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Evaluation of Association between *PPARGC1A* Gene Polymorphism and Competitive Performance of Elite Athletes

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Abstract

Limited number of researches exist on the relationship between PPARGC1A gene polymorphism (rs8192678) and affects the athletic performance. Thus, the present study aims to decipher any possible association of the rs8192678 polymorphism in the PPARGC1A gene with the competitive performances of Turkish elite track and field athletes. A total of 60 elite athletes (31 sprint/power and 29 endurance) and 20 control/sedentary with the ages of 18-35 voluntarily participated in the study. The International Association of Athletics Federations (IAAF) score scale was used to determine the performance levels of the personal best (PB) of the athletes. Whole exome sequencing (WES) was performed by the genomic DNA sample isolated from blood of the participants. The association between rs8192678 polymorphism and PB was examined by one-way analysis of covariance (ANCOVA) with the adjustment of sex and sport experience. According to the results, there were not any significant deviation between the wild-type (G/G), heterozygote (G/A) and homozygote (A/A) genotypes within and between the groups (p>0.05). Our results underlined that there were not any significances for association of rs8192678 polymorphism with PBs within the groups of the sprint/power and endurance athletes. However, it is recommended that similar studies be conducted with more participants to provide clearer information about the research.

Keywords: *Athletics, Sprint, Power, Endurance, PPARGC1A, Polymorphism, rs8192678*

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PPARGC1A Gen Polimorfizmi (rs8192678) ile Elit Sporcuların Yarışma Performansları Arasındaki İlişkinin Değerlendirilmesi

Öz

PPARGC1A (rs8192678) gen polimorfizmi ve atletik performans arasıdaki ilişkiler konusunda sınırlı sayıda araştırma mevcuttur. Bu nedenle, bu çalışmada PPARGC1A genindeki rs8192678 polimorfizminin Türk elit atletizm sporcularının yarışma performansları ile olası ilişkisin araştırılması amaçlamaktadır. Çalışmaya 18-35 yaşları arasında toplam 60 elit sporcu (31 sprint/güç ve 29 dayanıklılık) ve 20 kontrol/sedanter gönüllü olarak katıldı. Atletlerin kişisel en iyi (PB)/yarışma performans düzeylerini belirlemek için Uluslararası Atletizm Federasyonları Birliği (IAAF) puan ölçeği kullanıldı. Tüm ekzom dizilimi (WES), katılımcıların kanından izole edilen genomik DNA tarafından gerçekleştirildi. rs8192678 polimorfizmi ile PB arasındaki ilişki, cinsiyet ve spor deneyimi ayarlaması ile tek yönlü kovaryans analizi (ANCOVA) ile incelendi. Bulgulara göre grup içi ve gruplar arasında, G/G, G/A ve A/A genotip dağılımları arasında anlamlı bir farklılık tespit edilmemiştir (p>0.05). Sonuç olarak, PPARGC1A rs8192678 polimorfizmi ile sporcuların performansı arasında anlamlı hiçbir ilişki tespit edilmemiştir. Ancak, yapılan araştırma hakkında daha net bilgi verebilmek için daha fazla katılımcı ile yapılması önerilir.

Anahtar kelimeler: *Atletizm, Sürat, Güç, Dayanıklılık, PPARGC1A, Polimorfizm, rs8192678*

Introduction

Today, the relationship between athletic performance and genetic background is one of the main issues that scientists discuss (Bulğay & Zorba, 2022). It is estimated that around 66% of the variance in athletic status could be explained by genetic factors depending on the sport branch (Ahmetov et al., 2011; De Moor et al., 2007). The remaining variance is dependent on environmental ones such as sports experience, lifestyle, applied exercise types (intensity, duration, intensity, and frequency), neuromotor development, altitude, nutrition suitable for sports branch, knowledge of the trainer, cultural differences and psychological state (Bulğay, Çetin, Orhan & Ergün, 2020; Eynon et al., 2013; Yıldırım et al. 2022). As a genetic evaluation, at least 160 polymorphisms have been found to be associated with athletic performance. More than twenty of these polymorphisms have been associated with performance in elite athletes (De Moor et al., 2007).

The peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PPARGC1A*) is a gene located on chromosome 4 (4p15.2). PPARGC1A has been suggested to be associated with athletic performance because of its role in a wide variety of biological responses (Liang & Ward, 2016). PPARGC1A is a transcriptional coactivator that controls mitochondrial biogenesis and oxidative phosphorylation in skeletal muscle (Eynon et al., 2010). Since aerobic and anaerobic capacity highly depend on the mitochondrial function, anaerobic threshold and muscle fiber type of the skeletal muscle (Egan & Zierath, 2013; Puigserver & Spiegelman, 2003). Additionally, PPARGC1A regulates fatty oxidation, glucose utilization, thermogenesis, angiogenesis and formation of muscle fibers (Attie & Kendziorski, 2003). Recent studies revealed that PPARGC1A mRNA is highly expressed in skeletal muscle, myocardium 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, brain and pancreas (Esterbauer, Oberkofler, Krempler & Pasch 1999). Among the common single nucleotide polymorphisms in this gene, rs8192678 (in exon 8, G1444A/Gly482Ser) polymorphism forms by substitution the change of glycine with serine in codon 482 (Gly482Ser). The Gly482Ser polymorphism is viewed in terms of its impact on athletic phenotype (as endurance sports) as well as health (as diabetes and obesity) (Chen et al., 2019).

Several studies have investigated the association between *PPARGC1A* c.1459G>A:p.Gly482Ser (rs8192678) polymorphism and athletic performance. For example, a meta-analysis has revealed that G/G genotype and the allele G may predict the athletic performance regardless of the type of the sport (Chen et al., 2019). Additionally, a lower frequency of the allele A was associated with increased endurance performance ability (Eynon et al., 2010). Another study showed that the allele A has been shown to be independently associated with a lower increase in individual aerobic fitness after nine months of lifestyle intervention (Stefan et al., 2007). Results were also conformed by the findings of other studies in which allele A was proposed as useful in power activities (Gineviciene et al., 2016) and the lower aerobic capacity in Russian rowers (Ahmetov et al., 2007). Moreover, it was found that higher frequency of G/G genotype was associated with elite-level endurance athletes (Eynon et al., 2009). However, there are certain other studies that produced different results (Ginevicience et al., 2014; Peplonska et al., 2017). Although the *PPARGC1A* rs8192678 may be a promising candidate polymorphism for the association with the athletic performance, which may underlie differences in the potential to be an elite athlete, little is known about this polymorphism and its role in the development of athletic performance in Turkish population.

Thus, the main aim of the present study was to compare the genotype and the allele frequencies of *PPARGC1A* rs8192678 polymorphism in elite sprinter/power and long-distance athletes, as well as sedentary controls. The secondary purpose of this study was to evaluate the relationships between the personal best (PB) of the athletes and *PPARGC1A* c.1459G>A polymorphism in elite track and field athletes. We regard that the outcome of this and/or such studies could encouragace the trainers to properly guide the young athletes for choosing the exact sport branch.

Methods

Participants

Sixty elite athletes (31 sprint/power and 29 endurance) licensed in different clubs and affiliated to the Turkish Athletics Federation (Mean $_{\text{Age (year)}}$ = 25.07, SD = 4.80; Mean $_{\text{Length (cm)}}$ = 174.97, SD = 7.89; Mean $_{\text{Body weight (kg)}}$ 72.50, SD = 22.40; Mean $_{\text{Sport experience (year)}}$ = 9.40, SD = 4.80; Mean $_{\text{Personal-best (PB)}}$ = 1005.63, SD = 94.55) participated in the study. Healthy and unrelated citizens of Turkey without any competitive sports experience with a number of 20 (Mean $_{\text{Age (year)}}$ = 23.51, SD = 7.13) were involved in the study as a non-athlete control group. The athletes were categorized as either sprint/power or endurance athletes as

determined by the parameters, distance, duration and energy requirements of their events. All athletes were nationally ranked in the top ten in their sport disciplines.

Study design

The informed voluntary consent and demographic information forms were applied for the athletes and controls groups before the measurements. The International Association of Athletics Federations (IAAF; World Athletics) score scale was used to determine the performance levels of the athletes depending on their personal best/competitive performance (Spiriev, 2014).

Whole Exome Sequencing

DNeasy Blood and Tissue Kit (Qiagen, Germany) was used to isolate the total genomic DNA from the participants according to the supplier's instructions. 1% agarose gel electrophoresis was performed to evaluate the quality of the isolated DNA and NanoDrop (NanoDrop 1000 Spectrophotometer; Thermo Scientific, USA) was used the determination of the DNA concentrations.

