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Association of *SOD2* Polymorphism (Rs4880) and Competitive Performance in Track and Field Athletes

Elit Atletlerde *SOD2* Rs4880 Polimorfizminin Yarışma Performansı ile İlişkisi

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ASSOCIATION OF SOD2 POLYMORPHISM (RS4880) AND COMPETITIVE PERFORMANCE IN TRACK AND FIELD ATHLETES

ABSTRACT

The rs4880 polymorphism in the *SOD2* gene has frequently been associated with the athletic performance of the athletes in different populations. However, there were not any studies in the Turkish elite athletes. Thus, the aim of the study is to evaluate the impacts of *SOD2* rs4880 polymorphism on competitive performance of Turkish elite athletes. A total of 60 elite athletes (31 sprint/power and 29 endurance) and 20 controls with the ages of 18-35 voluntarily participated in the study. World Athletics (WA) score table was used to determine the performance levels of the competitive performance/personal best (PB) of the athletes. Whole exome sequencing (WES) was performed by the genomic DNA isolated from peripheral blood of the participants. Sport type, sex and competitive performance were chosen as the parameters to compare within and between the groups by linear regression models. There were not any significances between the genotype and allele frequencies. Finally, there were not any associations between competitive performance and genotype frequencies within the sprint/power athletes while competitive performance was significantly (p=0.049) correlated with rs4880 polymorphism according to the over-dominant model within the endurance athletes. The rs4880 polymorphism in the *SOD2* gene may be linked to the competitive performance of the endurance athletes. Still, further studies with more participants and analyzing multiple factors are needed.

Keywords: Athlete, Athletic Performance, Athletics, *SOD2*, rs4880 Polymorphism.

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ELİT ATLETLERDE SOD2 (RS4880) POLİMORFİZMİNİN YARIŞMA PERFORMANSI İLE İLİŞKİSİ

ÖZ

SOD2 rs4880 polimorfizmi, farklı popülasyonlarda, atletlerin atletik performanslarıyla sıkça ilişkilendirilen varyantlardandır. Ancak, Türk elit atletlerde, bu varyantın atletik performans üzerine etkisine yönelik herhangi bir çalışma yoktur. Bu nedenle, sunulan çalışmanın amacı, elit atletlerde, *SOD2* rs4880 polimorfizminin yarışma performansı üzerindeki olası etkilerini açığa çıkartmayı amaçlamaktadır. Çalışmaya 18-35 yaşları arasında 31 sprint/güç ve 29 dayanıklılık olmak üzere toplam 60 elit atlet ve 20 sedanter birey dahil edilmiştir. Atletlerin yarışma performansları/bireysel en iyi dereceleri (PB), Dünya Atletizm (WA) birliğinin

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performans puanlama sistemine göre belirlenmiştir. Katılımcıların kanlarından izole edilen genomik DNA ile tüm ekzom dizileme (WES) gerçekleştirilmiştir. Spor branşı, cinsiyet ve yarışma performansı, doğrusal regresyon modeli ile grup içi ve gruplar arası kıyaslanan parametreler olarak seçilmiştir. Grup içinde ve gruplar arasında, alel ve genotip frekansları arasında bir farklılık görülmemiştir. Sprint/güç grubu atletlerde, yarışma performansı ile genotip frekansı arasında anlamlı bir ilişki görülmezken dayanıklılık grubu atletlerde, rs4880 polimorfizminin yarışma performansı ile istatistiksel olarak anlamlı bir şekilde (p=0.049) ilişkili olduğu görülmüştür. Bu çalışma ile *SOD2* rs4880 polimorfizminin dayanıklılık branşı ile ilişkili olabileceği söylenebilir. Yine de çok katılımlı bir grupla diğer genetik varyasyonların dahiliyle ileri çalışmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Atlet, Atletik Performans, Atletizm, *SOD2*, rs4880 Polimorfizmi.

