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## The *PPARGC1A* gene Gly482Ser in Polish and Russian athletes

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### Abstract

Peroxisome proliferator-activated receptor gamma coactivator-1-alpha (PGC-1 $\alpha$ ; encoded by the gene *PPARGC1A* in humans) is a crucial component in training-induced muscle adaptation because it is a co-activator of transcriptional factors that control gene expression in coordinated response to exercise. It has been suggested that a Gly482Ser substitution in *PPARGC1A* has functional relevance in the context of human disorders and athletic performance. To test this hypothesis, we examined the genotype distribution of *PPARGC1A* Gly482Ser in a group of Polish athletes and confirmed the results obtained in a replication study of Russian athletes. We found that the 482Ser allele was under-represented in the cohort of Polish and Russian athletes examined compared with unfit controls ( $P < 0.0001$ ). A statistically significant low frequency of the 482Ser allele was observed among the *endurance*, *strength-endurance*, and *sprint-strength* groups of Polish athletes ( $P = 0.019$ ,  $P = 0.022$ , and  $P < 0.0001$ , respectively). The replication study revealed that the 482Ser allele was also less prevalent in Russian *endurance* and *strength-endurance* athletes ( $P = 0.029$  and  $P < 0.0001$ , respectively). Our results suggest that the *PPARGC1A* Gly482Ser polymorphism is associated with elite endurance athletic status. These findings support the hypothesis that the *PPARGC1A* 482Ser allele may impair aerobic capacity: thus, the Gly482 allele may be considered a beneficial factor for endurance performance.

**Keywords:** *PPARGC1A*, Gly482Ser, athletic performance

### Introduction

Endurance training is known to induce many adaptations in the body, including improving skeletal muscle fatty acid oxidation capacity and insulin sensitivity. The plasticity of these adaptations is influenced, at least in part, by genetic components. The molecular basis of the adaptive response to endurance training involves changes in the expression of specific genes; these changes lead to an increase in mitochondrial biogenesis with parallel increases in mitochondrial enzyme activity and, consequently, more oxidative muscle fibres and enhanced capillarization.

The coordinated changes in gene expression in response to endurance exercise are regulated by transcriptional factors and co-activators. Peroxisome proliferator-activated receptor gamma co-activator-1-alpha (PGC-1 $\alpha$ ; encoded by the gene *PPARGC1A* in humans and by *PGC-1 $\alpha$*  in rodents) is a crucial component in training-induced muscle adaptation

because it is a co-activator of a broad range of transcriptional factors that control a wide variety of biological responses (Lin, Handschin, & Spiegelman, 2005). This transcriptional co-activator has been called “cold-inducible” because its expression was found to be greatly elevated in both brown fat and skeletal muscle of mice upon cold exposure (Puigserver et al., 1998). Subsequent studies revealed that in humans, *PPARGC1A* mRNA is highly expressed in heart, skeletal muscle, and kidney tissues; it is also expressed in the liver, but to a slightly lesser extent and to an even lower extent in white adipose tissue, pancreas, and brain (Esterbauer, Oberkofler, Krempler, & Patsch, 1999). There is strong evidence that endurance training increases *PPARGC1A* mRNA levels in skeletal muscle, causing improvements in oxidative capacity (Kramer et al., 2006; Mathai, Bonen, Benton, Robinson, & Graham, 2008; Norrbom et al., 2004; Pilegaard, Saltin, & Neufer, 2003; Russell et al., 2003; Short et al., 2003; Tunstall et al., 2002) and promoting an adaptive transformation of

muscle fibre from glycolytic type IIb to the more mitochondria-rich types IIa and I, which primarily utilize oxidative metabolism (Lin et al., 2002). On the molecular level, the changes in the muscle metabolic profile caused by high *PPARGC1A* expression involve not only the conversion of muscle fibre types but also the control of energy substrate utilization pathways such as fatty acid oxidation, the tricarboxylic acid cycle (TCA) and glucose transportation, as well as a broad programme of oxidative phosphorylation up-regulation and mitochondrial biogenesis. The oxidative modification of muscle phenotype requires not only the regulation of energy substrate utilization and control of oxidative metabolism but also enhanced capillarization.

The *PPARGC1A* gene has been of special interest to molecular biologists ever since the cDNA encoding the *PGC-1 $\alpha$*  gene was cloned from murine brown adipose tissue by Puigserver and colleagues in 1998. The human cDNA sequence, genomic organization, and chromosomal location of *PPARGC1A* were described by Esterbauer and colleagues one year later (Esterbauer et al., 1999). Many studies have since revealed that several amino acid polymorphic sites exist within the coding region of *PPARGC1A*, including the frequent substitution (rs8192678) Gly482Ser (alone or in haplotype combination with other *PPARGC1A* polymorphic sites), which has been reported to have functional relevance because this single nucleotide polymorphism has been associated with important human disorders. Carriers of the 482Ser allele have been shown to display a higher genotype-relative risk of type II diabetes (Andrulionyte, Peltola, Chiasson, & Laakso, 2006; Ek et al., 2001; Kunej, Globocnik Petrovic, Dovc, Peterlin, & Petrovic, 2004), decreased *PPARGC1A* mRNA levels and reduced insulin secretion in pancreatic islets (Ling et al., 2004, 2008), higher blood pressure in younger adults (Vimaleswaran et al., 2008), altered lipid metabolism and susceptibility to obesity (Esterbauer et al., 2002; Franks et al., 2007). On the other hand, the 482Ser allele was associated with decreased hypertension in a Danish population (Andersen et al., 2005) and a decreased risk of diastolic left ventricular dysfunction in Swedish men, but not in women (Ingelsson et al., 2008).

