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**Do *PPARGC1A* and *PPARα* polymorphisms influence sprint or endurance phenotypes?**

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**Running head:** peroxisome polymorphisms and elite athletes

## **Abstract**

Functional Gly482Ser (rs8192678) and G/C (rs4253778) polymorphisms in the Peroxisome proliferator-activated receptor gamma coactivator1 (*PPARGC1A*) and Peroxisome proliferator-activated receptor alpha (*PPAR $\alpha$* ) genes, respectively, have been associated with mRNA and protein activity. The aim of this study was to determine their frequency distribution among 155 Israeli athletes (endurance athletes and sprinters) and 240 healthy controls. Results showed that there was a significant difference in *PPARGC1A* Ser482Gly polymorphism genotype frequencies between endurance athletes and sprinters ( $P=0.005$ ) as well as between endurance athletes and controls ( $p=0.0003$ ). However, the sprinters' genotype and allele frequencies were similar to that of the control group. A significantly lower proportion of *PPARGC1A* Ser482 allele (0.25) was noted for the endurance athletes compared to controls (0.43,  $p=0.0001$ ). Endurance athletes showed a trend of a higher yet a not significant proportion of the *PPAR $\alpha$*  GG genotype compared to sprinters ( $p=0.051$ ). As we compared between the subgroups of top-level endurance athletes and top-level sprinters, as well as between those of top-level and national-level endurance athletes, we reached more prominent results. In conclusion, our data indicate that a lower frequency of the Ser482 allele and possibly a higher frequency of the GG genotype are associated with increased endurance performance ability.

**Keywords:** Genetics, aerobic performance, anaerobic performance, metabolism

## Introduction

Elite athletic performance is influenced, at least partly, by genetic components (MacArthur & North, 2005; Rankinen et al., 2006). However, while human elite performance phenotypes are highly polygenic, it is still unknown whether different genetic elements play a role in an athlete's talent for a specific type of sport (Amir et al., 2007).

Peroxisome proliferator-activated receptor gamma coactivator1 $\alpha$  (*PPARGC1A*) is a transcription coactivator that probably plays a role in a wide variety of biological responses, including mitochondrial biogenesis (Liang & Ward, 2006; Gonzalez-freire et al., 2008). *PPARGC1A* controls glucose transportation and lipid and glucose oxidation through the regulation of peroxisome proliferator-activated receptor alpha (*PPAR $\alpha$* ) (Attie & Kendzierski, 2003). *PPARGC1A* and *PPAR $\alpha$*  are expressed at high levels in tissues that catabolize fatty acids, notably those in the liver, skeletal muscle, and myocardium (Braissant et al., 1996; Liang & Ward, 2006). In humans, the *PPARGC1A* and the *PPAR $\alpha$*  genes regulate the expression of genes encoding several key enzymes involved in fatty acid oxidation (Ahmetov et al., 2006) and controlling oxidative phosphorylation (Lucia et al., 2005). Endurance training increases *PPARGC1A* mRNA levels (Tunstall et al., 2002; Pilegaard et al., 2003; Short et al., 2003; Norrbom et al., 2004; Mathai et al., 2008), and thus, may enhance skeletal muscle oxidative capacity by *PPAR $\alpha$*  regulation of gene expression (Lin et al., 2002; Russell et al., 2003).

Based on the premise that *PPARGC1A* Gly482Ser and *PPAR $\alpha$*  G/C Single Nucleotide Polymorphisms (SNPs) are functional and therefore could

affect mRNA expression and/or protein levels, they have received recent attention in the medical literature. The Ser482 allele of the *PPARGC1A* gene was previously associated with type 2 diabetes (Ek et al., 2001; Hara et al., 2002), whereas the Gly482 allele has been associated with beneficial effects such as alteration of lipid oxidation and early insulin secretion (Muller et al., 2003). Furthermore, the C allele in the G/C polymorphism of the *PPAR $\alpha$*  gene is thought to be associated with higher plasma lipid levels (Flavell et al., 2000), cardiac growth (Jamshidi et al., 2002), and increasing risk of coronary artery disease (Flavell et al., 2002).

Only a few studies have tested the plausible effect of *PPARGC1A* and *PPAR $\alpha$*  on athletic performance. Ahmetov et al. (2006) suggested that elite aerobic performance is affected by the G allele of the *PPAR $\alpha$*  intron 7 G/C polymorphism. Lucia et al. (2005) reported an association between elite athletic performance and a common variant in the *PPARGC1A* gene (Gly482Ser), in which the frequency of the *PPARGC1A* minor Ser482 allele was lower in elite endurance athletes compared to unfit controls. However, a lack of association was noted between  $Vo_{2max}$  and the Gly482Ser polymorphism in the German and Dutch populations (Stumvoll et al., 2004), as well as in the Northern Chinese population (He et al., 2008).

