting associations between DNA sequence variation in specific genes and obesity phenotypes (41). One such gene, that for peroxisome proliferator-activated receptor gamma 2 (PPARγ2), is reported to be associated with metabolic syndrome (MetS) or adipocytokine dysregulation (37, 52–53). Two common polymorphisms, a proline (Pro)-to-alanine (Ala) substitution located at codon 12 (Pro12Ala)(54) and a synonymous C-to-T substitution in exon 6 at nucleotide 1431 (C1431T)(30), have been associated with a reduced risk for the development of diabetes (33), a low adiponectin concentration (45), and an exercise-mediated change in insulin resistance (18) in Japanese people. The protective effect of the Ala allele of Pro12Ala against Type 2 diabetes has been replicated in Japanese, Caucasian-American, Finnish, and Danish populations; however, a deleterious effect of this allele on Type 2 diabetes has been demonstrated in Canadians, Germans, and obese Finns (28). Conversely, the CT+TT genotypes of C1431T in the PPARγ2 gene in Scotland (7) and in Greek children (22) are associated with increases in body mass index (BMI) and waist circumference compared with the CC genotype and are associated with a reduced risk for MetS in 647 Caucasian-Australian patients (26). However, some investigators have shown that the C1431T variant by itself is not associated with BMI or risk factors for MetS (14, 35).

Previous studies regarding the relationship between cardiorespiratory fitness and MetS suggested that a low level of physical fitness is a strong determining factor in the prevalence of MetS (6, 11, 23–25, 38, 50), because cardiorespiratory fitness is strongly correlated with physical activity (39). Lakka et al. (23) suggested that a sedentary lifestyle and an especially low cardiorespiratory fitness measured by maximal oxygen uptake (VO2max) are not only associated with MetS but could also be considered features of MetS. In addition, Lee et al. (25) reported that high levels of cardiorespiratory fitness are associated with a substantial reduction in health risk for a given level of visceral and subcutaneous fat. Therefore, it is important to consider individual cardiorespiratory fitness to clarify the relationship between PPARγ2 genotypes and MetS. The present study was performed to investigate the influence of interaction between the PPARγ2 genotype and cardiorespiratory fitness on the risk of MetS.

METHODS

Subjects. The subjects included in this cross-sectional study were 716 Japanese adults between 18 and 84 yr of age, consisting of 211 men and 505 women, as described previously were the same subjects included in Ref. 32. All subjects were free of any overt signs or symptoms of chronic disease. They were sedentary or moderately active subjects who participated in a swimming, stretching, and “healthy gymnastics” program; however, they did not participate in other vigorous sports activities. All subjects were divided according to sex and age (young < 40 yr old and middle-aged/older ≥ 40 yr old), because metabolic profiles differ according to both sex and age. The
purpose, procedures, and risks of the study were explained to each participant prior to enrollment, and all subjects gave their written informed consent before participating in the study, which was approved by the Human Ethical Committee of Waseda University. The study was performed in accordance with the guidelines of the Declaration of Helsinki. Body weight and height were recorded, and BMI was calculated as weight in kilograms divided by the square of the height in meters. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) were measured at rest by using a vascular testing device (Colin Medical Technology, Tokyo, Japan).

Measurements of blood samples. All blood samples were drawn from the subjects in the seated position. Fasting (> 12 h) blood samples were collected by venipuncture in tubes with or without ethylenediamine tetraacetic acid (for plasma or serum). The blood samples were centrifuged at 1,500 rpm for 15 min and stored at −20°C. Serum concentrations of triglycerides were determined by using commercial kits (Mitsubishi Chemical Medience, Tokyo, Japan). Serum high-density lipoprotein (HDL) cholesterol was measured by an enzymatic method (Mitsubishi Chemical Medience). Fasting plasma glucose (FPG) was measured by the glucose dehydrogenase method (21). Whole blood glycohemoglobin A1c (HbA1c) was measured by an enzymatic method (Glycohemoglobin A1c kit; Mitsubishi Chemical Medience). As waist circumference data were not available, the following risk factors of MetS (highest value was determined by using a dry gas meter (NDS-2A-T; Arco System, Chiba, Japan), and gas spectrometry (WSMR-1400; Arco System, Chiba, Japan), and gas were encouraged during the ergometer test to exercise at the level of Sweden) (31). The incremental cycle exercise began at a work rate of increase in work rate. Subjects breathed through a low-resistance two-way valve, and the expired air was collected in Douglas bags. Expired O2 and CO2 gas concentrations were measured by mass

The highest value of VO2 during the exercise test was designated as VO2max. Moreover, these values can predict the presence of multiple metabolic risk factors similar to waist circumference in middle-aged Japanese subjects (43).