The *PPARGC1A* gene has also been the subject of several studies looking for associations between genotypes and athletic performance. Lucia et al. (2005) were the first to test the hypothesis that the minor 482Ser allele of *PPARGC1A* is less frequent in world-class endurance athletes. The authors reported that the 482Ser allele was less prevalent in a group of athletes compared with unfit controls and suggested that *PPARGC1A* may be one of the genetic factors that affect aerobic capacity. Further-

more, because it is associated with a predisposition to low cardiorespiratory fitness, the 482Ser allele could be regarded as a risk factor for individuals such as sedentary diabetics (Lucia et al., 2005). A study of the effectiveness of aerobic exercise training in participants in the Tuebingen Lifestyle Intervention Program also revealed that 482Ser carriers displayed low aerobic physical fitness (Stefan et al., 2007). In addition, the 482Ser allele has been reported to be associated with lower aerobic capacity in Russian rowers (Ahmetov et al., 2007). These results are in accordance with those of association studies by Eynon et al. (2009a, 2009b), who found a significantly lower proportion of the *PPARGC1A* 482Ser allele in a group of Israeli endurance athletes. However, in a study of a non-diabetic German and Dutch population, Gly482 and 482Ser variants in *PPARGC1A* were not associated with diabetes-related traits or skeletal muscle fibre type composition, and maximum oxygen uptake ( $\dot{V}O_{2\max}$ ) was similar between the *PPARGC1A* genotype groups (Stumvoll et al., 2004). Similarly, no association was detected between Gly482Ser variants and  $\dot{V}O_{2\max}$  in a northern Chinese population (He et al., 2008).

This discrepancy raises the question of whether *PPARGC1A* Gly482 and 482Ser variants are indeed genetic factors that can influence physical performance. To test this hypothesis, we examined the genotype distribution of *PPARGC1A* Gly482Ser in a group of Polish athletes. The athletes were divided into four groups, from the more endurance-oriented to the more strength-oriented, according to the following values: relative aerobic/anaerobic energy system contribution, time of competitive exercise performance, and intensity of exertion in each sport. To test the findings of this initial research, the same analyses were performed in an independent population of Russian athletes in a replication study.

## Methods

### Participants

The initial association study was undertaken with a group of 302 Polish athletes (221 males and 81 females, age  $27.8 \pm 7.1$  years) of the highest national competitive standard. The athletes were prospectively stratified into four groups based on their relative aerobic/anaerobic energy system contribution, time of competitive exercise performance, and intensity of exertion in each sport. The first group, designated as *endurance* athletes, consisted of individuals ( $n=26$ ) with predominantly aerobic energy production (duration of exertion over 30 min and a moderate intensity of exertion). This group included triathletes ( $n=4$ ), race walkers ( $n=6$ ), road cyclists ( $n=14$ ), and 15–50 km

cross-country skiers ( $n=2$ ). The second group, designated as *strength-endurance* athletes ( $n=66$ ), comprised athletes whose sports utilize a mixed anaerobic/aerobic energy production (duration of exertion ranging from 5 to 30 min and a moderate to high intensity of exertion). This group included rowers ( $n=41$ ), 3–10 km runners ( $n=17$ ), and 800–1500 m swimmers ( $n=8$ ). The third group, the *sprint-strength* athletes ( $n=110$ ), also included athletes with mixed energy production, but compared with the second group their competitive exercise time was shorter (1–5 min; in the case of combat sports, the duration of a single bout of competition was taken into account), while the intensity of exertion was higher and the balance between anaerobic/aerobic energy production was shifted towards the anaerobic system. This group comprised kayakers ( $n=10$ ), 800–1500 m runners ( $n=7$ ), 200–400 m swimmers ( $n=3$ ), judokas ( $n=13$ ), wrestlers ( $n=41$ ), boxers ( $n=19$ ), and fencers ( $n=17$ ). The fourth group, the *strength* athletes, consisted of individuals ( $n=100$ ) with predominant anaerobic energy production (duration of exertion  $<1$  min and intensity of exertion submaximal to maximal). This group was made up of 100–400 m runners ( $n=29$ ), powerlifters ( $n=22$ ), weightlifters ( $n=20$ ), throwers ( $n=14$ ), and jumpers ( $n=15$ ).

All the Polish athletes recruited for this study were ranked in the top 10 nationally in their sport discipline. The study population included 63 athletes classified as “top-elite” (gold medallist at the World and European Championships, World Cups or Olympic Games) and 149 athletes classified as “elite” (silver or bronze medallist in the World and European Championships, World Cups or Olympic Games). The others ( $n=90$ ) were classified as “sub-elite” (participants in international competitions). Various methods were used to obtain the samples, including targeting of national teams and providing information to national coaching staff and athletes attending training camps.

Control groups were recruited from 684 unrelated sedentary volunteers (students of the University of Szczecin, aged 19–23 years). All athletes and controls were Caucasian to reduce the possibility of racial gene skew and to overcome any potential problems due to population stratification. The procedures of the study received approval from the Pomeranian Medical University Ethics Committee. All participants provided informed consent for genotyping based on the understanding that it would be anonymous and the results would be treated as confidential.

The replication study was conducted with 1303 Russian athletes (888 males and 415 females, age  $24.4 \pm 0.3$  years) of regional and national competitive standard. The athletes were divided into four

groups according to the parameters established for the initial association study. The group of *endurance* athletes ( $n=352$ ) included biathletes ( $n=29$ ), triathletes ( $n=29$ ), race walkers ( $n=23$ ), road cyclists ( $n=108$ ), 5–10 km cross-country skiers ( $n=64$ ), 15–50 km cross-country skiers ( $n=78$ ), and very long-distance (5–25 km) swimmers ( $n=21$ ). The group of *strength-endurance* athletes ( $n=227$ ) consisted of rowers ( $n=191$ ), 3–10 km runners ( $n=5$ ), 800–1500 m swimmers ( $n=26$ ), and 5–10 km skaters ( $n=5$ ). The group of *sprint-strength* athletes ( $n=311$ ) was composed of kayakers ( $n=33$ ), 800–1500 m runners ( $n=7$ ), 200–400 m swimmers ( $n=24$ ), 1–3 km skaters ( $n=52$ ), boxers ( $n=30$ ), wrestlers ( $n=96$ ), alpine skiers ( $n=13$ ), and artistic gymnasts ( $n=56$ ). The group of *strength* athletes ( $n=413$ ) consisted of 100–400 m runners ( $n=122$ ), 500–1000 m skaters ( $n=52$ ), 50–100 m swimmers ( $n=35$ ), powerlifters ( $n=26$ ), weightlifters ( $n=61$ ), bodybuilders ( $n=74$ ), throwers ( $n=17$ ), jumpers ( $n=12$ ), and ski jumpers ( $n=14$ ). Altogether, 235 of the Russian athletes were classified as “elite” (ranked in the top 10 nationally), of whom 58 were “top-elite” athletes (medal winners at World and European Championships, World Cups or Olympic Games). A further 404 athletes were classified as “sub-elite” (participants in international competitions). The others ( $n=664$ ) were classified as “non-elite” athletes, all regional competitors with no less than 4 years experience participating in their sports.

