Does the *PPARA* Intron 7 Gene Variant (rs4253778) Influence Performance in Power/Strength-Oriented Athletes? A Case-Control Replication Study in three Cohorts of European Gymnasts

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Athletic ability is influenced by several exogenous and endogenous factors including genetic component. Hundreds of gene variants have been proposed as potential genetic markers associated with fitness-related phenotypes as well as elite-level athletic performance. Among others, variants within the PPARA gene that code for the peroxisome proliferator activated receptor α are of potential interest. The main goal of the present study was to determine PPARA (G/C, rs4253778) genotype distribution among a group of Polish, Lithuanian and Italian international level male gymnasts and to compare our findings with those of previous research on the frequency of the PPARA intron 7 C allele/CC genotype in power/strength-oriented athletes. A total of 464 male subjects (147 gymnasts and 317 controls) from Poland (n = 203), Italy (n = 146) and Lithuania (n = 107) participated in the study. No statistically significant differences were found in any of the analyzed cohorts. However, a significantly higher frequency of the CC genotype of the PPARA rs4253778 polymorphism was observed when all gymnasts were pooled and compared with pooled control using a recessive model of inheritance (OR = 3.33, 95% CI = 1.18-10, p = 0.022). It is important to know that we investigated a relatively small sample of male European gymnasts and our results are limited only to male participants. Thus, it is necessary to validate our results in larger cohorts of athletes of different ethnicities and also in female gymnasts to find out whether there is a gender effect.

Key words: PPARα, athletic performance, genetic polymorphism, candidate gene.

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Introduction

It is undoubtedly clear that athletic ability is influenced by several exogenous (environmental) factors including nutrition, supplementation, and specialized physical training. Endogenous factors include all components of the human body which are engaged in physical activity such as physique, neuromuscular coordination, immune response, cardiovascular capacity, thermoregulation, water and electrolyte balance, energy metabolism, as well as psychological factors. All of these components are, to a greater or lesser degree, determined by genetic factors (Brutsaert and Parra, 2009; Maciejewska-Skrendo et al., 2019b; Yan et al., 2016). To date, studies of genomic components of traits comprising athletic performance identified hundreds of gene variants as potential genetic markers associated with fitness-related phenotypes as well as elite-level athletic performance (Ahmetov et al., 2016; Moran and Pitsiladis, 2017). Among others, variants within the *PPARA* gene that code for a peroxisome proliferator activated receptor α (PPARα), a member of the nuclear steroid hormone receptor superfamily involved in glucose homeostasis and lipid metabolism, have gained attention of researchers (Maciejewska-Karlowska et al., 2013, 2014; Maciejewska-Skrendo et al., 2019a; Maciejewska et al., 2011, 2012; Petr et al., 2014, 2018; Zarebska et al., 2014). PPARα is the key regulator of expression of genes involved in fatty acid metabolism, including fatty acid transport, uptake by the cells, intracellular binding, and activation, as well as catabolism (particularly mitochondrial fatty acid oxidation) or storage. PPARα is mainly expressed in tissues with elevated mitochondrial and peroxisomal fatty acid oxidation rates, such as a liver, a heart, a kidney, skeletal muscle and brown fat (Desvergne and Wahli, 1999).

Unlike saturated fatty acids which are poor PPARα ligands, unsaturated fatty acids are the primary natural PPARα ligands that directly bind to the PPARα via a ligand binding domain (LBD) and enable to form heterodimers with the nuclear retinoid X receptor (RXR). PPAR:RXR complex binds via the PPAR DNA binding domain (DBD) to the PPRE (peroxisome proliferator response element) sequence within the promoters of the target genes (Kliewer et al.,