INTRODUCTION

In the world of professional sports, one of the most significant indicators of success for athletes is participating in important competitions including the Olympics and, beyond this, winning medals (Bulgay and Ergun, 2022). Multiple factors such as athletes' disposition to their branch, VO_2max capacity, non-contact injury risk, post-training recovery, individual diet and oxidative stress affect the performance of the athletes. Recently, genetic background has also been clarified as a factor influencing the athletic performances (Gineviciene et al., 2022).

In the molecular level, several genes including *ACTN3*, *ACE*, *EPO*, *COL5A1*, *PPARGC1A*, *ADRB2*, and *AMPD1* and/or nucleotide alterations, specifically called single nucleotide polymorphisms (SNPs), have been linked to the athletic performance under a research branch, called sports genetics. When the functions of the product encoded by these genes (*ACTN3* gene in muscle fiber type and power production; *ACE* gene in regulating blood pressure and cardiovascular function; *EPO* gene in the production of erythropoietin, a hormone involved in the regulation of red blood cells and oxygen delivery to muscles; *COL5A1* gene in collagen synthesis, which is important for maintaining healthy tendons and joints; *PPARGC1A* gene in energy metabolism; *ADRB2* gene in the regulation of breathing and the ability to handle high-intensity exercise; and *AMPD1* gene in ability to produce energy during intense exercise) was focused, any alterations in those genes could directly affect the performances of the athletes (Ahmetov and Fedotovskaya, 2015; Varillas-Delgado et al., 2022; Bulgay et al., 2023).

Another gene that sports scientists have recently become interested in and thought to have the capability to influence the athletic performance is superoxide dismutase 2 (*SOD2;* localized to the chromosome 6q25.3). The *SOD2* gene encodes the enzyme, superoxide dismutase 2, which is involved in the elimination of reactive oxygen species (ROS) in cells. ROS are the natural byproducts of the cellular metabolism and can contribute to oxidative stress, and cause cellular damage (Ben-Zaken, et al., 2013; Ahmetov et al., 2014; Dokumacı and Cakır-Atabey 2016; Jówko et al., 2017). Several studies have investigated the potential relationship between variations in the *SOD2* gene and the athletic performance. However, the findings have been inconsistent and the exact relationship between the *SOD2* gene and athletic performance is still not well-understood. Some studies have found an association between specific variations in the *SOD2* gene and improved athletic performance while others have not found a significant relationship. In addition to environmental factors, oxidative stress capacity is also controlled genetically and epigenetically, and differs among athletes in terms of the athletic performance (Shimoda-Matsubayashi et al., 1996; Akimoto et al., 2010; Ben-Zaken et al., 2013; Ahmetov et al., 2014; Jówko et al., 2017). In the context of previous studies carried out with different populations and groups, it can be said that T/T genotype or the T allele in the 47th nucleotide of the coding region (NM_000636.4:c.47T>C; rs4880; annotation is also available as A>G in the databases) could be linked to elevated oxidative stress. However, due to the limitations of previous studies, the effect mechanism of the rs4880 polymorphism on athletic performance could not be fully clarified.

By the frame of the information above, the main aim of the present study was to compare the genotype and the allele frequencies of *SOD2* rs4880 polymorphism between elite sprinter/power and endurance (long-distance) athletes in the presence of controls. The secondary purpose of the study was to investigate the possible association of the rs4880 polymorphism with the competitive performances in the elite endurance and sprint/power athletes. To our knowledge, this is the first study evaluating the *SOD2* rs4880 polymorphism in Turkish track and field elite athletes. For these aims, codominant, dominant and recessive genetic models were assessed to determine differences amongst athlete phenotypes (sprint/power and endurance). By this study, the associations between rs4880 polymorphism and athletic performance could guide sports scientists, trainers and athletes to determine the genetic factors influencing the athletic performance and direct athletes to proper branches.

