Association between the PPARGC1A Polymorphism and Aerobic Capacity in Japanese Middle-aged Men

Yuichiro Nishida¹, Minako Iyadomi², Yasuki Higaki³, Hiroaki Tanaka³, Yoshiaki Kondo⁴, Hiromi Otsubo¹, Mikako Horita¹, Megumi Hara¹ and Keitaro Tanaka¹

Abstract

Objective A lower frequency for the peroxisome proliferator-activated receptor γ coactivator 1α (PPARGC1A) Ser482 allele has been reported in elite-level endurance athletes among Caucasians, although this gene polymorphism has not been found to be associated with aerobic capacity in German, Dutch or Chinese populations. The purpose of the current study was to examine the associations between the Gly482Ser polymorphism and aerobic fitness in 112 Japanese middle-aged men.

Methods The PPARGC1A Gly482Ser polymorphism was identified according to a TaqMan® SNP genotyping assay. Habitual physical activity was objectively measured using an accelerometer. The lactate threshold (LT), an index of aerobic fitness, was measured based on a submaximal graded exercise test performed on an electric cycle ergometer. The association between the LT and the Gly482Ser polymorphism was assessed according to a multiple regression analysis and analysis of covariance, with adjustment for potential confounders (age, body mass index, cigarette smoking, physical activity level and regular exercise).

Results A significant association was observed between the PPARGC1A Gly482Ser polymorphism and LT, as carriers of the Ser482 had higher LT values than the Gly482 carriers.

Conclusion The current results suggest that the PPARGC1A Ser482 allele is associated with a higher aerobic capacity in Japanese middle-aged men.

Key words: aerobic capacity, anaerobic threshold, gene polymorphism


Introduction

Epidemiological studies have shown that a low level of aerobic fitness is a strong risk factor for the developments of type 2 diabetes (1, 2) and all-cause and cardiovascular death (3, 4). Although aerobic fitness is reasonably influenced by habitual physical activity and exercise training, aerobic capacity is also modulated by the polymorphisms of several genes involved in glucose and lipid metabolism as well as hemodynamic traits (5). Peroxisome proliferator-activated receptor γ coactivator 1α (PPARGC1A) is a transcriptional coactivator that controls mitochondrial biogenesis and oxidative phosphorylation in skeletal muscle (6). Since aerobic capacity highly depends on the skeletal muscle mitochondrial function (7), it is reasonable that functional polymorphisms in the PPARGC1A gene (Gly482Ser) would have an effect on the level of aerobic fitness. Previous studies have demonstrated a lower frequency of the PPARGC1A Ser482 allele in top-level endurance athletes among Caucasians (8-11). Additionally, the PPARGC1A Ser482 allele has been shown to be independently associated with a lower increase in individual aerobic fitness after nine months of lifestyle intervention (12). These results support the notion that the PPARGC1A Ser482 allele impairs aerobic capacity, while the Gly482 allele functions as a beneficial genetic factor increasing endurance capacity.

However, the findings of several other reports are incon-
sistent with this concept. For example, the endurance capacity before training [as assessed according to the maximal oxygen uptake (VO2 max)] is not associated with the Gly482Ser polymorphism in young Chinese men (13). Additionally, another study showed that changes in the VO2 max after 18 weeks of endurance training did not differ between Gly482 and Ser482 carriers in a young Chinese cohort (13). These results are in agreement with the findings of a molecular-level study showing that the expression of the PPARGC1A gene in skeletal muscle is similar between young Gly482 and Ser482 carriers, although the PPARGC1A expression is significantly reduced in elderly subjects with the Ser482 allele (14). Furthermore, the Gly482Ser polymorphism is not associated with either aerobic capacity (as assessed according to the VO2 max) or the composition of skeletal muscle fibers in non-diabetic German or Dutch populations (15).