1992). PPARα may also be regulated by insulin-induced trans-activation that occurs through the phosphorylation of two mitogen-activated protein (MAP) kinase sites at positions 12 and 21 located in the activation function (AF)-1-like domain within the PPARα receptor (Juge-Aubry et al., 1999). In humans, the *PPARA* gene has been mapped to the chromosome 22 and comprises eight exons and seven introns (Sher et al., 1993). Several polymorphic sites have been identified within the *PPARA* and the single nucleotide polymorphism (SNP) (G/C, rs4253778) localized within the intron 7 of the *PPARA* has been proposed to play a potential role in response to physical activity. Jamshidi et al. (2002) observed that *PPARA* rs4253778 polymorphism affected left ventricular growth in response to exercise and hypertension, specifically the CC ang CG individuals had significantly higher left ventricular mass when compared to GG genotype carriers (Jamshidi et al., 2002). Furthermore, the effect of possessing the C allele was additive: CG heterozygotes had a 2-fold greater, and CC homozygotes had a 3-fold greater increase in left ventricular mass than GG homozygotes. It was proposed that one of the molecular adaptation in the hypertrophied heart was a reduction in PPARα activity (Barger et al., 2000), an increase in glucose utilization and a decrease in fatty acid oxidation (FAO) (Allard et al., 1994; Sack et al., 1996). Furthermore, it was hypothesized that the *PPARA* intron 7 C allele impaired PPARα function and was associated with downregulation of the expression of mitochondrial FAO enzymes, leading to reduced FAO and impaired cellular lipid homeostasis (Jamshidi et al., 2002).

Further studies recruiting athletes that represented different sports disciplines have revealed that it was more likely to find C allele carriers in a group of power-oriented athletes who were involved in short and very intense anaerobic effort (Ahmetov et al., 2006), while GG homozygotes were more prevalent among endurance-type athletes performing predominantly prolonged aerobic exertion (Eynon et al., 2010; Maciejewska et al., 2011). Gineviciene et al. (2010) confirmed the results of previous studies in Lithuanian male athletes showing that those with allele *PPARA* rs4253778 C had significantly higher muscle mass and better results in explosive strength of lower extremities

than GG homozygotes (Ginevičienė et al., 2010). Those results were in part explained by the analysis of muscle fiber composition of young men. It was shown that GG homozygotes had a higher percentage of slow-twitch fibers compared to CC homozygotes and the C allele was associated with the propensity to skeletal muscle hypertrophy (Ahmetov et al., 2006).

In view of facts mentioned above, the aim of the present study was to determine *PPARA* (G/C, rs4253778) genotype distribution in a group of Polish, Lithuanian and Italian international level male artistic gymnasts and to compare our findings with those of previous research on the frequency of the *PPARA* intron 7 C allele in power/strength-oriented athletes.

Methods

Participants

A total of 464 male subjects (147 gymnasts and 317 controls) from Poland (n = 203), Italy (n = 146) and Lithuania (n = 107) participated in the study. All gymnasts recruited from Poland, Italy and Lithuania were international athletes defined as those who competed at major international tournaments, while all controls were healthy men without any competitive sport experience. Both gymnasts and controls were self-reported Caucasians for at least 3 generations. Polish participants (n = 203) included 58 gymnasts and 145 controls, Italian participants (n = 154) included 54 gymnasts and 100 controls, while Lithuanian participants (n = 107) included 35 gymnasts and 72 controls.

Ethical approval

The procedures followed in the study were conducted in accordance with the principles of the World Medical Association Declaration of Helsinki and were approved by the local Ethics Committees (Pomeranian Medical University Ethics Committee, No. BN-001/45/08; Clinical Research at the Regional Chamber in Gdansk, No. KB12/15). All participants were provided with an information sheet concerning study particulars including the purpose of the study and the procedures involved, in addition to the possible risks and benefits associated with participation. All participants provided written informed consent to genotyping with the understanding that it was anonymous and that the obtained results would be confidential. This case-control

genetic association study was conducted in accordance with the set of guiding principles for reporting the results of genetic association studies defined by the Strengthening the Reporting of Genetic Association studies (STREGA) Statement (Little et al., 2009).