The Russian controls were 1132 healthy unrelated citizens of St. Petersburg, Moscow, Naberezhniye Chelny, and Surgut (537 males and 595 females, age  $17.2 \pm 0.2$  years) without any competitive sport experience. The geographic ancestry of the athletes and control groups was self-reported. The athletes and control groups were all Caucasian: 89.3% of athletes and 84.5% of controls were Russian, while other frequently reported nationalities included Tatar and Ukrainian. The University of St. Petersburg Ethics Committee approved the study, and written informed consent was obtained from each participant.

### Genetic analyses

*Polish study.* The buccal cells donated by the participants were collected in Resuspension Solution (GenElute Mammalian Genomic DNA Miniprep Kit, Sigma, Germany) with the use of sterile foam-tipped applicators (Puritan, USA). DNA was extracted from the buccal cells using a GenElute Mammalian Genomic DNA Miniprep Kit (Sigma, Germany) according to the manufacturer’s protocol. All samples were genotyped using an allelic discrimination assay on a Rotor-Gene real-time polymerase chain reaction (PCR) instrument (Corbett,

Australia) with Taqman<sup>®</sup> probes. For the discrimination of *PPARGC1A* Gly482 and 482Ser alleles (rs8192678), a TaqMan<sup>®</sup> Pre-Designed SNP Genotyping Assay was used (Applied Biosystems, USA) (assay ID: C\_1643192\_20), including primers and fluorescently labelled (FAM and VIC) MGB<sup>™</sup> probes for the detection of both alleles.

**Russian study.** Genotyping was performed on DNA samples obtained from epithelial mouth cells by alkaline extraction (Bolla, Haddad, Humphries, Winder, & Day, 1995) or with a DNK-sorb-A sorbent kit according to the manufacturer's instructions (Central Research Institute of Epidemiology, Russia), depending on the method of sample collection (buccal swab or scrape). Genotyping for the *PPARGC1A* Gly482Ser polymorphism was performed by PCR and restriction enzyme digestion. The PCR primers used were 5'-GAGCCGAGCTG AACAAAGCAC-3' (forward) and 5'-GGAGACACA TTGAACAATGAATAGGATTG-3' (reverse), generating a fragment of 238 bp. The PCR products were digested with *MspI* (SibEnzyme, Russia) for 12 h at 37°C and were then separated by 8% polyacrylamide gel electrophoresis, stained with ethidium bromide, and visualized in UV light.

#### Statistical analysis

The STATISTICA software package, version 7.0, was used to perform all statistical evaluations. Allele frequencies were determined by gene counting. A  $\chi^2$  test (for large groups) and  $\chi^2$  test with Yates correction (for small groups) were used to compare the *PPARGC1A* Gly482Ser alleles and genotype frequencies between athletes and controls. The odds were calculated according to Daly and colleagues (Daly, Bourke, & McGilvray, 1991). Statistical significance was set at  $P < 0.05$ .

#### Results

The results of the distribution of *PPARGC1A* Gly482 and 482Ser variants in Polish and Russian athletes versus controls are presented in Table I and Table II, respectively. In both athletes and controls, the Gly482Ser genotype met Hardy-Weinberg expectations ( $P > 0.05$  in all groups tested separately).

The initial association study conducted with the Polish athletes (Table I) revealed that the frequency of the minor 482Ser allele was significantly lower in all athletes than in controls (24.7% vs. 36.1%;  $P < 0.0001$ ). When considering the frequency of the 482Ser allele in the four groups of athletes separately, statistically significant differences were observed in the *endurance* athletes (19.2%;  $P = 0.019$ ), *strength-endurance* athletes (25.7%;  $P = 0.022$ ), and

*sprint-strength* athletes (20.4%;  $P < 0.0001$ ). Statistically significant differences in genotype distribution were observed in all athletes combined (Gly482/Gly482 56.3%, Gly482/482Ser 38.1%, and 482Ser/482Ser 5.6%;  $P < 0.0001$ ) as well as in the group of *endurance* athletes (Gly482/Gly482 65.4%, Gly482/482Ser 30.8%, and 482Ser/482Ser 3.8%;  $P = 0.038$ ) and group of *sprint-strength* athletes (Gly482/Gly482 62.7%, Gly482/482Ser 33.6%, and 482Ser/482Ser 3.7%;  $P = 0.0001$ ) compared with controls (Gly482/Gly482 40.9%, Gly482/482Ser 45.9%, and 482Ser/482Ser 13.2%). The frequencies of the *PPARGC1A* gene Gly482 allele were also analysed in the four groups of Polish athletes stratified by elite status. The lowest frequencies of the Gly482 allele were always observed in "sub-elite" athletes, regardless of the group analysed (Figure 1). In the group of Polish athletes, the odds ratio of the *PPARGC1A* 482Ser/482Ser genotype for each group of athletes was as follows: 0.26 for *endurance* athletes (95% confidence interval [CI] 0.03–1.97), 0.31 for *strength-endurance* athletes (95% CI 0.10–1.02), 0.24 for *sprint-strength* athletes (95% CI 0.09–0.69), and 0.65 for *strength* athletes (95% CI 0.32–1.34).

In the replication study (Table II), the differences in 482Ser allele frequencies between all Russian athletes combined and the controls remained significant (30.3% vs. 34.5%;  $P = 0.002$ ). Differences also remained significant in the *endurance* athlete and *strength-endurance* athlete groups, in which the allelic frequencies for the 482Ser variant were 30% ( $P = 0.029$ ) and 24.7% ( $P < 0.0001$ ), respectively. The genotype distributions of *PPARGC1A* Gly482Ser in all Russian athletes combined (Gly482/Gly482 47.8%, Gly482/482Ser 43.7%, and 482Ser/482Ser 8.5%;  $P = 0.004$ ) and in the *strength-endurance* group (Gly482/Gly482 55.1%, Gly482/482Ser 40.5%, and 482Ser/482Ser 4.4%;  $P = 0.0002$ ) were significantly different from the controls (Gly482/Gly482 43.2%, Gly482/482Ser 44.6%, and 482Ser/482Ser 12.2%). As in the initial study, the analysis of *PPARGC1A* gene Gly482 allele frequencies in the four groups of Russian athletes stratified by elite status revealed lower frequencies of the Gly482 allele in "sub-elite" and "non-elite" athletes (Figure 2). In the Russian athletes as a whole, the odds ratio of the *PPARGC1A* 482Ser/482Ser genotype for each group of athlete was as follows: 0.62 for *endurance* athletes (95% CI 0.41–0.95), 0.33 for *strength-endurance* athletes (95% CI 0.17–0.64), 0.88 for *sprint-strength* athletes (95% CI 0.59–1.32), and 0.75 for *strength* athletes (95% CI 0.52–1.09).

