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PPARA and *IL6*: exploring associations with athletic performance and genotype polymorphism

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ABSTRACT

This study aims to investigate the Interleukin (*IL*)-6 rs1800795 and peroxisome proliferator-activated receptor alpha (*PPARA)* rs4253778 polymorphism distributions in the relatively faster and slower subgroups of national cross-country skiing athletes and to identify advantageous genotypes for endurance performance. IL-6 is an inflammatory mediator that is effective in muscle tissue hypertrophy, repair, and the immune system. On the other hand, PPARA transcription factor is a molecule associated with fatty acid, sugar metabolism and inflammation formation. Total of 30 professional cross-country skiing athletes were examined in three groups as athletes, female athletes, and male athletes. DNA of the participants were isolated from blood and genetic polymorphisms were determined by RT-PCR. Athletes were divided into two subgroups as faster and slower referring to their "1-kilometer cross-country skiing time averages (CCSTA)". Polymorphism distributions in these subgroups were analyzed statistically with Fisher's exact test and descriptive tests. In addition, the 1 km-CCSTA values of the genotypes were determined by descriptive statistical methods and the time advantages were calculated. It was determined that the combination of *IL-6* rs1800795 GC and *PPARA* rs4253778 GG genotypes was observed to be more prominent among the faster categories of cross-country skiing competitors, particularly in the athletes and male athletes categories, and it had a time advantage at 1 km-CCSTA. The GC genotype (p= 0.0098) and C-allele (p=0.0398) of *IL-6* rs1800795 polymorphism were detected at a higher rate in the fast subgroup in male athletes. These genotypes may support endurance performance.

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Introduction

Athletic performance is a concept with multifactorial components affected by both polygenetic and epigenetic mechanisms, and the rates of this influence are the subject of genetic studies. One of the main purposes of sports genetics is to determine the genes that affect athletic performance. Determination of the polymorphisms in genes that affect sports performance traits can be used for the identification of talent for sports, and as of today, there are many genes associated with athletic performance (1).

Different human phenotypes (e.g. skeletal structure, muscle strength) influence athletic performance. Each phenotype is the result of complex interactions between various anatomical, biochemical, and physiological systems. Genetic factors are likely to have an impact on the effectiveness of muscle activity and contraction as well as their mass. Differences in endocrine function based on genotype, which is important for the proper growth and function of skeletal muscles, may have implications. There are intricate interactions among thyroxine, growth hormone, and the downstream regulators of the pathways that lead to anabolic processes (such as IGF-1 and IGF-2) (2).

Cross-country skiing is a sport that requires uninterrupted performance for a long time and requires endurance. This sport is a long-distance sport with skis and poles in mountainous and rough terrain. It originated in Scandinavian countries as a form of transportation and entertainment. The skis used are narrower and lighter, while the poles are longer. This sport requires a high level of endurance performance.

Interleukine 6 (IL-6) is a cytokine and it has a variety of functions in various organs and tissues, creating a range of effects. After extended periods of exercise, the skeletal muscle generate and discharge substantial quantities of IL-6, which categorizes it as a myokine (3). Conflictingly, there are claims that IL-6 may have harmful effects, including the advancement of atrophy and the deterioration of muscle. The rate of *IL-6* expression in skeletal muscle cells increases in events such as increased muscle activity and oxidative stress, decreased blood glucose level, hyperthermia, ischemia-reperfusion, and muscle-tissue injury (4,5). The amount of IL-6 in the blood increases considerably during exercise. Depending on the load of physical activity, IL-6 can increase up to 100 times the normal level in the blood and muscle tissue during exercise. The rise of IL-6 levels during physical activity indicated a traditional reaction of the acute phase which began due to the harm caused to the muscles in use. Macrophages have been hypothesized to be responsible for this increase (6). The

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genes responsible for the production of IL-6 are active in various immune cells and various adipose cells, apart from skeletal muscle cells. *IL-6* is located at 7p15.3 and the most frequently analyzed polymorphism is rs1800795; a C/G transversion. G allele is related with increased amounts C allele is related with decreased amounts (7). There are studies in the literature stating that they could not detect any significant relation between this polymorphism and power phenotype (8,9) or endurance phenotype (10, 11, 12, 13).