Genetic analyses

The buccal cell samples donated by participants were collected in PBS Solution (VWR, USA) with the use of sterile foam-tipped applicators (Puritan, USA). DNA was extracted from the buccal cells using a High Pure PCR Template Preparation Kit (Roche, Switzerland) according to the manufacturer's protocol. Allelic discrimination of the *PPARA* (G/C, rs4253778) polymorphic site was performed using TaqMan Pre-Designed SNP Genotyping Assays (C___2985251_20, Applied Biosystems, USA), including primers and fluorescently labelled (FAM and VIC) MGB probes for the detection of alleles. All samples were genotyped and visualized with the use of a StepOnePlus real-time polymerase chain reaction (PCR) instrument and StepOne software version 2.2.2 (Applied Biosystems, Foster City, CA, USA). Thermal cycler conditions were as follows: an initial step at 95°C for 5 min, followed by 45 cycles of denaturation at 94°C for 15 s and anneal/extend at 60°C for 1 min.

Statistical analysis

All statistical analyses were conducted in the R programming environment using specific R packages (version 3.4.0, The R Foundation for Statistical Computing, https://cran.r-project.org). Genotype and allele frequency distributions, in addition to HWE probabilities, were determined applying different models of inheritance (codominant, dominant, recessive and over-dominant) using the SNPassoc package; *p* values <0.05 were considered statistically significant.

Results

The genotype frequencies in the Polish, Italian and Lithuanian gymnast and control groups as well as the pooled gymnast-control cohorts conformed to the expectations of Hardy-Weinberg equilibrium (Table 1).

Tables 2-4 present the genotype and allele frequency distributions of the *PPARA* gene variant in the investigated Polish (Table 2), Italian (Table 3) and Lithuanian (Table 4) cohorts. No statistically significant differences were found in

any of the analyzed cohorts; the genotype distribution amongst the Polish, Italian and Lithuanian cohort of gymnasts was not significantly different from that amongst respective controls when analyzed using the codominant, dominant, recessive and over-dominant models (Tables 2-4).

However, significant differences in genotype distribution were observed when all gymnasts from Poland, Italy and Lithuania were pooled and compared with pooled control groups from Poland, Italy and Lithuania using the recessive model of inheritance (OR = 0.3, 95% CI = 0.1-0.85, p = 0.022; Table 5).

Table 1

Minor allele frequency and Hardy-Weinberg equilibrium probabilities for the PPARA G/C rs4253778 variant in the gymnast and control groups investigated in the recruited Polish, Italian and Lithuanian cohorts.

Cohort	MAF (% of C)		HWE (*p* value)		
	GYM	CON	GYM	CON	GYM+CON
Polish	15.5	14.8	0.108	0.435	0.818
Italian	23.1	19.0	0.397	0.692	0.783
Lithuanian	20.0	12.5	0.526	0.893	0.644
Total	19.4	15.6	0.067	0.461	0.531

MAF - Minor allele frequency, HWE - Hardy-Weinberg equilibrium, GYM – gymnasts, CON – controls

Table 2

Distribution of PPARA G/C rs4253778 genotypes in gymnasts and controls in the Polish cohort

Model†	GYM	%	CON	%	OR	95% CI		*p*
Codominant								
G/G	43	74.1	104	71.7	1			
G/C	12	20.7	39	26.9	0.75	0.36	1.56	0.243
C/C	3	5.2	2	1.4	3.57	0.58	25.00	
Dominant								
G/G	43	74.1	104	71.7	1			
G/C-C/C	15	25.9	41	28.3	0.88	0.44	1.75	0.727
Recessive								
G/G-G/C	55	94.8	143	98.6	1			
C/C	3	5.2	2	1.4	3.85	0.63	25.00	0.139
Overdominant								
G/G-C/C	46	79.3	106	73.1	1			
G/C	12	20.7	39	26.9	0.71	0.34	1.47	0.351

*GYM – gymnasts, CON – controls; * p-values; OR – odds ratio, 95% CI – confidence intervals*