Taking the results of the initial and replication studies together (Table III), significant differences in the frequency of the 482Ser allele were found in the whole cohort of Polish and Russian athletes when compared with the controls (29.5% vs. 35.1%;

Table I. *PPARGC1A* genotype distribution and frequencies of *PPARGC1A* gene 482Ser allele in Polish athletes stratified by the relative aerobic/anaerobic energy system contribution, duration of competitive exercise performance, and intensity of exertion in each sport (Initial study).

Sport	n	Genotypes (n)			P	482Ser allele (%)	P
		Gly482/Gly482	Gly482/482Ser	482Ser/482Ser			
<b>1. Endurance athletes</b>							
Triathlon	4	4	0	0	0.057	0.0	0.079
Race walking	6	2	3	1	0.923	41.7	0.923
Road cycling	14	9	5	0	0.138	17.9	0.072
Cross-country skiing 15–50 km	2	2	0	0	0.238	0.0	0.327
<i>Total</i>	26	17	8	1	0.038*	19.2	0.019*
<b>2. Strength-endurance athletes</b>							
Rowing	41	22	17	2	0.153	25.6	0.070
Running 3–10 km	17	7	9	1	0.652	32.4	0.787
Swimming 800–500 m	8	6	2	0	0.133	12.5	0.090
<i>Total</i>	66	35	28	3	0.053	25.7	0.022*
<b>3. Sprint-strength athletes</b>							
Kayaking	10	9	1	0	0.007*	5.0	0.008*
Running 800–1500 m	7	5	2	0	0.230	14.3	0.157
Swimming 200–400 m	3	0	2	1	0.297	66.7	0.259
Judo	13	9	3	1	0.121	19.2	0.116
Wrestling	41	21	18	2	0.211	26.8	0.113
Boxing	19	12	7	0	0.081	18.4	0.038*
Fencing	17	13	4	0	0.011*	11.8	0.006*
<i>Total</i>	110	69	37	4	<0.0001*	20.4	<0.0001*
<b>4. Strength athletes</b>							
Running 100–400 m	29	18	8	3	0.074	24.1	0.084
Powerlifting	22	11	9	2	0.666	29.5	0.463
Weightlifting	20	12	5	3	0.163	27.5	0.341
Throwing events	14	4	10	0	0.117	35.7	0.965
Jumping events	15	4	10	1	0.276	40.0	0.805
<i>Total</i>	100	49	42	9	0.242	30.0	0.107
<b>All Polish athletes</b>	302	170	115	17	<0.0001*	24.7	<0.0001*
<b>Polish controls</b>	684	280	314	90	1.000	36.1	1.000

Note: P-values are calculated by  $\chi^2$  test for comparisons between groups of athletes and control group.

\*Statistically significant differences ( $P < 0.05$ ).

$P < 0.0001$ ). Of the four groups of athletes, the frequency of the 482Ser allele and the genotype distribution of *PPARGC1A* Gly482Ser only did not reach statistical significance in the strength athletes.

## Discussion

The present study demonstrates that the *PPARGC1A* gene Gly482Ser polymorphism is associated with elite athlete status. We found that the 482Ser allele was under-represented in the cohort of athletes examined compared with the sedentary controls. In the initial association study of Polish athletes, a statistically significant low frequency of the 482Ser allele was observed among the groups of athletes described as *sprint-strength*, *strength-endurance*, and *endurance*. These groups of athletes are characterized by an increased contribution of the aerobic system to the production of energy required for exertion. Among these three groups of Polish athletes, the lowest frequency of the 482Ser allele was observed in

the group of endurance athletes, for whom energy is generated mostly by aerobic metabolism. The findings of the initial study were confirmed by a replication study in a large group of Russian athletes. The replication study also determined that the 482Ser allele was less prevalent in the endurance and strength-endurance athletes compared with the controls, with the lowest frequency of the 482Ser allele being observed in the group of strength-endurance athletes.

The aerobic and anaerobic energy systems do not function independently of each other, as both are turned on at the beginning of exercise. Creatine phosphate and anaerobic glycolysis provide sufficient energy only for the first 20–30 s or so of exercise (Finn, Gastin, Withers, & Green, 2000); thus, the anaerobic system is considered to be essential for strength athletes (the fourth group in the present study), who perform sports that involve lifting, jumping, throwing, and short sprints. During prolonged exertion, the lactate produced during

Table II. *PPARGC1A* genotype distribution and frequencies of *PPARGC1A* gene 482Ser allele in Russian athletes stratified by the relative aerobic/anaerobic energy system contribution, duration of competitive exercise performance, and intensity of exertion in each sport (Replication study).