The purpose of this study was to analyze the frequency distribution of *PPARGC1A* Gly482Ser (rs8192678) and *PPAR $\alpha$*  G/C (rs4253778) polymorphisms in athletic and non-athletic Israeli populations. Another goal of this work was to compare within the athletic population the frequency distribution of the above SNPs between elite athletes of sports with different

demands (endurance vs. sprinters) and competitive levels (top-level vs. national level).

### **Material and methods**

**Subjects:** One hundred and fifty-five athletes (119 men and 36 women, age=35.9±12.2 yrs) volunteered to participate in the study. Athletes were included in the study sample only if they had participated in national/international track and field championships. The control group consisted of 240 non-athletic Israeli healthy individuals that were randomly assigned from the Israeli population. Controls were not engaged in physical activity on a regular basis. Athletes were divided into two groups: 1) Endurance-type group that included 74 long distance runners, whose main event was the 10000m run or the marathon, and 2) Sprint-type group that included 81 sprinters whose main event was the 100-200m dash. According to their individual best performance, athletes within each group were further divided into two subgroups: top-level (those who had represented Israel in a world track and field championship or in the Olympic Games) and national level athletes. All subjects, athletes and non-athletes, were Israeli Caucasians, with an equivalent ratio of non-Ashkenazi and Ashkenazi descent in each group (2:1). (subjects' genotype characteristics are presented in Table 1).

The study was approved by the Helsinki Committee of the Hillel Yaffe Medical Center, Hadera, Israel, according to the Declaration of Helsinki. A written informed consent was obtained from each participant.

## Genotyping

Genomic DNA was extracted from peripheral EDTA treated anti-coagulated blood using a standard protocol (Sambrook et al., 1989). Genotyping of the *PPARGC1A* Gly482Ser (G/A) (rs8192678) and *PPAR $\alpha$*  G/C (rs4253778) polymorphisms was performed using polymerase chain reaction (PCR) according to the methods of Kunej et al. (2004) and Jamshidi et al. (2002), respectively. The resulting PCR products were genotyped (in the Genetics and Molecular Biology Laboratory of the Zinman College of Physical Education and Sport Sciences at the Wingate Institute, Netanya, Israel) by restriction fragment length polymorphism (RFLP). Briefly, the Gly482Ser polymorphism was amplified using PCR primers F - 5' TAAAGATGTCTCCTCTGATT '3 and R - 5' GGAGACACATTGAACAATGAATAGGATTG '3. The amplified fragment subsequently underwent digestion by *HPAII* (New England Biolabs, Beverly, MA, USA). This method yields a 378-bp fragment in the presence of the Ser482 allele, and 209 and 169 bp in the presence of the Gly482 allele. The *PPAR $\alpha$*  G/C polymorphism in intron 7 was amplified using PCR primers F- 5' ACAATCACTCCTTAAATATGGTGG '3 and R- 5' AAGTAGGGACAGACAGGACCAGTA '3. The amplified fragment subsequently underwent digestion by *Taq I* (New England Biolabs, Beverly, MA, USA). This method yields a 266-bp fragment in the presence of the C allele, and a 216 and 50 bp in the presence of the G allele. To ensure proper internal control, for each genotype analysis we used positive and negative controls from different DNA aliquots which were previously genotyped with the

same method according to recent recommendations for replicating genotype-phenotype association studies (Chanock et al., 2007). The RFLP results were scored by two experienced and independent investigators who were blind to subject data.

### **Data analysis**

The SPSS statistical package, version 15.0, was used to perform all statistical evaluations (SPSS Inc., Chicago, IL, USA). Allele frequencies were determined by gene counting. A  $\chi^2$  test was used to confirm that the observed genotype frequencies were in Hardy-Weinberg equilibrium, and to compare the *PPARGC1A* Gly482Ser and the *PPAR $\alpha$*  G/C alleles and genotype frequencies between athletes and control subjects as well as between genders and between athletes from different sports and competitive levels. The level of significance was set at  $P < 0.05$ .