Table 3

Distribution of PPARA G/C rs4253778 genotypes in gymnasts and controls in the Italian cohort

Model†	GYM	%	CON	%	OR	95% CI		*p*
Codominant								
G/G	33	61.1	65	65	1			
G/C	17	31.5	32	32	1.04	0.51	2.17	0.472
C/C	4	7.4	3	3	2.63	0.56	12.50	
Dominant								
G/G	33	61.1	65	65	1			0.633
G/C-C/C	21	38.9	35	35	1.18	0.60	2.33	
Recessive								
G/G-G/C	50	92.6	97	97	1			0.223
C/C	4	7.4	3	3	2.56	0.56	12.50	
Overdominant								
G/G-C/C	37	68.5	68	68	1			0.947
G/C	17	31.5	32	32	0.98	0.48	2.00	

*GYM – gymnasts, CON – controls; * p-values; OR – odds ratio, 95% CI – confidence intervals*

Table 4

Distribution of PPARA G/C rs4253778 genotypes in gymnasts and controls in the Lithuanian cohort

Model†	GYM	%	CON	%	OR	95% CI		*p*
Codominant								
G/G	23	65.7	55	76.4	1			
G/C	10	28.6	16	22.2	1.49	0.59	3.85	0.333
C/C	2	5.7	1	1.4	4.76	0.41	50.00	
Dominant								
G/G	23	65.7	55	76.4	1			0.249
G/C-C/C	12	34.3	17	23.6	1.69	0.69	4.17	
Recessive								
G/G-G/C	33	94.3	71	98.6	1			0.222
C/C	2	5.7	1	1.4	4.35	0.38	50.00	
Overdominant								
G/G-C/C	25	71.4	56	77.8	1			0.476
G/C	10	28.6	16	22.2	1.41	0.56	3.57	

*GYM – gymnasts, CON – controls; * p-values; OR – odds ratio, 95% CI – confidence intervals*

Table 5

Distribution of PPARA G/C rs4253778 genotypes in pooled gymnasts and controls

Model†	GYM	%	CON	%	OR	95% CI		*p*
Codominant								
G/G	99	67.3	224	70.7	1			
G/C	39	26.5	87	27.4	1.01	0.65	1.59	0.072
C/C	9	6.1	6	1.9	3.45	1.18	10.00	
Dominant								
G/G	99	67.3	224	70.7	1			0.472
G/C-C/C	48	32.7	93	29.3	1.16	0.77	1.79	
Recessive								
G/G-G/C	138	93.9	311	98.1	1			**0.022**
C/C	9	6.1	6	1.9	3.33	1.18	10.00	
Overdominant								
G/G-C/C	108	73.5	230	72.6	1			0.837
G/C	39	26.5	87	27.4	0.95	0.61	1.49	

*GYM – gymnasts, CON – controls; * p-values; OR – odds ratio, 95% CI – confidence intervals*

Discussion

This genetic association study investigated distribution of G/C SNP (rs4253778) located in the intron 7 of the *PPARA* gene within elite Polish, Italian and Lithuanian gymnasts and non-athletic controls. The main findings of the study were: 1) no significant differences in genotype frequency distributions in the analyzed Polish, Italian and Lithuanian cohorts when tested separately, 2) the over-representation of the CC genotype in the combined group of Polish, Italian and Lithuanian gymnasts compared to the combined control group.

Artistic gymnastics is characterized by performing short routines that range from about 30 up to 90 seconds on different apparatuses. It has been stated that isometric and explosive strength, power speed, strength endurance, as well as dynamic and static flexibility are the most determinant physical fitness aspects of artistic gymnasts (Mkaouer et al., 2018). The intensity and duration of a particular routine determines the contribution primarily from the anaerobic energy system. That is why men's routines such as the pommel horse, floor, parallel bars as well as rings apparatus are disciplines where power/strength is of greater importance than endurance (Morucci et al., 2014).