Sport	<i>n</i>	Genotypes ( <i>n</i> )			<i>P</i>	482Ser allele (%)	<i>P</i>
		Gly482/Gly482	Gly482/482Ser	482Ser/482Ser			
<b>1. Endurance athletes</b>							
Biathlon	29	16	12	1	0.246	24.1	0.133
Triathlon	29	16	11	2	0.392	25.9	0.219
Race walking	23	14	8	1	0.196	21.7	0.099
Road cycling	108	49	49	10	0.660	31.9	0.496
Cross-country skiing 5–10 km	64	28	32	4	0.333	31.3	0.511
Cross-country skiing 15–50 km	78	37	34	7	0.622	30.8	0.388
Swimming 5–25 km	21	9	9	3	0.956	35.7	0.999
<i>Total</i>	352	169	155	28	0.057	30.0	0.029*
<b>2. Strength-endurance athletes</b>							
Rowing	191	102	81	8	0.0012*	25.4	0.0006*
Running 3–10 km	5	2	3	0	0.642	30.0	0.765
Swimming 800–1500 m	26	18	7	1	0.027*	17.3	0.015*
Speed skating 5–10 km	5	3	1	1	0.535	30.0	0.765
<i>Total</i>	227	125	92	10	0.0002*	24.7	<0.0001*
<b>3. Sprint-strength athletes</b>							
Kayaking	33	18	13	2	0.342	25.8	0.179
Running 800–1500 m	7	3	4	0	0.577	28.6	0.855
Swimming 200–400 m	24	8	12	4	0.586	41.7	0.379
Speed skating 1–3 km	52	18	32	2	0.03*	34.6	0.980
Boxing	30	24	6	0	0.0002*	10.0	0.0001*
Wrestling	96	45	40	11	0.784	32.3	0.590
Alpine skiing	13	6	6	1	0.884	30.8	0.849
Artistic gymnastics	56	21	21	14	0.019*	43.6	0.045*
<i>Total</i>	311	143	134	34	0.643	32.5	0.371
<b>4. Strength athletes</b>							
Running 100–400 m	122	51	58	13	0.788	34.4	0.983
Speed skating 500–1000 m	52	25	22	5	0.739	30.8	0.498
Swimming 50–100 m	35	22	10	3	0.069	22.9	0.058
Powerlifting	26	11	12	3	0.986	34.6	0.986
Weightlifting	61	29	26	6	0.752	31.1	0.508
Bodybuilding	74	32	36	6	0.543	32.4	0.672
Throwing events	17	8	8	1	0.729	29.4	0.662
Jumping events	12	3	9	0	0.089	37.5	0.927
Ski jumping	14	5	7	2	0.852	39.3	0.742
<i>Total</i>	413	186	188	39	0.319	32.2	0.251
<b>All Russian athletes</b>	1303	623	569	111	0.004*	30.3	0.002*
<b>Russian controls</b>	1132	489	505	138	1.000	34.5	1.000

Note: *P*-values are calculated by  $\chi^2$  test for comparisons between groups of athletes and control group.

\*Statistically significant differences ( $P < 0.05$ ).

anaerobic glycolysis causes acidosis; thus, alternative fuel sources, such as glycogen and fatty acids, utilized in aerobic metabolism are needed. At the beginning of aerobic metabolism, when the main energy source is muscle glycogen (which is completely oxidized to CO<sub>2</sub> during the TCA cycle inside mitochondria), the intensity of ATP production increases rapidly. The aerobic system that utilizes glycogen turns on quickly and plays an important role in high-intensity endurance performance that is characteristic of strength-endurance athletes. The prolonged aerobic exertion experienced by endurance athletes is characterized by the precise selection of glycogen and fatty acids as energy sources and by

cooperation between muscle, liver, and adipose tissue energy stores. The glycogen stores in muscles and liver are insufficient to provide the ATP needed for endurance challenges (Shulman & Rothman, 2001). Much larger quantities of ATP can be obtained by the oxidation of fatty acids in adipose tissue; however, ATP generated in this way is produced much more slowly than ATP from phosphocreatine, which explains why these differences in the velocities of aerobic and anaerobic events are responsible for the variations in the intensity of exertion between strength and endurance competitions. Elite endurance athletes consume similar amounts of glycogen and fatty acids during

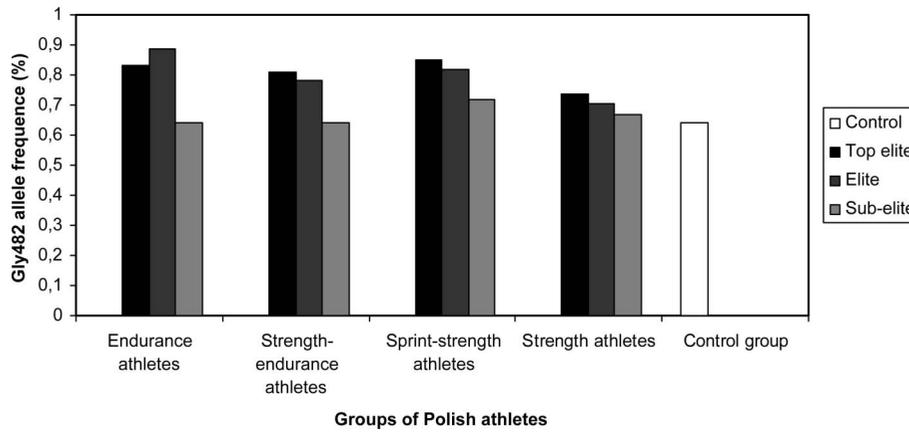


Figure 1. The frequencies of the *PPARGC1A* gene Gly482 allele in four groups of Polish athletes stratified by elite status and in the control group.

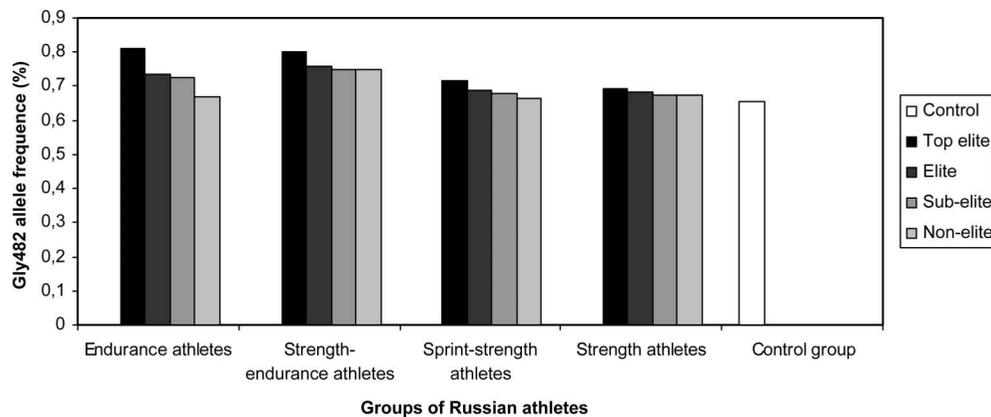


Figure 2. The frequencies of the *PPARGC1A* gene Gly482 allele in four groups of Russian athletes stratified by elite status and in the control group.

exercise (Holloszy & Kohrt, 1996). Such optimal use of these two energy sources is achieved by a high glucagon/insulin ratio (caused by low blood-sugar concentrations), which in turn mobilizes fatty acids from adipose tissue. Fatty acid oxidation decreases the use of glucose in the citric acid cycle so that just enough of it remains available at the end of exertion (Horowitz & Klein, 2000). The simultaneous use of both fuels ensures the maintenance of an appropriate level of metabolism and a constant high rate of ATP synthesis, which prevents interruptions in the energy supply when glycogen is consumed before fatty acid oxidation starts (Holloszy & Kohrt, 1996).