### **Results**

The results of the distribution of *PPARGC1A* Gly482Ser and the *PPAR $\alpha$*  G/C polymorphisms genes in 155 Israeli athletes compared with 240 healthy sedentary Israeli individuals revealed that subjects' age, male/female genotype distribution, and allele frequencies did not differ by genotype, as summarized in Table 1. In addition, there were no differences across *PPARGC1A* and *PPAR $\alpha$*  genotypes between Ashkenazi and non-Ashkenazi descendants. Our control population consisted of Israeli Caucasians, where the observed Ser482 allele frequency of the *PPARGC1A* was consistent with reports of Chinese (He et al., 2008) and Koreans (Kim et al., 2005), and



slightly lower than Danish (Ling et al., 2004), Germans (Stumvoll et al., 2004), British (Franks et al., 2003), and Spanish (Lucia et al., 2005) populations. The C/G allele frequencies in the present study were similar to those in the general population of Russia (Ahmetov et al., 2006). The *PPARGC1A* Gly482Ser and the *PPARα* G/C genotype and allele frequencies met Hardy-Weinberg expectations in the endurance athletes ( $P = 0.1$  for Gly482Ser, and  $P = 0.64$  for G/C), sprinters ( $P = 0.98$  for Gly482Ser, and  $P = 0.98$  for G/C), and control group ( $P = 0.98$  for Gly482Ser, and  $P = 0.96$  for G/C). The *PPARGC1A* Gly482Ser allele frequency and genotype distribution of the whole cohort of athletes differed from the control group (Table 1). The endurance athletes' genotype distribution percentage of the *PPARGC1A* Gly482Ser genotype differed markedly from that of the sprinters, and the control group, as presented in Table 2. However, the sprinters' genotype distribution percentage was similar to that of the control group ( $X^2 = 3.96$ , d.f=2,  $p=0.13$ ). Allele frequency in the endurance group was significantly different than that in the controls (Table 2). Nevertheless, allele frequency of the endurance group and the sprinters did not reach significant difference ( $X^2 = 3.4$ , d.f=1,  $p=0.07$ ). We observed a significantly lower proportion of Ser/Ser genotype among endurance athletes (0%) in comparison with the sprinters (17%,  $X^2 = 5.82$ , d.f=1,  $p=0.016$ ) and controls (16.3%,  $X^2 = 6.34$ , d.f=1,  $p=0.012$ ). The endurance athletes' genotype distribution percentage and allele frequencies of the *PPARα* G/C polymorphism did not differ from those of sprinters and controls, as shown in Table 2. However, a trend of a higher yet not a

significant proportion of the *PPARα* GG genotype was noted in endurance athletes (10%) compared with the sprinters (1%,  $X^2 = 3.8$ , d.f=1,  $p=0.051$ ).

As shown in Table 4, the comparisons of genotype and allele frequencies for *PPARGC1A* revealed significant differences between the subgroups of top-level endurance athletes vs. top-level sprinters, as well as between top-level vs. national level endurance athletes. However, no difference in genotype distribution ( $X^2 = 1.5$ , d.f=2,  $P=0.47$ ) and allele frequencies ( $X^2 = 1.56$ , d.f=1,  $P=0.21$ ) was noted between top-level and national level sprinters. *PPARα* GG genotype was more prevalent in the group of top-level endurance athletes (20%) than in the national level endurance athletes, although it did not reach statistical significance ( $X^2 = 3.46$ , d.f=1,  $P=0.06$ ).

## **Discussion**

Our main findings are the low levels of *PPARGC1A* Ser482 allele, and the *PPARGC1A* Ser/Ser genotype among the Israeli endurance athletes. These findings are interesting and fairly unique, given the fact that this is one of the few studies comparing between sedentary controls and "extreme" phenotypes (endurance athletes and sprinters).

Our study demonstrated a significant difference in the *PPARGC1A* Ser482Ser genotype between the group of endurance athletes and sprinters. Thus, a trade off between endurance and sprint performance traits seems plausible, since none of the elite endurance athletes harbored the Ser482Ser genotype, as opposed to 13% of the elite sprinters. Interestingly, as we decided to compare the frequency distribution of the above SNPs between

elite athletes of sports with different demands (endurance vs. sprinters) and competitive levels (top-level vs. national level), our results were more significant, indicating that the Gly482Ser SNP may be an important genetic factor in determining top-level aerobic performance.

It seems that *PPARGC1A* and *PPAR $\alpha$*  mRNA and/or protein increase fatty acid metabolism, and thus play an important role in the control of fatty acid oxidation. *PPARGC1A* and *PPAR $\alpha$*  mRNA and/or protein are expressed in high levels mainly in cells with abundant mitochondria and, consequently, with a predominant oxidative metabolism as during endurance performance (Liang & Ward, 2006) *PPARGC1A* modulates muscle oxidative capacity, primarily via the coactivation of nuclear respiratory factors (NRF-1 and NRF-2), cytochrome-c oxidase 4 (COX4), mitochondrial transcription factor A (Tfam), and other proteins required for mitochondrial function which induce mitochondrial biogenesis (Wang et al., 2004).