The precise reasons for the disparities among the findings of these previous studies remain unclear. However, in most of the aforementioned studies, the subjects were limited to athletes (8-11) or healthy individuals with relatively high VO2 max values (13, 15), whose aerobic capacity levels may be considerably influenced by non-genetic factors associated with regular sports/exercise training and/or habitual physical activity. In these previous studies, potential differences in the context of sports/exercise frequency (intensity, duration) and/or levels of daily physical activity between Gly482 and Ser482 groups were not taken into account; therefore, these critical environmental factors were not matched between Gly482 and Ser482 carriers. To date, no previous studies have investigated unfit subjects (e.g., patients with metabolic syndrome), whose aerobic fitness can be assumed to be less affected by regular sports/physical training and/or high levels of daily physically activity, or adjusted for the confounding factors of habitual physical activity or regular exercise in order to examine whether gene polymorphisms are associated with aerobic fitness, independent of physical activity. Additionally, although there is evidence that the impact of the angiotensin-1-converting enzyme (ACE) gene insertion (I)/deletion (D) polymorphism on endurance performance in Japanese runners is not necessarily the same as (or rather contrary to) that observed in Caucasian athletes (16), no studies have investigated the influence of the PPARGC1A Gly482Ser polymorphism on aerobic fitness in a Japanese population. Therefore, in the current study, we examined the association between the PPARGC1A Gly482Ser polymorphism and aerobic fitness in Japanese middle-aged men.

Materials and Methods

Subjects

The current subjects (n=114) were male Japanese employees at a silicon wafer manufacturer (Saga, Japan) and participants of the Specific Health Guidance (http://www.mhlw.go.jp/english/wp/wp-hw3/dl/2-007.pdf) program conducted between 2009 and 2011. The inclusion criteria for the Specific Health Guidance program for middle-aged men (40-74 years of age) were as follows: abdominal obesity (waist circumference ≥85 cm) in addition to one or more of the following three components, 1) dyslipidemia (triglycerides ≥150 mg/dL and/or high-density lipoprotein cholesterol [HDL] <40 mg/dL), 2) high blood pressure (systolic/diastolic blood pressure ≥130/85 mmHg), 3) high blood glucose (fasting plasma glucose ≥100 mg/dL and/or hemoglobin A1c [HbA1c] [Japan Diabetes Society: JDS value] ≥5.2%, which is equivalent to a National Glycohemoglobin Standardization Program (NGSP) value of 5.6%).

Additionally, in cases in which the waist circumference was less than 85 cm, men with a body mass index [BMI] of ≥25 kg/m² as well as at least one of three above-mentioned components (i.e., dyslipidemia, high blood pressure or high blood glucose) met the requirements to participate in the Specific Health Guidance program. Current patients with type 2 diabetes, hypertension or dyslipidemia were excluded. Participation in the Specific Health Guidance program was determined (according to the above-mentioned criteria) based on the results of Specific Health Checkups conducted within the same year or the year prior to participating in the Specific Health Guidance program for administrative reasons.

The current analysis comprised 112 eligible participants who underwent genotyping of the PPARGC1A Gly482Ser polymorphism using genomic DNA extracted from saliva and exercise testing using a cycle ergometer (two subjects were excluded because they were not able to perform incremental exercise tests according to abnormal resting electrocardiogram findings). The study analysis was based on baseline cross-sectional data obtained prior to the lifestyle intervention conducted as part of the Specific Health Guidance program for improving metabolic syndrome. None of the subjects had a medical history of cerebral stroke, myocardial infarction or kidney disease, and no patients had abnormal resting 12-lead electrocardiogram findings. The nature, purpose and risks of the study were explained to all subjects, and written informed consent was obtained prior to the start of the study. The study protocol was approved by the ethics committee of Saga Medical School. This study is registered with ClinicalTrials (ClinicalTrials.gov Identifier: NCT01278628).