In general, our results indicate that the *PPARGC1A* Gly482 allele benefits athletes who are characterized by an increased contribution of the aerobic system to the production of energy required for exercise and is especially important for endurance-oriented athletes performing prolonged exertion. Our analysis of the frequencies of the *PPARGC1A* Gly482 allele in four groups of Polish and Russian athletes stratified by elite status showed that the lowest frequencies of the Gly482 allele were always

observed in “sub-elite”/“non-elite” athletes, regardless of the group analysed. Moreover, the Gly482 allele was over-represented in the cohort of athletes in the combined study compared with sedentary controls (70.5% vs. 64.9%). In this context, the 482Ser allele might be considered a disadvantageous factor for athletes who require moderate to high levels of oxidative metabolism in their muscles for a prolonged time. Similar results have been reported for groups of Spanish and Israeli athletes, suggesting that the *PPARGC1A* Gly482Ser polymorphism may play an important role in endurance performance because the 482Ser allele might impair aerobic capacity (Eynon et al., 2009a, 2009b; Lucia et al., 2005). In addition, in a study of Russian rowers, it was shown that the 482Ser allele was associated with lower aerobic capacity (Ahmetov et al., 2007). The correlation between the *PPARGC1A* Gly482Ser polymorphism and human aerobic capacity has also been observed in non-athletic individuals: the capacity of aerobic exercise training to increase aerobic fitness was found to be associated with the presence of a specific *PPARGC1A* Gly482 allele,

Table III. *PPARGC1A* genotype distribution and frequencies of *PPARGC1A* gene 482Ser allele in Polish and Russian athletes stratified by the relative aerobic/anaerobic energy system contribution, duration of competitive exercise performance, and intensity of exertion in each sport (Combined study).

Sport	<i>n</i>	Genotypes ( <i>n</i> )			<i>P</i>	482Ser allele (%)	<i>P</i>
		Gly482/Gly482	Gly482/482Ser	482Ser/482Ser			
<b>1. Endurance athletes</b>							
Biathlon	29	16	12	1	0.212	24.1	0.110
Triathlon	33	20	11	2	0.099	22.7	0.049*
Race walking	29	16	11	2	0.339	25.9	0.185
Road cycling	122	58	54	10	0.285	30.3	0.148
Cross-country skiing 5–10 km	64	28	32	4	0.309	31.3	0.421
Cross-country skiing 15–50 km	80	39	34	7	0.417	30.0	0.215
Swimming 5–25 km	21	9	9	3	0.964	35.7	0.934
<i>Total</i>	378	186	163	29	0.007*	29.2	0.002*
<b>2. Strength-endurance athletes</b>							
Rowing	232	124	98	10	0.00011*	25.4	<0.0001*
Running 3–10 km	22	9	12	1	0.459	31.8	0.768
Swimming 800–1500 m	34	24	9	1	0.004*	16.2	0.002*
Speed skating 5–10 km	5	3	1	1	0.526	30.0	0.995
<i>Total</i>	293	160	120	13	<0.0001*	24.9	<0.0001*
<b>3. Sprint-strength athletes</b>							
Kayaking	43	27	14	2	0.021*	20.9	0.009*
Running 800–1500 m	14	8	6	0	0.288	21.4	0.189
Swimming 200–400 m	27	8	14	5	0.361	44.4	0.200
Speed skating 1–3 km	52	18	32	2	0.033*	34.6	0.918
Judo	13	9	3	1	0.147	19.2	0.138
Wrestling	137	66	58	13	0.333	30.7	0.154
Boxing	49	36	13	0	<0.0001*	13.2	<0.0001*
Fencing	17	13	4	0	0.014*	11.8	0.008*
Alpine skiing	13	6	6	1	0.865	30.8	0.798
Artistic gymnastics	56	21	21	14	0.023*	43.8	0.074
<i>Total</i>	421	212	171	38	0.006*	29.3	0.002*
<b>4. Strength athletes</b>							
Running 100–400 m	151	69	66	16	0.651	32.4	0.386
Speed skating 500–1000 m	52	25	22	5	0.661	30.8	0.418
Swimming 50–100 m	35	22	10	3	0.052	22.9	0.045*
Powerlifting	48	22	21	5	0.850	32.3	0.644
Weightlifting	81	41	31	9	0.336	30.2	0.236
Bodybuilding	74	32	36	6	0.510	32.4	0.562
Throwing events	31	12	18	1	0.186	32.3	0.740
Jumping events	27	7	19	1	0.028*	38.9	0.664
Ski jumping	14	5	7	2	0.882	39.3	0.793
<i>Total</i>	513	235	230	48	0.102	31.8	0.052
<b>All Polish and Russian athletes</b>	1605	793	684	128	<0.0001*	29.5	<0.0001*
<b>Polish and Russian controls</b>	1816	769	819	228	1.000	35.1	1.000

Note: *P*-values are calculated by  $\chi^2$  test for comparisons between groups of athletes and control group.

\*Statistically significant differences ( $P < 0.05$ ).

indicating the relevance of the 482Ser allele in low aerobic physical fitness (Stefan et al., 2007). It is likely that in sedentary individuals, the *PPARGC1A* Gly482 allele is not a limiting factor necessary for a healthy state, but the presence of the *PPARGC1A* Gly482 allele may be essential for athletes because it enhances cardiorespiratory fitness. The results of this study suggest that the Gly482 allele is important for every athlete regardless of the type of exercise; however, it is particularly crucial for individuals characterized by an increased contribution of the

aerobic energy system for performing prolonged exertion of moderate to high intensity.