Measurement of VO2max. The VO2max was measured by an incremental cycle exercise test using a cycle ergometer (Monark, Varberg, Sweden) (31). The incremental cycle exercise began at a work rate of 90 W (60 rpm), and power output was increased by 30 W/min until the subjects could not maintain the fixed pedaling frequency. The subjects were encouraged during the ergometer test to exercise at the level of maximum intensity. VO2 was monitored during the last 30 s of each increase in work rate. Subjects breathed through a low-resistance two-way valve, and the expired air was collected in Douglas bags. Expired O2 and CO2 gas concentrations were measured by mass spectrometry (WSMR-1400; Arco System, Chiba, Japan), and gas volume was determined by using a dry gas meter (NDS-2A-T; Shinagawa Dev., Tokyo, Japan). The highest value of VO2 during the exercise test was designated as VO2max. Moreover, these values were consistent with the reference values for the maximal oxygen uptake for health promotion by sex and age, as described by the Japanese Ministry of Health, Labor, and Welfare to prevent lifestyle-related diseases (12, 17).

Single nucleotide polymorphism genotyping. Genomic DNA was extracted from plasma buffy coats and buccal cells by using a QIAamp DNA Blood Maxi Kit (Qiagen, Tokyo, Japan). Single nucleotide polymorphism (SNP) genotypes were determined by real-time PCR with TaqMan probes using an ABI Prism 7700 Sequence Detector (Perkin-Elmer Applied Biosystems, Foster City, CA) as described previously with minor modifications (16). The gene-specific primers and TaqMan probes for each SNP were synthesized by using Primer Express v. 1.5 software (Perkin-Elmer Applied Biosystems) according to the published DNA sequences for each SNP as follows: Pro12Ala (C>G) in exon 1 of PPARγ2 (NCBI accession ID: rs1805192) and C1431T in exon 6 of PPARγ2 (NCBI accession ID: rs3856806). The sequences of the oligonucleotides used were as follows:

Pro12Ala forward: 5′-GTATGGGTGAAACTCTGGGAGATT-3′, Pro12Ala reverse: 5′-GCAGACAGTGATCATGAAAGAAT-3′, Pro12Ala/C probe: 5′-CTGTCTGGCCAGCAGAAG-3′, Pro12Ala/G probe: 5′-GTTATGGGTGAAACTCTGGGAGATT-3′, C1431T forward: 5′-GAAAATGACAGACCTCAGTGAAGGAAT-3′, C1431T /G probe: 5′-CTGCACGTCTCGCC-3′, C1431T /A probe: 5′-CTGCACGTCTCGCC-3′.

PCR 96-well plates were read on an ABI-7700 using the endpoint analysis mode of the SDS v. 1.7a software package (Perkin-Elmer Applied Biosystems). Genotypes were determined automatically by the single processing algorithms in the software.

Statistical analysis. The PPARγ2 allelic frequencies were calculated by using a gene-counting method, and Hardy-Weinberg equilibrium was confirmed by performing the χ² test. The variables BMI, MBP, HbA1c, and serum triglyceride/HDL cholesterol were standardized to Z-score variables with mean = 0 and standard deviation (SD) = 1 [(individual value − sex and age-specific mean value)/SD]. We tested the influence of genotype and fitness on the risk of MetS by using two-way ANCOVA with adjustment for age as a covariate (genotype and fitness), and when a significant difference was observed in the interaction, comparisons between groups were tested by using the unpaired Student’s t-test. Regression analyses were conducted to explore the relationship between VO2max and MetS risk, excluding variance produced by age by use of partial correlations (partial correlation coefficient). Values were expressed as means ± SE. In all analyses, P < 0.05 was taken to indicate statistical significance.

RESULTS

There were no significant differences in the frequencies of C1431T and Pro12Ala polymorphisms between age groups in either sex (Table 1). The genotype frequencies did not deviate from the expected Hardy-Weinberg equilibrium.