Connecting these data with muscle function, Pilegaard et al. (2003) and recently Mathai et al. (2008) demonstrated that a single bout of prolonged endurance exercise induces a marked increase in transcription and mRNA content of *PPARGC1A* in skeletal muscle, which peaks within the first 2 h after exercise. Studies also showed that both animals (Baar et al., 2002; Terada et al., 2002; Terada & Tabata, 2004;) and humans (Russell et al., 2003; Short et al., 2003; Norrbom et al., 2004) increase *PPARGC1A* mRNA levels as a response to chronic endurance exercise training, whereas *PPARGC1A* protein controls muscle plasticity, suppresses a broad

inflammatory response, and mediates the beneficial effects of exercise (reviewed by Handschin & Spiegelman, 2008).

The expression level of *PPAR $\alpha$*  has been shown to be higher in type I (slow twitch) than in type II (fast twitch) muscle fibers, when homozygotes for the G allele of the *PPAR $\alpha$*  G/C polymorphism had a significantly higher percentage of slow-twitch fibers (Ahmetov et al., 2006). These accumulating findings are notable since they suggest that the expression levels of *PPARGC1A* and *PPAR $\alpha$*  may be genotype-dependent. Keeping in mind that the muscle phenotype of endurance runners is mainly composed of type I muscle fibers with a high mitochondrial density and size enables their reliance mainly on mitochondrial oxidation of free fatty acids and carbohydrates. Therefore, we assume that the expressed levels of *PPARGC1A* and *PPAR $\alpha$*  will influence ability of the muscles to achieve the required phenotype as previously suggested (Russell et al., 2003; Short et al., 2003; Norrbom et al., 2004).

Both *PPAR $\alpha$*  intron 7 G/C and *PPARGC1A* Gly482Ser SNPs studied in the present study have been associated with improved aerobic performance (Ahmetov et al., 2006; Lucia et al., 2005). In addition, the present study is in agreement with those previous reports (Lucia et al., 2005; Ahmetov et al., 2006) regarding the positive role of the Gly482Ser and the G/C SNPs with endurance performance, and disagrees with others (Stumvoll et al., 2004; He et al., 2008). The discrepancy between the present study and those of Stumvoll et al., (2004) and He et al., (2008) may be due to different study populations and methods. .

In conclusion, our data indicate that a lower frequency of the *PPARGC1A* Ser482 allele and possibly a higher frequency of the *PPARα* GG genotype are associated with top-level endurance athletes, and further support the notion that increased *PPARGC1A* and *PPARα* mRNA and/or protein activity may be advantageous to the performance of endurance-type athletes. In addition, data suggest that the above SNPs may belong to a group of several genetic variations that influence top-level endurance performance

### **Perspectives**

The process of talent identification could, in principle, be revolutionized by the discovery of genetic variants that strongly influence athletic performance (MacArthur & North, 2005), primarily at the top level. However, there is still no evidence that any of the genetic variants that were previously investigated have substantial value in the prediction of potential top-level athletes. One rationale for this study was the understanding of the importance and influence that genome factors such as *PPARGC1A* and *PPARα* have on athletic performance. It seems that further investigation is needed on top athletes at the Olympic level among different ethnic groups in order to clarify the potential role of both the Gly482Ser and the G/C polymorphisms in determining endurance and sprint ability.

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**Table 1.** Genotype and allele frequencies of *PPARGC1A* Gly482Ser and *PPAR $\alpha$*  G/C polymorphisms with gender and age. Values are absolute and relative frequencies (in parentheses).  $\chi^2$  and P values correspond to gender comparisons in genotype and allele frequencies.