These results suggest that the presence of the *PPARGC1A* Gly482 allele may be a key element associated with the efficiency of aerobic metabolism in an individual. The physiological explanation for these observations is the role played by PGC-1 $\alpha$  in the coordination of energy metabolism, mitochondrial biogenesis, and mitochondrial regulation. PGC-1 $\alpha$  is an inducible transcriptional co-activator of numerous transcription factors. This protein is

involved in the regulation of many aspects of energy metabolism and mediates changes in multiple pathways in a coordinated response to physical training in tissues with high energy consumption, such as skeletal muscle, heart, brain, liver, kidney, pancreas, and adipose tissue (Esterbauer et al., 1999; Puigserver et al., 1998). The molecular mechanisms behind these exercise-induced adaptations in working skeletal muscle involve the PGC-1 $\alpha$ -mediated co-activation of many different regulatory proteins engaged in the control of energy substrate utilization, which, in turn, causes an up-regulation of oxidative metabolism and parallel changes in muscle fibre types. The transformation of a muscle fibre to the oxidative type is directly connected to an interaction between PGC-1 $\alpha$  and MEF2 (myocyte enhancer factor). In cooperation with the calcineurin signalling pathway, the PGC-1 $\alpha$ /MEF2 complex induces the expression of genes such as *MB* (myoglobin) and *TNNI1* (troponin I, slow skeletal muscle), which are specific for type I slow-twitch fibres (Lin et al., 2002). The training-induced activation of PGC-1 $\alpha$  can also induce increased levels of mRNA and/or proteins engaged in oxidative phosphorylation, such as mitochondrial respiratory chain proteins (including the nuclear-encoded cytochrome c oxidase subunit IV [*COX IV*] as well as the mitochondria-encoded cytochrome c oxidase subunit II [*COX II*] and cytochrome c [*CytC*] and  $\beta$ -ATP synthase (encoded by a nuclear gene) (Wu et al., 1999). Moreover, PGC-1 $\alpha$  has been shown to be a regulator of the expression of the mitochondrial enzyme aminolevulinic acid synthase (*ALAS1*), which is a rate-limiting factor in heme production for the cytochromes (Handschin et al., 2007). PGC-1 $\alpha$  is found exclusively in the cell nucleus and can affect the transcription and replication of mitochondrial genes through co-activation of the transcription factors NRF1 and NRF2 (nuclear respiratory factor 1 and 2), which directly regulate the expression of mitochondrial transcription factor A (*TFAM*). *TFAM* is a nuclear gene encoding a mitochondrial transcription factor that is translocated to mitochondria, where it is a key activator of mtDNA transcription and is essential for mitochondrial genome replication (Wu et al., 1999). Both types of transcription factors (NRFs and *TFAM*) can act together to induce mitochondrial biogenesis and increase oxidative phosphorylation in response to endurance training (Baar et al., 2002; Kelly & Scarpulla, 2004). Simultaneously, PGC-1 $\alpha$  is engaged in the regulation of fatty acid oxidation and the TCA cycle through co-activation of the PPAR (peroxisome proliferator-activated receptor) proteins (PPAR $\alpha$ , PPAR $\gamma$ , PPAR $\beta/\delta$ ), which are transcription factors that regulate genes encoding key enzymes in fatty acid metabolism such as carnitine palmitoyltransferase

(CPTI) and medium-chain acyl-coenzymeA dehydrogenase (MCAD) (Vega, Huss, & Kelly, 2000). Through energy substrate regulation and control of the balance between fatty acid and glucose metabolism, PGC-1 $\alpha$  enables molecular adaptation to metabolic or physiological stress. At the same time, elevated levels of PGC-1 $\alpha$  mRNA/protein can also change the thermogenic programme in muscle by stimulating expression of the mitochondrial protein UCP-1 (uncoupling protein 1), causing the uncoupling of oxidative phosphorylation and heat generation. All of the PGC-1 $\alpha$ -regulated processes described above can be considered as a part of a broader programme of adaptive thermogenesis centred on muscle and brown adipose tissue (Lehman et al., 2000; Lin et al., 2005; Wu et al., 1999).

The aforementioned data suggest that the muscle metabolic profile depends on the presence of specific proteins that act together to maintain a specific fibre phenotype, which is connected to both the regulation of energy substrate utilization and the control of the expression of proteins involved in oxidative metabolism and mitochondrial biogenesis. However, an equally important element of this regulatory system is the capillarization of muscle. The PGC-1 $\alpha$ -mediated regulation of exercise-induced angiogenesis involves  $\beta$ -adrenergic signalling, which leads to the induction of *PPARGC1A* expression in skeletal muscle. PGC-1 $\alpha$  co-activates the orphan nuclear receptor ERR $\alpha$  (oestrogen-related receptor alpha) to induce the genes for vascular endothelial growth factors (VEGFs), which are known to be critical in the process of blood vessel formation (Chinsomboon et al., 2009). In addition to  $\beta$ -adrenergic signalling, several other signal transduction pathways are activated during exercise (for example, those involving calcineurin A and calcium/calmodulin-dependent protein kinase [CaMK]; AMP-sensitive AMP kinase [AMPK]; the stress-responsive p38 mitogen-activated protein kinase [MAPK]; and the production of reactive oxygen species [ROS]). These pathways can influence *PPARGC1A* expression through the direct activation of gene transcription or by releasing its repression and increasing PGC-1 $\alpha$  protein stability (Berchtold, Brinkmeier, & Muntenner, 2000; Handschin, Rhee, Lin, Tam & Spiegelman, 2003; Kramer & Goodyear, 2007; Puigserver et al., 2001; Sakamoto & Goodyear, 2002).