### Table 1. Genotype and allele frequencies of the peroxisome proliferator-activated receptor γ2 gene

<table>
<thead>
<tr>
<th></th>
<th>Pro12Ala</th>
<th>C1431T</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ProPro</td>
<td>ProAla</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr &lt;40</td>
<td>197 (93.8)</td>
<td>12 (5.7)</td>
</tr>
<tr>
<td>MAF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr ≥40</td>
<td>274 (92.9)</td>
<td>20 (6.8)</td>
</tr>
<tr>
<td>MAF</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr &lt;40</td>
<td>86 (93.5)</td>
<td>6 (6.5)</td>
</tr>
<tr>
<td>MAF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr ≥40</td>
<td>113 (95.0)</td>
<td>6 (5.0)</td>
</tr>
</tbody>
</table>

MAF: minor allele frequency. There were no significant differences in the frequencies of C1431T and Pro12Ala polymorphisms between age in both sexes. The allele frequencies did not deviate from the expected Hardy-Weinberg equilibrium.
Significant simple and partial correlations (age-adjusted) were observed between VO$_{2\text{max}}$ (ml·kg$^{-1}$·min$^{-1}$) and MetS risk (Z-score) in both men (simple correlation $r = -0.410$, $P < 0.001$, partial correlation $r = -0.371$, $P < 0.001$) and women (simple correlation $r = -0.309$, $P < 0.001$, partial correlation $r = -0.253$, $P < 0.001$); therefore, these findings were independently associated with age.

Neither C1431T nor Pro12Ala was associated with lower BMI regardless of age or sex in healthy Japanese adults. Women with low cardiorespiratory fitness in both age groups and in C1431T genotype groups had a higher BMI than those with high cardiorespiratory fitness ($P < 0.05$), but these associations did not hold for men (Tables 2 and 3). Low cardiorespiratory fitness in younger women of both C1431T genotypes was associated with higher SBP, DBP, and MBP than high cardiorespiratory fitness ($P < 0.05$), but this association was not observed in younger men or in middle-aged/older men and women. The risk of MetS in both C1431T genotypes of younger women with a low level of fitness was significantly higher than that in those with a high level of fitness ($P < 0.01$), but this association was absent in younger men and middle-aged/older people of either sex (Tables 2 and 3, respectively).

The interaction between fitness and genotype significantly affected the risk of MetS in younger men ($P < 0.05$, Fig. 1). Moreover, the MetS risk in low-fitness younger men with the CC genotype in the C1431T polymorphism of the PPARγ2 gene was significantly higher than that in the other groups ($P < 0.05$, Table 2). There was no significant interaction between fitness and genotype in determining MetS risk in middle-aged/older men and younger and middle-aged/older women.

On the other hand, with regard to the Pro12Ala genotype of the PPARγ2 gene, there were no significant differences in fitness or genotype effects nor were there any interactions between measurement variables.

**DISCUSSION**

A previous study reporting associations between DNA sequence variation in specific genes and obesity phenotypes has increased considerably, with 426 findings of positive associations with 127 candidate genes (41). One of these genes, PPARγ2, which encodes a transcription factor belonging to the nuclear receptor family, is related to lipid metabolism, carbohydrate metabolism, and fatty acid transport (51) and is a candidate gene for susceptibility to obesity and Type 2 diabetes (2, 8, 19, 34). It is directly involved in adipogenesis (46) and muscle responses to glucose (15). A common structural defect has been detected in the PPARγ2 gene, resulting in a Pro-to-Ala substitution (54), located at codon 12 (Pro12Ala); and a

**Table 2. Relationships among cardiorespiratory fitness, C1431T genotype of the peroxisome proliferator-activated receptor γ2 gene, and metabolic syndrome risk in younger subjects (age <40 yr)**