		Genotype			Allele frequencies					
<i>PPARGC1A</i>	n	Gly/Gly	Gly/Ser	Ser/Ser	$\chi^2$	P	Allele Gly482	Allele Ser482	$\chi^2$	P
<u>Athletes</u>										
All	155	72 (46) *	73 (47) *	10 (7) *			217 (0.70) §	93 (0.30) §		
Male	119	58 (49)	55 (46)	6 (5)	1.18	0.55	171 (0.72)	67 (0.28)	1.31	0.25
Female	36	14 (39)	18 (50)	4 (11)			46 (0.64)	26 (0.36)		
Age		34.9±12	34.9±12	36.9±12						
<u>Controls</u>										
All	240	79 (33)	117 (49)	44 (18)			275 (0.57)	205 (0.43)		
Male	170	60 (35)	78 (46)	32 (19)	1.57	0.45	198 (0.58)	142 (0.42)	0.3	0.58
Female	70	19 (27)	39 (56)	12 (17)			77 (0.55)	63 (0.45)		
Age		26±3	25±3	27±3						
<i>PPAR-<math>\alpha</math></i>		GG	GC	CC			Allele G	Allele C		
<u>Athletes</u>										
All	155	8 (5)	43 (28)	104 (67)			59 (0.19)	251 (0.81)		
Male	119	7 (6)	34 (29)	78 (65)	0.22	0.9	48 (0.20)	190 (0.80)	0.57	0.45
Female	36	1 (3)	9 (25)	26 (72)			11 (0.15)	61 (0.85)		
Age		34.9±12	34.9±12	36.9±12						
<u>Controls</u>										
All	240	10 (4)	67 (28)	163 (68)			87 (0.18)	393 (0.82)		
Male	170	8 (5)	48 (28)	114 (67)	0.11	0.95	64 (0.19)	276 (0.81)	0.38	0.54
Female	70	2 (3)	19 (27)	49 (70)			23 (0.16)	117 (0.84)		
Age		26±3	25±3	27±3						

\*  $\chi^2 = 14.3$ , d.f=2, P=0.0008 for genotype frequencies in athletes vs. controls

§  $\chi^2 = 12.9$ , d.f=1, P=0.0003 for allele frequency in athletes vs. controls

**Table 2.** The *PPARGC1A* Gly482Ser and *PPAR $\alpha$*  G/C genotype and allele frequencies in all groups

<i>PPARGC1A</i>	Athlete groups	n	Genotype			Allele frequencies	
			Gly/Gly	Gly/Ser	Ser/Ser	Allele Gly482	Allele Ser482
	Endurance	74	37 (50)*†	37 (50)*†	0 (0)*†	111 (0.75) §	37 (0.25) §
	Sprinters	81	35 (43)	36 (44)	10 (13)	106 (0.65)	56 (0.35)
	Control	240	79 (33)	117 (49)	44 (18)	275 (0.57)	205 (0.43)
<i>PPAR-<math>\alpha</math></i>	Athlete groups		GG	GC	CC	Allele G	Allele C
	Endurance	74	7 (10)	21 (28)	46(62)	35 (0.24)	113 (0.76)
	Sprinters	81	1 (1)	22 (27)	58 (72)	24 (0.15)	138 (0.85)
	Control	240	10 (4)	67 (28)	163 (68)	87 (0.18)	393 (0.82)

\*  $X^2 = 16.04$ , d.f=2, p=0.0003 for genotype frequencies in endurance athletes vs. controls

†  $X^2 = 10.6$ , d.f=2, p=0.005 for genotype frequencies in endurance athletes vs. sprinters

§  $X^2 = 14.48$ , d.f=1, p=0.0001 for allele frequency in endurance athletes vs. controls

**Table 3.** The *PPARGC1A* Gly482Ser and *PPAR $\alpha$*  G/C genotype and allele frequencies in athletes divided by subgroups

			Genotype			Allele frequencies		
Athlete groups	Competitive level	n	Gly/Gly	Gly/Ser	Ser/Ser	Allele Gly482	Allele Ser482	
<b><i>PPARGC1A</i></b>	Endurance	Top-level	20	15 (75) &	5 (25) &	0 (0) &	35 (0.87) ‡	5 (0.13) ‡
		National level	54	22 (41)	32 (69)	0 (0)	72 (0.67)	36 (0.33)
	Sprinters	Top-level	26	8 (31)	14 (54)	4 (15)	30 (0.58)	22 (0.42)
		National level	55	27 (49)	22 (40)	6 (11)	76 (0.69)	34 (0.31)
			GG	GC	CC	Allele G	Allele C	
<b><i>PPAR-<math>\alpha</math></i></b>	Endurance	Top-level	20	4 (20)	4 (20)	12 (60)	12 (0.30)	28 (0.70)
		National level	54	3 (6)	17 (31)	34 (63)	23 (0.21)	85 (0.79)
	Sprinters	Top-level	26	0 (0)	11 (42)	15 (58)	11 (0.21)	41 (0.79)
		National level	55	1 (2)	11 (20)	43 (78)	13 (0.12)	97 (0.88)

&  $X^2 = 5.55$ , d.f=1, P=0.018 for genotype frequencies in top-level vs. national level endurance athletes

‡  $X^2 = 5.38$ , d.f=1, P=0.02 for allele frequencies in top-level vs. national level endurance athletes