Anthropometric and aerobic fitness measurements

The body mass index (BMI) was determined by dividing the body weight in kilograms by the square of the height in meters. Waist circumference was measured at the level of the umbilicus. Aerobic fitness was determined according to the above-mentioned criteria based on the results of Specific Health Checkups conducted within the same year or the year prior to participating in the Specific Health Guidance program for administrative reasons.
level of oxygen consumption was estimated based on the subject’s workload and body weight using the American College of Sports Medicine leg ergometer equation, as follows: estimated oxygen consumption (mL/kg/min) = workload (watts) × 6.12 × 1.8/body weight (kg) + 7 (17). The value of METs was calculated as the estimated oxygen consumption divided by 3.5. The endpoint of the exercise test was determined based on either the attainment of a blood lactate concentration of 4 mM or the American College of Sports Medicine criteria (18). The heart rate was measured in real time using a sensor (installed in the cycle ergometer Model EC-3600) attached to the earlobe. The heart rate and rating of perceived exertion (RPE) (19) were recorded every three minutes during the tests. Blood samples (5 μL) were also obtained from the earlobe every three minutes in order to measure the blood lactate concentration using a portable blood lactate test meter (Lactate Pro, ARKRAY, Kyoto, Japan). The blood lactate concentration (mM) was plotted against the exercise workload (watts) for each subject. The estimated oxygen consumption (or METs) at the first breakpoint of the lactate concentration was used as the value of the lactate threshold (LT). The LT is a reliable indicator of aerobic fitness that is in no way inferior to the VO2 max (20, 21) and can be simply and precisely measured during a graded exercise test using a portable lactate analyzer (22). Additionally, VO2 max was estimated according to the age-predicted maximum heart rate (220 minus age in years) (17, 18). The estimated VO2 max data were not available in two subjects (one subject in the Gly/Ser group and one subject in the Ser/Ser group) due to a malfunction in the sensor attached to the earlobe used to measure the heart rate.

**Genotyping of gene variants**

Genomic DNA was extracted from saliva (2 mL) collected from each subject using the Oragene DNA kit (DNA Genotek, Ottawa, Canada). The DNA was purified from 200-μL aliquots of the Oragene DNA/saliva samples according to the ethanol precipitation protocol supplied with the kit. The purified DNA was redissolved in 200 μL of Tris ethylenediaminetetraacetic acid buffer (10 mM Tris-HCl, 1 mM ethylenediaminetetraacetic acid, pH 8.0), and the PPARGC1A polymorphism (rs8192678) was analyzed based on a TaqMan® SNP Genotyping Assay (Assay ID: C___1643192_20, context sequence: AACCTGCTGGAGATCTTC TATTGAC[C/G]CAGAAACGGATCTCCACTGAC) using the StepOne Plus real-time PCR system (Applied Biosystems, Foster City, USA).

**Measurement of objective physical activity in daily life**

The level of daily physical activity was assessed using an uniaxial accelerometer (Lifecorder, Suzuken, Nagoya, Japan), as previously described (23). Briefly, the subjects were instructed to wear the accelerometer on their waist just above the midline of the thigh (right or left) during waking hours, except when bathing. After 10 days of continuous wear, the device was retrieved, and the data were downloaded into a computer and analyzed using the Microsoft Excel software program (Microsoft, Redmond, USA). In order to minimize any potential effect of wearing the device on the physical activity level and assess the degree of habitual physical activity in daily life, the data for the first three days were excluded. In addition, only data for the last seven days on which the accelerometer was worn for ≥28 h/day were used for the data analyses. The average (standard deviation) number of days of accelerometer data included in the current analysis was 5.7 (1.4). The physical activity level (PAL) was calculated as the total energy expenditure divided by the basal metabolic rate.

**Questionnaire survey and blood sampling/analysis**

Each subject’s history of lifestyle-related diseases (cerebrovascular, myocardial infarction or kidney disease), use of medications (for type 2 diabetes, hypertension or dyslipidemia) and lifestyle factors, including smoking, alcohol drinking and regular exercise, were evaluated using a questionnaire. Smoking was categorized as never/former (non-smoker or ≥1 month after abstaining from smoking) or current (current smoker or <1 month after abstaining from smoking). Drinking was categorized as never (0 day/week), sometimes (1-6 days/week) or every day (7 days/week). A habit of regular exercise sweating lightly (≥30 min/day, ≥2 days/week for ≥1 year) was categorized as yes or no.

For the biochemical tests, blood samples were obtained from the antecubital vein after an overnight fast. The serum uric acid level was determined according to the uricase peroxidase method. The total cholesterol (TC) and triglyceride levels were measured enzymatically, and the HDL-C and low-density lipoprotein cholesterol (LDL-C) levels were measured directly. The HbA1c level was measured according to a latex aggregation immunoassay (JDS value) and estimated as the NGSP equivalent value calculated using the following formula: HbA1c [NGSP (%)] = 1.02 × HbA1c [JDS (%)] + 0.25% (24, 25). The ratio of triglycerides to HDL-C (triglycerides/HDL-C) was used as a surrogate estimate of insulin resistance (26).