Nevertheless, the functional status of the Gly482-Ser polymorphic site at *PPARGC1A* remains unclear. How do these Gly482 and 482Ser variants affect cardiorespiratory capacity? The 482Ser variant has been associated with important human disorders (Andersen et al., 2005; Andrulionyte et al., 2006; Ek et al., 2001; Esterbauer et al., 2002; Franks et al., 2007; Ingelsson et al., 2008; Kunej et al., 2004; Ling et al., 2008; Vimalaswaran et al., 2008). Further-

more, it has been demonstrated that the 482Ser variant is associated with lower *PPARGC1A* mRNA expression, with elderly patients (Ling et al., 2004) and patients both with and without type II diabetes (Ling et al., 2008; Patti et al., 2003) displaying a greater decline in gene expression than those without the variant. To explain their own results, some authors have rejected the role of Gly482 and 482Ser variants as direct casual factors because this amino acid change does not create or eliminate any functional protein motifs (Andrulionyte et al., 2006; Esterbauer et al., 2002), while others have suggested that this polymorphism could be in linkage disequilibrium with an unidentified variant within the *PPARGC1A* gene locus or in other genes nearby (Andersen et al., 2005; Kunej et al., 2004). It has also been suggested that the decreased expression of *PPARGC1A* mRNA observed in some patients may be independent of the 482Ser variant and could instead be an effect of epigenetic modulation of the *PPARGC1A* gene promoter (Ling et al., 2008).

Studies in cell culture using plasmid constructs bearing Gly or Ser at position 482 in the PGC-1 $\alpha$  protein have directly shown the effect of the single nucleotide polymorphism on the functional activity of PGC-1 $\alpha$ ; however, these results are controversial. The first report of this kind was by Choi and colleagues (Choi, Hong, Lim, Ko, & Pak, 2006), who suggested that the PGC-1 $\alpha$  482Ser variant was more efficient as a co-activator of the *TFAM* promoter, leading to a higher mtDNA content in 482Ser homozygotes compared with Gly482 homozygotes. These authors also hypothesized that Gly482 carriers might have a defect in PPAR-mediated lipid metabolism; however, they did not observe any significant association between the Gly482 allele and type II diabetes or any other clinical characteristics in a Korean population (Choi et al., 2006). In contrast, others have reported no difference in activity between the PGC-1 $\alpha$  Gly482 and 482Ser variants when interacting with the uncoupled protein 1 promoter (Esterbauer et al., 2002) or adiponectin receptor (Okauchi et al., 2008). To further complicate this matter, Zhang et al. (2007) reported that the 482Ser allele was correlated with susceptibility to type II diabetes because 482Ser carriers had higher levels of triglycerides and low-density lipoprotein (LDL) and a higher frequency of the 482Ser allele was observed in diabetic patients. These results are in accordance with previous findings that 482Ser allele carriers have a higher genotype-relative risk of type II diabetes (Andrulionyte et al., 2006; Ek et al., 2001; Kunej et al., 2004). Experiments with recombinant plasmids by Zhang et al. (2007) also indicated that the change from Gly to Ser at position 482 in PGC-1 $\alpha$  caused relatively less binding with MEF2C, which is a transcription

factor that has been implicated in the control of muscle-selective gene expression and is particularly important in the regulation of glucose transportation in skeletal muscle. MEF2C binds specifically to the MEF2 binding sequence in the promoter of *GLUT4* (glucose transporter 4) and is responsible for the activation of this gene. GLUT4, the main insulin-responsive glucose transporter in fat and muscle tissue, is localized to an intracellular compartment from which it translocates to the plasma membrane in response to insulin receptor activation and facilitates glucose uptake by the cell (Fukumoto et al., 1989; James, Brown, Navarro, & Pilch, 1988). The overall GLUT4 pool size in heart, skeletal muscle, and adipose tissue determines insulin resistance and in transgenic mice overexpressing the human *GLUT4* gene, an enhancement of insulin-sensitive glucose transport in muscle tissue was observed (Liu et al., 1993). Functional analysis of the *GLUT4* promoter has indicated that a conserved MEF2-binding site is necessary but not sufficient for the normal tissue-specific expression of the GLUT4 protein (Thai, Guruswamy, Cao, Pessin, & Olson, 1998). It has also been shown that in cultured muscle cells, the MEF2C isoform is preferentially co-activated by PGC-1 $\alpha$  when it activates the *GLUT4* promoter (Michael et al., 2001). The reason that the PGC-1 $\alpha$  Gly482 and 482Ser variants influence the co-activation of MEF2C by PGC-1 $\alpha$  could lie in the fact that this polymorphic site is located between amino acids 403–570, which is a site of a domain critical for the binding interaction between these two proteins (Michael et al., 2001; Zhang et al., 2007). The change in the interaction between PGC-1 $\alpha$  and MEF2C may alter its dependence on GLUT4 insulin-stimulated glucose uptake, which would then influence glycogen synthesis and the subsequent synthesis of fatty acids. Thus, the PGC-1 $\alpha$  482Ser allele may impair the efficiency of aerobic metabolism by decreasing the binding interaction between PGC-1 $\alpha$  and MEF2C, which may have consequences not only for glucose uptake and homeostasis but also for the transformation of muscle fibre type. This process requires direct PGC-1 $\alpha$ /MEF2 co-activation, which, through the calcineurin signalling pathway, induces the expression of genes specific for type I slow-twitch fibres such as *MB* or *TNNI1* (Lin et al., 2002). Moreover, the PGC-1 $\alpha$ /MEF2C interaction has been shown to regulate the murine *PGC-1 $\alpha$*  gene itself, as this complex is able to increase transcription from the *PGC-1 $\alpha$*  promoter, implying a positive autoregulatory loop (Handschin et al., 2003). In this way, the Gly482Ser polymorphism may have an impact on *PPARGC1A* gene expression, which could explain the age-related decline in *PPARGC1A* mRNA levels in 482Ser allele carriers (Ling et al. 2004) and the lower expression of

*PPARGC1A* in diabetic patients and non-diabetic individuals carrying the 482Ser variant (Ling et al., 2008; Patti et al., 2003).

## Conclusions

In summary, we found that the *PPARGC1A* Gly482Ser polymorphism is associated with elite athletic status. We observed a significantly lower frequency of the 482Ser allele in endurance-oriented athletes (the endurance and strength-endurance groups in this study) compared with sedentary controls. Our results support the hypothesis that the *PPARGC1A* 482Ser allele may impair aerobic capacity; thus, the Gly482 allele may be considered beneficial to endurance performance. To date, a few clues about the molecular mechanism underlying this association have been provided by functional studies using *PPARGC1A* Gly482Ser mutants; however, in light of their controversial results, additional investigations should be conducted. In addition, further studies of *PPARGC1A* haplotypes are needed to determine whether the Gly482Ser variants act alone or in combination with other polymorphisms in the *PPARGC1A* gene to influence an athlete's capacity for prolonged exertion.

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