The results of our research on international level male gymnasts corroborate the previous studies that investigated distribution of intron 7 G/C SNP (rs4253778) of the *PPARA* in the recruited athletes and showed that the C allele or the CC genotype was a candidate for speed/power performance. It has been shown that there was a tendency for power oriented athletes (ie. 60–400 m runners, 500 m skaters, 50–100 m swimmers and weightlifters) to possess the C allele or the CC genotype rather than the GG

genotype (Ahmetov et al., 2006). The C allele carriers had also significant hypertrophy of skeletal muscle (due to a higher percentage of fast twitch fibers), what may facilitate glucose utilization in response to anaerobic exercise resulting in higher muscle mass. Finally, it was indicated that *PPARA* 7C carriers had better results in explosive strength and exhibited higher speed strength measures in the 30-s Wingate Test (WT30) (Ginevičienė et al., 2010; Petr et al., 2014).

In the view of the above, we assumed that CC genotype carriers within the cohort of international artistic gymnasts may possess a metabolic advantage towards anaerobic metabolism. There were several attempts to determine the functional role of the *PPARA* intron 7 G/C SNP (rs4253778) polymorphism. The 7 intron C allele has been associated with progression of atherosclerosis (Flavell et al., 2002) and was positively correlated with left ventricular growth in response to exercise (Jamshidi et al., 2002). It has been found that reduced PPARα activity as well as downregulation of mitochondrial FAO enzymes expression is associated with the hypertrophied heart (Barger et al., 2000; Sack et al., 1996).

Despite the fact that the 7 G/C polymorphism is located in a noncoding region, it seems to influence the gene's expression probably by linkage disequilibrium with an unidentified functional variant in a promoter or enhancer element within the *PPARA* regulatory region that the *PPARA* intron 7 polymorphism may change and disrupt a microRNA site what in consequence alters encoded PPARα protein levels and may change the PPARα target genes (Ahmetov et al., 2006; Chen et al., 2010; Cresci et al., 2008).

Therefore, it has been proposed that the intron 7 C allele and CC genotype involved in the reduction of the *PPARA* gene expression by downregulating the expression of key metabolic enzymes, may impair the cellular lipid and glucose homeostasis with the elevation of the expression of genes encoding glycolytic enzymes crucial for the anaerobic metabolism (Allard et al., 1994; Maciejewska-Skrendo et al., 2019a).

Moreover, because C allele carriers are more prone to rely on anaerobic processes what may be an adaptive stimulus leading to muscle fiber transformation, it has also been suggested that the *PPARA* i7 G/C polymorphism may play an important role in training induced fiber shifts and related muscle metabolism changes (Petr et al., 2014).

We are aware that our study is affected by several limitations. Firstly, as almost every genetic association study, we investigated a relatively small sample of male European artistic gymnasts. We nonetheless tried our best to gain the highest possible number of international level male athletes from Poland, Italy and Lithuania. It is very important to underline, what our results clearly indicate, that a smaller sample size has greater likelihood of not obtaining statistically significant results. It is also important to know that our results are limited only to male participants. Thus, it is necessary to validate our results in larger cohorts of athletes of different ethnicities and also in female gymnasts to find out whether there is a gender effect. Secondly, it is highly probable that variation within the *PPARA* gene does not affect physiological traits alone. That's why it is important to stress that polymorphic variants of *PPARA* probably account for only a small portion of phenotypic variability, due to the polygenic character of the traits analyzed, implying that multiple gene-gene as well as gene-environment interactions may contribute to the observed differential effects.

Despite these limitations we believe that our results regarding the intron 7 G/C SNP of *PPARA* association with athletic status of high-level gymnasts may contribute to better understanding whether and how genetic composition of the *PPARA* gene influences physical performance. We believe that it is quite probable that in near future genetic tests may be applied to identify talented individuals in their respective disciplines as well as to adjust training methods to the genotypic capabilities of athletes.

Acknowledgements

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