METHODS

Study Design

Before the measurements and analyses, the informed voluntary consent and demographic information forms were obtained from the participants.

Participants

Sixty elite athletes (sprint/power: 11 (35.5%) females and 20 (64.5%) males, and endurance: 10 (34.5%) females and 19 (65.5%) males) licensed in different clubs and affiliated to the Turkish Athletics Federation ($M_{\text{Age(year)}} = 25.07$, SD = 4.80; $M_{\text{Sports experience(year)}} = 9.40$, SD = 4.80; $M_{\text{Personal bests(PBs)}} = 1005.63$, SD = 94.55) participated in the study. The number of the controls (non-athletes) were 20 (6 (30.0%) females and 14 (70.0%) males; $M_{\text{Age(year)}} = 23.51$, SD = 7.13) and they were healthy unrelated citizens of Turkiye and without any competitive sport experiences. The athletes were categorized as either sprint/power or endurance as determined by the distance, duration and energy requirements of their events. All athletes were ranked in the top ten in their sport disciplines nationally.

Personal Best (PB)

The International Association of Athletics Federations (IAAF; World Athletics; WA) score table was used to determine the performance levels of the athletes depending on their personal best/competitive performance. The WA score table are useful to ascertain the performances of the athletes from diverse events and genders (Spiriev, 2014). For instance, the WA score table of a male sprint runner who runs 100 meters in 10.05 sec is 1189 while that of a marathon runner who complete the race in 2 h 20 min 11 sec is 997. Therefore, the performance score of the marathon runner is less than that of 100 m runner.

Whole Exome Sequencing

Total genomic DNA was isolated from peripheral blood of the participants using DNeasy Blood and Tissue Kit (Qiagen, Germany) by supplier's instructions. The quality of the isolated DNA was confirmed using 1% agarose gel electrophoresis and NanoDrop (NanoDrop 1000 Spectrophotometer; Thermo Scientific, USA) according to optical density ratios, and the concentrations were found out by NanoDrop.

Twist Human Comprehensive Exome Panel (Twist Biosciences, USA) was used for the library preparation for Whole Exome Sequencing (WES) according to the instructions of the supplier. Briefly, DNA was fragmented enzymatically, size is selected and hybridization was applied using Twist Hybridization probes and Dynabeads™ MyOne™ Streptavidin T1 (Invitrogen, USA), and the library was enriched by polymerase chain reaction (PCR). The concentration and size of the libraries were determined and sequencing was carried out using Illumina NextSeq500 (Illumina Inc., USA) according to manufacturer's standard protocol.

Raw data were processed to by the Genome Analysis Toolkit (GATK)'s (Van der Auwera et al., 2013). Haplotype Caller program was chosen 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 and Kakonarson, 2010) and SNPs were analyzed manually.

Statistical analyses

Statistical Package for Social Sciences (SPSS) for Windows 25.0 was used for data analysis. In the primary evaluation of the data, descriptive statistical methods (number, percentage and mean) were used and the data was analyzed for parametric statistics. The variables were tested for normality while Kolmogorov-Smirnov ($p=0.200$) and Shapiro-Wilk ($p=0.785$) were used for homogeneity of variance. As result of these tests, parametric statistics were performed for the variables. Genotype and allele frequencies were calculated for the polymorphism and Hardy-Weinberg equilibrium (HWE) was assessed using the chi-square (χ^2) or Fisher's exact test. Allele and genotype frequencies and the association approaches were obtained by SNPStats (Sole et al., 2006) using linear regression with linear regression multiple inheritance models: co-dominant, dominant, recessive and over-dominant. To confirm the results obtained using the linear regression models, the data was also analyzed by one-way analysis of covariance (ANCOVA), adjusting for sex and sports experience. Data were significant when $p<0.05$.

Ethical approval

The study was carried out in accordance with the Declaration of Helsinki and the approval was obtained from the Gazi University Non-Interventional Clinical Research Ethics Committee with the decision dated April 05, 2021 and numbered 09.