Metabolic syndrome was defined according to the guidelines for diagnosis used in Japan (27), in which Japanese men with abdominal obesity (waist circumference ≥85 cm) are defined as having metabolic syndrome if they additionally meet at least two of the following three components: 1) dyslipidemia (triglycerides ≥150 mg/dL and/or HDL-C <40 mg/dL), 2) high blood pressure (systolic/diastolic blood pressure ≥130/85 mmHg) and 3) high blood glucose (fasting plasma glucose ≥110 mg/dL) (note that this definition of metabolic syndrome is not exactly the same as the criteria for participation in the Specific Health Guidance program).

**Statistical analysis**

The values are presented as the mean ± standard deviation for continuous variables and n (%) for categorical variables,
Table. Characteristics of the Subjects According to PPARGC1A Gly482Ser Genotype

<table>
<thead>
<tr>
<th>Middle-aged Japanese men (n=112)</th>
<th>Gly/Gly</th>
<th>Gly/Ser</th>
<th>Ser/Ser</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>32 (28.6)</td>
<td>58 (51.8)</td>
<td>22 (19.6)</td>
<td>–</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.2±3.5</td>
<td>47.5±4.1</td>
<td>47.6±5.1</td>
<td>0.298</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.9±2.7</td>
<td>25.6±2.3</td>
<td>25.4±2.1</td>
<td>0.734</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>90.4±5.9</td>
<td>89.6±5.3</td>
<td>89.8±5.4</td>
<td>0.793</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>121.6±10.9</td>
<td>126.7±10.2</td>
<td>123.0±12.1</td>
<td>0.079</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80.8±9.7</td>
<td>82.5±8.2</td>
<td>82.8±8.2</td>
<td>0.629</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>100.3±13.3</td>
<td>100.5±9.8</td>
<td>98.2±8.0</td>
<td>0.688</td>
</tr>
<tr>
<td>HbA1c (JDS) (%)</td>
<td>5.2±0.6</td>
<td>5.1±0.4</td>
<td>5.0±0.2</td>
<td>0.452</td>
</tr>
<tr>
<td>HbA1c (NGSP) (%)</td>
<td>5.5±0.6</td>
<td>5.5±0.4</td>
<td>5.4±0.2</td>
<td>0.452</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>142.7±59.4</td>
<td>168.4±144.6</td>
<td>141.9±87.8</td>
<td>0.495</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>49.0±10.6</td>
<td>49.5±11.1</td>
<td>52.8±13.9</td>
<td>0.447</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>132.9±27.1</td>
<td>132.3±27.7</td>
<td>134.8±26.7</td>
<td>0.933</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>206.8±27.8</td>
<td>214.4±31.0</td>
<td>217.0±33.4</td>
<td>0.410</td>
</tr>
<tr>
<td>Serum uric acid (mg/dL)</td>
<td>6.5±1.2</td>
<td>6.2±1.1</td>
<td>6.2±1.2</td>
<td>0.588</td>
</tr>
<tr>
<td>Triglycerides/HDL-C</td>
<td>3.12±1.59</td>
<td>3.84±4.14</td>
<td>2.82±1.62</td>
<td>0.361</td>
</tr>
<tr>
<td>Metabolic syndrome, n (%)</td>
<td>6 (18.8)</td>
<td>13 (22.4)</td>
<td>4 (18.2)</td>
<td>0.878</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td>12 (37.5)</td>
<td>19 (32.8)</td>
<td>9 (40.9)</td>
<td>0.771</td>
</tr>
<tr>
<td>Alcohol drinking, n (%)</td>
<td>20 (62.5)</td>
<td>39 (67.2)</td>
<td>13 (59.1)</td>
<td></td>
</tr>
<tr>
<td>Never or former</td>
<td>16 (50.0)</td>
<td>28 (48.3)</td>
<td>6 (27.3)</td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td>12 (37.5)</td>
<td>22 (37.9)</td>
<td>11 (50.0)</td>
<td>0.175</td>
</tr>
<tr>
<td>Every day</td>
<td>4 (12.5)</td>
<td>8 (13.8)</td>
<td>5 (22.7)</td>
<td></td>
</tr>
<tr>
<td>Habit of regular exercise, n (%)</td>
<td>2 (6.3)</td>
<td>12 (20.7)</td>
<td>6 (27.3)</td>
<td>0.103</td>
</tr>
<tr>
<td>Number of steps (counts/day)</td>
<td>9,757±3,535</td>
<td>10,928±3,195</td>
<td>9,787±3,486</td>
<td>0.193</td>
</tr>
<tr>
<td>Total energy expenditure (kcal/day)</td>
<td>2,327±176</td>
<td>2,374±195</td>
<td>2,314±153</td>
<td>0.311</td>
</tr>
<tr>
<td>PAL</td>
<td>1.49±0.09</td>
<td>1.53±0.08</td>
<td>1.51±0.09</td>
<td>0.075</td>
</tr>
<tr>
<td>VO₂ max (mL/kg/min)</td>
<td>34.7±5.4</td>
<td>35.0±5.1</td>
<td>34.6±5.3</td>
<td>0.939</td>
</tr>
<tr>
<td>LT (METs)</td>
<td>4.53±0.51</td>
<td>4.79±0.56</td>
<td>4.92±0.54</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Values are means ± SD for continuous variables and n (%) for categorical variables. BMI: body mass index, HbA1c: hemoglobin A1c, JDS: Japan Diabetes Society, NGSP: National Glycohemoglobin Standardization Program, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol, PAL: physical activity level, LT: lactate threshold, METs: metabolic equivalents. VO₂ max data were missing in 1 subject in Gly/Ser genotype group and 1 subject in Ser/Ser genotype group.