<table>
<thead>
<tr>
<th>CC Individuals With Low Fitness</th>
<th>CC Individuals With High Fitness</th>
<th>CT+TT Individuals With Low Fitness</th>
<th>CT+TT Individuals With High Fitness</th>
<th>P</th>
<th>Genotype</th>
<th>Fitness</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td>46</td>
<td>91</td>
<td>23</td>
<td>50</td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
<td></td>
<td>26.5±1.0</td>
<td>26.6±0.7</td>
<td>25.0±1.1</td>
<td>24.1±0.8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td>21.6±0.4</td>
<td>20.9±0.2</td>
<td>21.1±0.5</td>
<td>20.7±0.3</td>
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<td>Systolic blood pressure, mmHg</td>
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<td></td>
<td>105.3±1.5</td>
<td>107.4±0.9</td>
<td>103.5±1.7</td>
<td>105.5±0.9</td>
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<tr>
<td>Mean blood pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
<td>79.1±1.4</td>
<td>79.3±0.8</td>
<td>76.0±1.3</td>
<td>77.0±0.8</td>
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<td>Serum triglyceride, mg/dl</td>
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<td></td>
<td>68.7±4.6</td>
<td>57.2±2.4</td>
<td>61.9±4.3</td>
<td>60.3±3.0</td>
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<tr>
<td>HDL cholesterol, mg/dl</td>
<td></td>
<td></td>
<td></td>
<td>66.5±1.9</td>
<td>71.0±1.4</td>
<td>64.7±2.0</td>
<td>69.3±2.0</td>
</tr>
<tr>
<td>Serum triglyceride/ HDL cholesterol</td>
<td></td>
<td></td>
<td></td>
<td>1.09±0.09</td>
<td>0.83±0.04</td>
<td>0.99±0.08</td>
<td>0.90±0.05</td>
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<tr>
<td>Fasting plasma glucose, mg/dl</td>
<td></td>
<td></td>
<td></td>
<td>86.9±1.0</td>
<td>86.4±0.6</td>
<td>86.7±1.1</td>
<td>87.0±0.8</td>
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<tr>
<td>HgA1c, %</td>
<td></td>
<td></td>
<td></td>
<td>4.87±0.04</td>
<td>4.80±0.03</td>
<td>4.81±0.06</td>
<td>4.82±0.04</td>
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<td>Number of MetS risk factors</td>
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<td></td>
<td>0.24±0.08</td>
<td>0.07±0.03</td>
<td>0.04±0.04</td>
<td>0.02±0.07</td>
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<tr>
<td>MetS risk, Z-score</td>
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<td></td>
<td></td>
<td>0.79±0.40</td>
<td>-0.34±0.17</td>
<td>-0.21±0.41</td>
<td>-0.44±0.25</td>
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<tr>
<td>Maximal oxygen uptake, ml·kg$^{-1}$·min$^{-1}$</td>
<td></td>
<td></td>
<td></td>
<td>29.1±0.4</td>
<td>39.2±0.6</td>
<td>29.9±0.4</td>
<td>40.3±0.7</td>
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<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td>31</td>
<td>42</td>
<td>5</td>
<td>14</td>
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<tr>
<td>Age, yr</td>
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<td></td>
<td></td>
<td>34.8±0.7</td>
<td>27.2±1.0</td>
<td>33.4±2.1</td>
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<td>25.5±0.8</td>
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<td>22.9±0.6</td>
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<td>Systolic blood pressure, mmHg</td>
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<td></td>
<td>120.7±2.9</td>
<td>116.0±1.6</td>
<td>117.2±1.9</td>
<td>118.4±2.2</td>
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<td>Mean blood pressure, mmHg</td>
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<td></td>
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<td>83.5±1.3</td>
<td>86.0±1.8</td>
<td>84.8±1.9</td>
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<td>Serum triglyceride, mg/dl</td>
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<td></td>
<td>111.2±13.4</td>
<td>62.8±3.9</td>
<td>80.0±12.1</td>
<td>80.2±12.6</td>
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<tr>
<td>HDL cholesterol, mg/dl</td>
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<td></td>
<td></td>
<td>49.3±1.4</td>
<td>60.7±1.7</td>
<td>56.2±5.5</td>
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<td>Serum triglyceride/ HDL cholesterol</td>
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<td></td>
<td></td>
<td>2.29±0.27</td>
<td>1.09±0.08</td>
<td>1.54±0.33</td>
<td>1.41±0.33</td>
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<td>Fasting plasma glucose, mg/dl</td>
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<td></td>
<td>90.7±1.2</td>
<td>90.4±1.5</td>
<td>88.6±3.5</td>
<td>92.9±1.3</td>
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<td>HgA1c, %</td>
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<td></td>
<td></td>
<td>4.79±0.04</td>
<td>4.75±0.04</td>
<td>4.64±0.13</td>
<td>4.76±0.08</td>
</tr>
<tr>
<td>Number of MetS risk factors</td>
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<td></td>
<td></td>
<td>0.94±0.15</td>
<td>0.33±0.09</td>
<td>0.20±0.20</td>
<td>0.43±0.14</td>
</tr>
<tr>
<td>MetS risk, Z-score</td>
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<td></td>
<td></td>
<td>2.14±0.67</td>
<td>-0.53±0.26</td>
<td>-0.27±0.67</td>
<td>0.01±0.65</td>
</tr>
<tr>
<td>Maximal oxygen uptake, ml·kg$^{-1}$·min$^{-1}$</td>
<td></td>
<td></td>
<td></td>
<td>33.6±0.6</td>
<td>49.2±1.3</td>
<td>36.5±0.4</td>
<td>52.5±2.8</td>
</tr>
</tbody>
</table>