RESULTS

The present study aims to figure out any possible association of the *SOD2* rs4880 polymorphism with the competitive performances of two groups, sprint/power and endurance, of the Turkish elite athletes in the presence of control group. According to analyses, there were not any significance between the genotype and allele frequencies (Table 1).

When the PBs were analyzed, there were not any associations between competitive performance and genotype frequencies within the sprint/power ($p>0.05$; Table 2) while competitive performance was significantly correlated with rs4880 polymorphism according to the over-dominant model within the endurance athlete group ($p=0.049$; Table 3).

Table 1. Genotype and allele frequencies of *SOD2* rs4880 polymorphism in sprint/power and endurance elite athletes and controls.

Branch	Genotype			p-Value	Allele		p-Value
	G/G	G/A	A/A		G	A	
Sprint/Power	11(35.5%)	12(38.7%)	8(25.8%)	0.853	34(54.8%)	28(45.2%)	0.890
Endurance	8(27.6%)	15(51.7%)	6(20.7%)		31(53.45)	27(46.6%)	
Controls	5(25.0%)	10(50.0%)	5(25.0%)		20(50.0%)	20(50.0%)	

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

Table 2. rs4880 association with the competitive performance within the sprint/power athletes.

Model	Genotype	n	Mean score (PB)	P-value
Codominant	A/A	11	983.64	0.87
	A/G	12	993.42	
	G/G	8	981.88	
Dominant	A/A	11	983.64	0.75
	A/G-G/G	20	988.8	
Recessive	A/A-A/G	23	988.74	0.8
	G/G	8	981.88	
Over-Dominant	A/A-G/G	19	982.89	0.59
	A/G	12	993.42	

Table 3. rs4880 association with the competitive performance within the endurance athletes.

Model	Genotype	n	Mean score (PB)	P-value
Codominant	A/A	8	1034.75	0.12
	A/G	15	1013.07	
	G/G	6	1028	
Dominant	A/A	8	1034.75	0.43
	A/G-G/G	21	1017.33	
Recessive	A/A-A/G	23	1020.61	0.16
	G/G	6	1028	
Over-Dominant	A/A-G/G	14	1031.86	**0.049**
	A/G	15	1013.07	

DISCUSSION

The relationship between athletic performance and genetics is complex and not fully understood. Studies have shown that genetic factors could play a role in determining an individual's athletic potential and performance but the extent to which genetic background influence athletic ability varies depending on the sport and the specific trait (Yıldırım et al., 2022). Thus, more researches illuminating genetic associations in the elite athletes are needed. In this context, the present study investigated the genotype distributions and allele frequencies of the *SOD2* gene rs4880 polymorphism within and between the elite endurance and sprint/power athletes, and matched controls. To the best of our knowledge, this is first study to analyze the association of rs4880 polymorphism in *SOD2* gene with the competitive performance of the Turkish elite endurance and sprint/power athletes.

According to the findings obtained in the present study, although there were not any significances in the distribution of the genotype and allele frequencies in the sprint/power athletes (Table 1), it was found that the G allele frequency was higher compared to the A allele in this group. In a study conducted by Ahmetow et al., (2014) on 2664 Caucasian athletes (2262 Russian and 402 Polish athletes), the frequency of the *SOD2* A/A genotype was significantly lower in the power/strength athletes compared to controls or athletes involved in low-intensity sports. In another study conducted in a different population, it was found that the number of the power and endurance athletes with the G allele was higher compared to the control group (Ben-Zaken et al., 2013). Thus, it can be said that the findings of the present study regarding the power/sprint athletes are close to those in the literature. However, in order to determine whether the *SOD2* rs4880 polymorphism is more prone in athletes in anaerobic or aerobic branches, further studies with wider populations and different branches are needed.