Twist Human Comprehensive Exome Panel (Twist Biosciences, USA) was used for the preparation of the next-generation sequencing libraries to perform Whole Exome Sequencing (WES). Shortly, enzymatic DNA fragmentation, size selection, hybridization using Twist Hybridization probes and Dynabeads™ MyOne™ Streptavidin T1 (Invitrogen, USA) and by polymerase chain reaction (PCR)-based library enrichment were carried out according to the instructions of the suppliers. Sequencing was performed by Illumina NextSeq500 according to manufacturer's standard protocol after determination of library size and concentration.

Genome Analysis Toolkit (GATK)'s (Van der Auwera et al., 2013) was chosen to process the raw data. Haplotype Caller program to obtain Binary Alignment Map (BAM) files and subsequently produce an output Variant Call Format (VCF) file via the GRCh38/hg38 reference genome. Variants were annotated by ANNOVAR (Wang, Li & Kakonarson, 2010) and each single nucleotide polymorphisms (SNPs) were analyzed manually.

Statistical analysis

SPSS (Statistical Package for Social Sciences) for Windows 25.0 was used for data analysis. Descriptive statistical methods (numeric, percentage, mean and standard deviation) were used in the assessment of the data. The heterogeneity degree between the studies was assessed with the Skewness and Kurtosis test (Kline, 2011). Chi-square analysis was applied to test the fit ($p>0.05$) to Hardy-Weinberg equilibrium and the difference between categorical variables. Chi square/Fisher's exact test was used to compare the allele frequencies within and between the groups. Hypotheses were tested with a 95% confidence interval and 0.05 significance level. The association between *PPARGC1A* gene rs8192678 polymorphism and PB was examined by one-way analysis of covariance (ANCOVA) with the adjustment of sex and sport experience. In addition,

SNPStats was used to confirm the results. (Allele and genotype frequencies and association approaches were obtained SNPStats (Sole, Guino, VallS & Iniesta, 2006) using logistic regression with logistic regression multiple inheritance models: co-dominant, dominant, recessive, over-dominant and additive. Data were significant when $p<0.05$).

Ethics Statement

Declaration of Helsinki and Gazi University Non-Interventional Clinical Research Ethics Committee with the decision dated March 29, 2021 and numbered 343 was followed to conduct the study.

Results

The present study aims to clarify whether there are any associations between athletic performance and the *PPARGC1A* Gly482Ser (rs8192678) polymorphism. Three groups that were sprint/power, long distance and control have been chosen to asses this aim.

Firstly, the genotype and allele frequencies were determined. According to the results, there were not any significant deviation between the wild-type (G/G), heterozygote (G/A) and homozygote (A/A) genotypes within and between the groups ($p>0.05$). For allele frequencies, although the number of allele G was higher compared to the allele A, there were not any significance within and between the groups ($p>0.05$; Table 1).

Importantly, *PPARGC1A* 1459G>A Gly482Ser (rs8192678) polymorphism was evaluated whether it associated with personal bests (PBs) within the sprint/power or endurance athletes using different genetic models, codominant, dominant, recessive and over-dominant. Our results underlined that there were not any significances for association of rs8192678 polymorphism with PBs within the groups of the sprint/power ($p>0.05$; Table 2) and endurance ($p>0.05$; Table 3) athletes.

Table 1. Genotype and allele frequencies of *PPARGC1A* 1459G>A (rs8192678) polymorphism in Turkish elite athletes and controls

	Genotype			***p-Value***	***Allele***		***p-Value***
	G/G	*G/A*	*A/A*		*G*	*A*	
Sprint/Power	*14 (45.2%)*	*14 (45.2%)*	*3 (9.7%)*		*42 (567.7%)*	*20 (32.3%)*	
Endurance	*13 (44.8%)*	*14 (48.3%)*	*2 (6.9%)*	*0,591*	*40 (69.0%)*	*18 (31.0%)*	*0,192*
Control	*6 (30.0%)*	*9 (50.0%)*	*5 (20.0%)*		*21 (52.5%)*	*19 (47.5%)*	

** Statistically significant differences ($p<0.05$). x^2-chi square result*

Table 2. Association of rs8192678 with the PB within the sprint/power athletes

Model	Genotype	n	Mean score (PB)	p-value
Codominant	G/G	14	1013.14	0,13
	G/A	14	952.29	
	A/A	3	1060.00	
Dominant	G/G	14	1013.14	0,978
	G/A-A/A	17	971.29	
Recessive	G/G-G/A	28	982.71	0,170
	A/A	3	1060.00	
Over-dominant	G/G-A/A	17	1015.53	0,099
	G/A	14	952.29	