The genotype distribution of the PPARGC1A Gly482Ser polymorphism (rs8192678) in the present subjects did not deviate from the Hardy-Weinberg equilibrium (p>0.05). This genotype distribution was confirmed to be similar to the data for Japanese populations reported in the public database for dbSNP [HapMap-JPT G/G (Gly/Gly): 26.7%; G/A (Gly/Ser): 55.6%; A/A (Ser/Ser): 17.8%]. As shown in Table, the data for age, anthropometric indices (BMI and waist circumference), blood pressure (systolic and diastolic), biochemical variables (fasting glucose, HbA1c, triglycerides, HDL-C, LDL-C, TC, serum uric acid and triglycerides/HDL-C) and lifestyle factors (cigarette smoking, alcohol drinking, step count, total energy expenditure, PAL and regular exercise) did not differ significantly according to the Gly482Ser genotype. The rate of metabolic syndrome was also similar between the genotype groups. Regardless of the genotype, the present subjects were relatively unfit, with a mean VO₂ max of only 35 mL/kg/min or mean LT of less than 5 METs.

A significant association was observed between the PPARGC1A Gly482Ser polymorphism and the LT, as the

The characteristics of the subjects are shown in Table.

Results

The characteristics of the subjects are shown in Table.
Ser482 carriers had higher LT values than the Gly482 carriers (p trend=0.026, Fig. 1). The ANCOVA showed the difference in LT between the subjects with the Gly/Gly and Gly/Ser genotypes to be marginal (p=0.052), whereas the differences between the subjects with the Gly/Gly and Ser/Ser genotypes was statistically significant (p=0.032). On the other hand, the estimated VO2 max levels were similar among the genotype groups (p trend=0.587, Fig. 2). Similarly, the ANCOVA showed no statistically significant differences in the VO2 max levels between the Gly/Gly and Gly/Ser groups (p=0.738) or between the Gly/Gly and Ser/Ser groups (p=0.760).

Discussion

To our knowledge, the current study is the first study to investigate the association between the PPARGC1A Gly482Ser polymorphism and aerobic capacity in a Japanese population. We found that the Ser482 carriers had higher levels of aerobic capacity (as assessed according to the LT) than the Gly482 carriers among Japanese middle-aged men. The major strengths of the present study include: 1) adjustment for the potential influence of critical confounding factors of habitual physical activity in order to examine whether the Gly482Ser polymorphism is associated with aerobic fitness independent of habitual physical activity and 2) an investigation of a Japanese population, which has not been conducted. Our findings are unexpected, as several previous studies have reported that the opposite allele of Gly482 is favorable for exceptional endurance performance (8-11).