According to another finding of the present study, without any significance in the genotype and allele frequencies, the PBs were correlated with the rs4880 polymorphism according to the over-dominant model within the endurance athletes (p=0.049; Table 3). In this context, it can be said that the rs4880 polymorphism could be linked to the endurance branch. Nevertheless, as multiple genetic and environmental factors affect the athletic performances (Ben-Zaken, et al., 2015; Ulucan, 2016; Switala and Leonska-Duniec, 2021; Antrobus et al., 2022), the limited number of studies on the relationship between the rs4888 polymorphism and athletic success limits the interpretation of the results. In this context, it can be said that the debates on the validity of genetic tests and the results obtained from them in athlete selection maintain their topicality.

According to the literature, rs4880 T/T genotype has been linked with increased creatine kinase (CK) and oxidative stress in anaerobic branches (power/

sprint). For instance, Akimoto et al., (2010) found that there was an increase in the post-competition CK levels of athletes with the rs4880 T/T genotype. It was also determined that the athletes with the G/G genotype had a lower rate of muscle injuries. In another similar study, it was found that the increased *SOD2* mRNA expression in male individuals with the rs4880 G/G genotype after the intense exercise was effective in keeping oxidative stress at a minimal level. The possible mechanism was explained as the increased activity of the protein by the G allele causing alanine to valine amino acid alteration (Bresciani et al., 2013). Moreover, researchers have also reported that three-month training programs applied to the athletes from different branches (swimming and wrestling) caused changes in the lipid profile as well as the parameters of oxidative stress and muscle damage, and these changes were linked to the *SOD2* rs4880 polymorphism (Manica-Cattani et al., 2012; Ewa et al., 2017; Jówko et al., 2017).

Importantly, rs4880 A/A genotype were also related to the increased production of proinflammatory cytokines (Montano et al., 2012), having a negative impact on athletes. Proinflammatory cytokines are small proteins that are produced by the immune system in response to injury or infection and have a critical role in the inflammation. However upon excess production, they can cause systemic inflammation and affect the athletic performance and athlete's overall health. (Montano et al., 2012; Forte et al., 2022; de Morais Mourão et al., 2022). Thus, it could be favorable to have G allele in the athletes for both overall health and performances.

Nowadays, branch selection and training approaches according to the genetic background have been under-progress. Through genetic and epigenetic screening in addition to field and laboratory tests, prospective athletes will be enabled to develop themselves in applicable athletic branches in the future. The identification of cellular components such as CK and oxidative stress by genetic analyses, supplementation of antioxidants, detection of muscle damage levels, implementation of in-branch guidance and application of individual training programs will benefit athletes in terms of improving performance. In this context, it is thought that genotype-phenotype association studies should be conducted with physical, physiological and biochemical variables for a larger number of athletes and branches in future studies. In parallel, the present study aimed to reveal the relationship between the *SOD2* rs4880 polymorphism and the athletic performance as a part of ongoing project. It is thought that the present study conducted on athletes will contribute to the literature and the results will spearhead future studies.

CONCLUSION

For the evaluation of the athletic performance, it is considered that drawing a conclusion through only one candidate gene and SNP on it may mislead the literature but multi-gene and multi-factor approaches (epigenetics, psychology and environmental) can play a key role in the exploration of the endurance or sprint/power athlete parameters. Moreover, it is important to consider the homogeneity and quantity of the study groups as an important detail in terms of the consistency of the genetic reflections explained as a result of the research studies conducted. Still, such single gene and/or SNP studies are required as the pilot studies for further ones. In summary, the rs4880 polymorphism in the *SOD2* gene may be linked to the competitive performance of the endurance athletes.

Author Contribution Rates:

Design of Study: CB (%50), HHK (%50)

Data Acquisition : EZ (%40), IB (%60)

Data Analysis : MAE (%60), MC (%40)

Writing Up : CB (%50), HHK (%50)

Submission and Revision : CB (% 50), HHK (% 50)

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