*Statistically significant differences (p<0.05); adjusted by sports experience + sex

Table 3. Association of rs8192678 with the PB within the endurance athletes

Model	Genotype	n	Mean score (PB)	p-value
Codominant	G/G	13	1038.85	0,53
	G/A	14	1005.36	
	A/A	2	1031.00	
Dominant	G/G	13	1038.85	0,26
	G/A-A/A	16	1008.56	
Recessive	G/G-G/A	27	1021.48	0,94
	A/A	2	1031.00	
Over-dominant	G/G-A/A	15	1037.80	0,28
	G/A	14	1005.36	

*Statistically significant differences (P<0.05); adjusted by sports experience + sex

Discussion

In the present study, we investigated the genotype distributions and allele frequencies of the *PPARGC1A* rs8192678 polymorphism in elite sprint/power, elite endurance athletes and matched controls. To our best knowledge, the current study is first investigation to determine whether the rs8192678 polymorphism influences competitive performance of elite endurance and elite sprint/power athletes.

In general, A/A genotype could associate to the athletic performance. In a study, the individuals with A/A genotype were reported to have lower aerobic capacity, which may be disadvantageous for the endurance athletes (Ahmetov et al., 2007; Peplonska et al., 2017). Accordingly, lower allele A frequency has been associated with the increase endurance performance in the Israeli athletes (Eynon et al., 2010). In addition, some studies reported the A allele as useful in power activities. Thus, the allele A was reported to be disfavor with the endurance branch (Gineviciene et al., 2016). However, in the present study there were not any significant differences in terms of distribution of the allele A between and within the groups even when the competitive performance were also evaluated.

The effects of the allele A have molecularly investigated by different research groups. According to one of these studies, the allele A has resulted in the downregulation of the *PPARGC1A* in mRNA level (Ling et al., 2004), nevertheless, the downregulation of the gene expression has been linked to the epigenetic modulations in another study (Ling et al., 2008). In other words, besides the possible role of polymorphism (rs8192678), growing evidence supports the concept that epigenetics can also play a role in determining competitive performance. Hence, further genetic mechanisms should also be investigated in addition to the screening of the polymorphisms in the *PPARGC1A* gene. We believe that epigenetic studies bring new information and get better knowledge to the fact that athletics performance is associated with genotype variants.

In the present study, the results figured out that the ratio of the allele G was higher in the athletes compared to the control group although the deviation was not significant. Moreover, the number of the allele G was insignificantly higher in the endurance athletes compared to the sprint/power athletes. Even there were not any significance, the tendency of the distribution of the allele G was similar to the studies in the literature. The allele G was associated with the endurance in the Polish and Russian athletes (Macıejewska et al., 2012). Similarly, G/G genotype was linked to the elite-level endurance athletic performance in another studies (Eynon et al., 2009; Jin et al., 2016; Tural et al., 2014). Therefore, the distribution of the allele G in the present study confirmed the previous studies.

Genetic background of the athletic performance could differ between the athletes when diverse populations have been investigated. The reasons could be the branches of the athletes, statistical errors, heterogeneous groups, limited number of the participants, ethnicity of the athletes and sport experiences (Bulğay & Zorba, 2022). These drawbacks, particularly the number of the participants, were also faced during the conduction of the present study. Still, the study is critical to explore the genetic tendency of the athletes to specific disciplines. Moreover, further studies with higher number of the participants and more than one polymorphisms are needed to reach goal. Thus, these issues are under progress in our research group.

Conclusion

According to the findings of the research, there were not any significant differences in the frequency of the analyzed genotypes between the sprint/power and endurance athletes. *PPARGC1A* Gly482Ser (rs8192678) G/G genotype was found to have a better PB performance compared to the A/A genotype in the endurance group but G/G genotype had a poorer PB performance compared to the A/A genotype in sprint/power athletes. It is recommended that similar studies be conducted with more participants to provide clearer information about the research.

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Conflict of interest

All authors declare having no conflict of interest.

Author Contributions

Research Idea: CB; Research Design: CB, HHK; Analysis of Data: MAE, HHK, OA, CB; Writing: CB, HHK; Critical Review: EZ, KU, IB

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