A possible reason for the inconsistency in results between previous and the current study may be differences in the levels of cardiorespiratory fitness of the study subjects. In addition to the above-mentioned reports of top-level Caucasian athletes, previous studies have demonstrated no effects of the PPARGC1A Gly482Ser polymorphism on aerobic capacity (VO2 max) in German or Dutch individuals with relatively higher VO2 max values (42-43 mL/kg lean body mass/min) (15). Similarly, the Gly482Ser polymorphism is not associated with the VO2 max at baseline or after training in Chinese men with high levels of baseline aerobic fitness (VO2 max: 55-60 mL/kg/min) (13). On the other hand, the mean VO2 max in the current subjects was estimated to be approximately 35 mL/kg/min (as shown in Table), which is far lower than that reported in the above-mentioned previous studies. Franks et al. (28) showed that Ser482 allele carriers exhibit superior health benefits in increasing the VO2 max values when engaging in a physically active lifestyle compared to Gly482 allele carriers; the participants in that study were also unfit middle-aged adults (average VO2 max: 28.2 mL/kg/min). Therefore, the favorable impact of the Ser482 allele on aerobic fitness may be observed only in relatively unfit middle-aged individuals, whose level of aerobic fitness is assumed to be less affected by regular exercise training and/or a high frequency of habitual physical activity.

Cell culture studies using PPARGC1A-expression plasmids bearing glycine or serine at position 482 have directly demonstrated the effects of the Gly482Ser polymorphism on the functional activity of PPARGC1A proteins. Choi et
al. (29) showed the PPARGC1A Ser482 variant to be more efficient than the Gly482 variant as a coactivator on the promoter of mitochondrial transcription factor A, a direct controller of mitochondrial biogenesis. In that study, the Korean subjects with a Gly/Ser or Ser/Ser status had a higher mitochondrial DNA content than those with a Gly/Gly status (29). It is well known that aerobic capacity is crucially dependent on the muscle mitochondrial function (7). Therefore, similar to the Korean subjects in the above study, the Ser482 allele carriers among the current Japanese participants may have had a higher mitochondrial DNA content linked to their higher aerobic capacity.

In the current study, the PPARGC1A Gly/Ser polymorphism had an impact on the LT values, whereas no such influence was observed on the VO2 max values. Although the LT is a superior index of aerobic capacity, similar to the VO2 max, it is not synonymous with the VO2 max. It is thought that the VO2 max is primarily limited by the capacity for oxygen delivery (or central factors), not the ability of the mitochondria to consume oxygen in the skeletal muscle (or peripheral factors), whereas the LT is considered primarily to reflect the latter peripheral mitochondrial function (30). Consistently, our previous work showed that moderate exercise training enhances the expression levels of a number of muscle genes encoding mitochondrial enzymes and concomitantly increases the LT, but not VO2 max, after training (31). As mentioned in the introduction, PPARGC1A is a key gene regulating mitochondrial biogenesis and oxidative phosphorylation in the muscle (6); therefore, it is conceivable that the LT, rather than the VO2 max, is subject to PPARGC1A Gly/Ser polymorphism. The present observations regarding the VO2 max are in agreement with the findings of previous studies showing no influence of the Gly/Ser polymorphism on aerobic capacity, as assessed according to the VO2 max only (13, 15).

Additionally, other researchers have shown that, among non-diabetic Pima Indians, PPARGC1A Ser482 allele carriers displayed increased lipid oxidation, lower plasma free fatty acid levels and smaller adipocytes (32). It has also been demonstrated that increased fat oxidation due to physical activity is associated with higher insulin sensitivity in individuals with obesity (33). Consistently, endurance training has been reported to be associated with the characteristic features of increased lipid oxidation (33), low plasma free fatty acids (34) and a decreased adipocyte size (35, 36). Therefore, we speculate that the current PPARGC1A Ser482 carriers may have had higher levels of lipid oxidation and consequent enhanced lipid oxidation, which would have contributed to their higher levels of aerobic capacity.

Previous reports of the effects of the PPARGC1A Gly482Ser polymorphism on lifestyle-related diseases are inconsistent. Among Korean and Pima Indian populations, the Gly482Ser polymorphism is not associated with either obesity or type 2 diabetes (29, 32). However, other studies of subjects with type 2 diabetes have suggested that the Ser482 allele is a risk allele in Danish, Chinese and Japanese populations (37-39). Since a lower level of aerobic fitness is associated with increased susceptibility to type 2 diabetes (40), these previous findings are inconsistent with the present results.