Data are means ± SE unless otherwise indicated. $P < 0.05$ for a significant difference from CC individuals of the C1431T variant with the “low fitness” group using the unpaired Student’s t-test. $P$ values are for significant effects using 2-way ANCOVA with adjustment for the covariate of age (genotype × fitness). Boldface indicates significance ($P < 0.05$).
synonymous C-to-T substitution in exon 6 has been identified at nucleotide 1431 (C1431T)(30) of this gene. However, the reported associations between increased body mass and BMI with the Pro12Ala genotype are inconsistent, with some studies indicating that the Ala allele is associated with either a higher BMI (3, 19, 29, 47) or a lower one (8–10, 40, 48), while other studies have suggested that low physical fitness is a strong predictor of BMI (3, 19, 29, 47) or a lower one (8–10, 40, 48), while other studies have suggested that low physical fitness is a strong predictor of BMI (3). We examined the relationship between the fitness level and PPARγ2 genotype, when the subjects were divided based on their sex and age. The results of this study indicated that low cardiorespiratory fitness was associated with MetS risk independent of age and that cardiorespiratory fitness levels corresponding to this risk may be used as target fitness values for prevention of MetS in Japanese adults.

At present, it is unclear which of the two contributions to MetS is more important: the PPARγ2 genotype or cardiorespiratory fitness. In the present study, the subjects were classified into high- and low-fitness groups according to the criteria issued by the Ministry of Health, Labor, and Welfare of Japan (17). We examined the relationship between the fitness level and PPARγ2 genotype, when the subjects were divided based on their sex and age. The results of this study indicated that younger men with low levels of fitness and the CC genotype of C1431T possessed more risk factors for MetS than those with high fitness levels and the CT and TT genotypes, even after adjustment for age (Table 2 and Fig. 1). These results, therefore, suggest that in younger men (age < 40 yr) with the CC genotype of C1431T and low cardiorespiratory fitness, these factors increase the risk of MetS.
On the other hand, cardiovascular fitness itself is influenced not only by environmental factors such as daily physical activity but also by genetic factors. Bouchard et al. (4) reported a heritability estimate of ~50%, which was correlated with \( \dot{V}O_2 \text{max} \) in various parent-offspring and sibling relations, but not among the spouses. In the present study, there were no significant differences in \( \dot{V}O_2 \text{max} \) between the CC genotype and CT/TT genotypes of C1431T in the PPAR\( \gamma_2 \) gene in any of the groups (data not shown). Furthermore, in the human gene map for performance and health-related fitness phenotypes, the fitness and performance map now includes 214 autosomal gene entries and quantitative trait loci plus seven others on the X chromosome (5), but the PPAR\( \gamma_2 \) genotype is not included in these association studies with candidate genes. Therefore, the CC genotype of C1431T in PPAR\( \gamma_2 \) affects the relationship between cardiorespiratory fitness and MetS risk but does not separately affect each phenotype. One of the most interesting findings of the present study is that the CC genotype of C1431T in PPAR\( \gamma_2 \) in younger men, present in 79.3% of the subjects, was associated with MetS risk. These findings indicate that to prevent MetS, it is important to maintain high cardiorespiratory fitness in young male subjects with this genotype.

Some case-control studies have reported evidence of associations between the Pro12Ala genotype in PPAR\( \gamma_2 \) and responses of glucose and insulin metabolism phenotypes to habitual physical activity or regular exercise (1, 18, 36, 49). However, in the Pro12Ala variant of the PPAR\( \gamma_2 \) gene, there were no significant differences in fitness or genotype effects nor were there any interactions between measured variables as determined by two-way ANCOVA in this study. Thus, the lower allele frequency for the Ala12 variant in Japanese (2–4%) (33, 45) compared with Europeans and North Americans (14–16%) (2, 10) may have affected these results.

In the present study, the interaction between fitness and genotype significantly affected the MetS risk in younger men, but not in younger women. Younger women in this study had fewer MetS risk factors than younger men, and therefore this effect of PPAR\( \gamma_2 \) polymorphism may be attenuated in women. However, in middle-aged/older subjects, no interaction between fitness and genotype was observed for either sex. An environmental factor with long-term exposure may participate in attenuation of the genetic factors. Additionally, the interpretation of the observations made in this cross-sectional study must be partly tempered due to the small sample size obtained when the subjects were divided based on their sex, age, fitness, and genotypes. Further study will be necessary using larger numbers of samples, and an intervention study should also be performed.

In conclusion, we found that low cardiorespiratory fitness was associated with MetS risk independent of age and that the CC genotype of C1431T in the PPAR\( \gamma_2 \) gene associated with low cardiorespiratory fitness increased the risk of MetS in younger men (age < 40 yr), even if these factors were adjusted for age.

GRANTS

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