We considered ethnic differences as one possible reason for the inconsistency in results between reports. However, Hara et al. (38) showed that subjects carrying the Ser/Ser genotype have higher levels of insulin resistance, as assessed according to the homeostasis model assessment of insulin resistance (HOMA-IR), among non-diabetic Japanese patients. Simultaneously, that study showed no differences in genotype distribution between the type 2 diabetic and non-diabetic subjects according to the Gly482Ser polymorphism (38). As mentioned by the authors, results obtained using the HOMA-IR (as a convenient approximation calculated simply based on the levels of fasting glucose and insulin) should be interpreted with caution until confirmed with a euglycemic clamp (38). Moreover, another study reported that non-diabetic subjects carrying the Ser allele display a higher insulin secretory response to glucose, despite that the fact that the insulin sensitivity values measured using a euglycemic clamp did not differ between the Gly/Gly carriers and the Ser allele (Gly/Ser+Gly/Ser) carriers (32). Since the Gly482Ser polymorphism may affect insulin secretion, measurements of the HOMA-IR, which is a function of the insulin concentration, may not be appropriate for examining the effects of this polymorphism on insulin sensitivity. We attempted to use the ratio of triglycerides to HDL-C (tri-glycerides/HDL-C) as a surrogate estimate of insulin resistance independently calculated based on the fasting insulin level; however, the triglycerides/HDL-C ratios did not differ significantly among the Gly482Ser genotype groups, as shown in Table. Since this ratio is also an indirect estimate of insulin resistance based on lipid metabolism (26), additional research investigating the influence of the PPARGC1A Gly482Ser polymorphism on insulin sensitivity, as assessed directly with a euglycemic clamp, in a Japanese population is warranted.

There are also reports showing that the Ser482 allele has a favorable effect in preventing cardiovascular diseases. For instance, the PPARGC1A Ser482 allele is associated with a reduced risk of hypertension in the Danish population (41). Similarly, the Ser482 allele is associated with a decreased risk of diastolic left ventricular dysfunction in Swedish men (42). These previous studies support the conclusions of the current study that a higher level of aerobic fitness is associated with reduced cardiovascular disease mortality (4).

It is also unclear at present whether ethnicity modifies the impact of the PPARGC1A Gly482Ser polymorphism on physical fitness. The current study is not likely alone in showing that the influence of gene polymorphisms on aerobic capacity is opposite between Caucasians and Japanese. The I allele of the ACE gene I/D polymorphism has been demonstrated to be favorable for enhanced performance in endurance sports athletes among Caucasians, such as British mountaineers (43) and Australian and Polish row-
ers (44, 45). In contrast, the D allele has been reported to be associated with enhanced performance among long distance running Japanese runners (16). In that study, all elite Japanese runners who had completed a marathon within two hours and 10 minutes were either D/D or I/D carriers (16), demonstrating that the impact of the ACE gene I/D polymorphism on the endurance capacity is opposite in Japanese and Caucasians. Hence, the effects of gene polymorphisms on physical fitness are not necessarily the same in all ethnic groups, although the underlying mechanisms remain to be clarified.

In conclusion, the current results suggest that the PPARGC1A Ser482 allele may be associated with higher aerobic capacity in Japanese middle-aged men. Further studies are needed to understand the precise mechanisms underlying this association. Additionally, the current cohort included only middle-aged Japanese men, and the relatively small sample size is a potential concern. Therefore, further research is also needed to examine whether similar associations are observed in larger samples of Japanese subjects with various characteristics, such as middle-aged women and elderly individuals.

Author’s disclosure of potential Conflicts of Interest (COI).
Minako Iyadomi: Leadership position, SUMCO Corporation

Financial Support
This work was partially supported by grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology (No. 19200049, Strategic Research Infrastructure) and the Global FU Program, funded by Fukuoka University.

References
29. Choi YS, Hong JM, Lim S, et al. Impaired coactivator activity of the Gly482 variant of peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) on mitochondrial transcription factor A

© 2015 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html