The peroxisome proliferator-activated receptor alpha (PPAR-A) is a nuclear receptor and coded by *PPAR-A* gene, which is located at 22q12-q13.1 It is highly expressed in skeletal muscle cells. PPAR-A is involved in the fatty acid oxidation pathway and ATP requirement (14), and also have functions in vascular inflammation (15). *PPAR-A* expression in increased in fasting (14,16). Mostly analyzed single nucleotide polymorphism of *PPAR-A* is rs4253778; a G/C transversion. (17).

Some hypothesis shows strong evidance about the effect of IL-6 on PPAR-A metabolism. Accordingly, IL-6 suppresses PPARA, but this mechanism is still open to research (18).

In order to examine the effect of *PPARA* rs4253778 polymorphism on athletic performance, some studies found significant relations between alleles and phenotypes in endurance athletes (19), but some studies could not find. Likewise, studies on *PPARA* rs4253778 polymorphism with the endurance phenotype (20, 21) and with the strength phenotype (22) showed contraversal results. Therefore, in the current study, we aimed to determine the *IL-6* rs1800795 and *PPARA* rs4253778 polymorphisms for cross-country skiing athletes, for the first time in literature.

Materials and Methods

Study groups

A total of 30 cross-country skiing athletes (10 females and 20 males) participated in the study. The study was carried out with a protocol in accordance with the Declaration of Helsinki. Uskudar University Ethics Committee approved the study protocol (Number: B.08.6.YÖK.2. US.0.05.0.06/2018/553).

Genotyping

DNA isolation from blood samples taken from athletes was performed with a PureLink DNA isolation kit (Invitrogen, Van Alley Way Carlsbad Nano, USA) in accordance with user protocol. Genotyping and generation of gene amplicons from isolated DNAs were performed by real time-PCR method and for this purpose Roch Light Cycler Nano's PCR device, Taqman's genotyping kit (Applied Biosystems Foster City, CA, USA), and VIC/FAM probes were used.

Classification of subgroups

The athletes were divided into fast and slow athletes according to their "1-kilometer cross-country skiing time averages (1km-CCSTA)" records. The genotypes and the alleles were genotyped within these athletes. In addition, the genotype distribution of the *IL-6* rs1800795 and *PPARA* rs4253778 polymorphisms of the groups were compared with 1 km-CCSTA values. The differences between the 1 km-CCSTAs of the genotypes and the 1 km-CCSTAs of the athlete groups were determined, and according to time differences it was revealed which genotypes completed 1km in a shorter time. Finally, genotypes with a higher rate in the faster subgroups were compared with the genotypes that had a time advantage in the group. In this way, advantageous genotypes in the groups were aimed to be determined.

Statistical analysis

SPSS Statistics 25 program (SPSS, version 25.0, IBM, USA) was used for descriptive statistics and non-parametric analysis of the data obtained. For Fisher's exact test results, significance was accepted as less than 0.05 ($p< 0.05$).

Results

All the athletes were successfully genotyped for *PPARA* rs4253778 and *IL-6* rs1800795 polymorphisms, and compared with the average skiing times and the 1km-CCSTA records. The average age, height, weight, 1 km-CCSTA values of the athletes participating in the study, and the number of individuals in the faster and slower subgroups are given in Table 1.

The genotype distributions of the *IL-6* rs1800795 and *PPARA* rs4253778 polymorphisms are shown in Table 2. *IL-6* rs1800795 GC genotype, and *PPARA* rs4253778 GG genotypes were the dominant genotypes in cross-country skiing athletes (Table 2).

The *IL-6* rs1800795 and *PPARA* rs4253778 allele distributions of the groups are shown in Table 3. When the allele gene distributions of the groups were examined, no statistically significant difference was detected in *PPARA* rs4253778 polymorphism. For *IL-6* rs1800795 polymorphism, we detected a signinificant difference in male athletes (P=0.0398). However, according to our data, the increased rate of the C allele in the faster group is due to the heterozygous genotype, not the homozygous genotype (Table 3).

The distribution of genotypes of *IL-6* rs1800795 and *PPARA* rs4253778 polymorphisms of faster and slower subgroups, and their comparisons were shown in Tables 4, 5 and 6, respectively. For both polymorphisms, genotypes did not show a statistically significant difference between

Table 1. Phenotypic characteristics of the athletes.

Phenotypic features	Athletes (n=30)	Female athletes (n=10)	Male athletes (n=20)
Average age (Year)	18.0±1.2	17.3±0.7	18.4±1.2
Average height (cm)	168.2±6.7	163.3±6.3	170.6±5.5
Average weight (kg)	59.1±6.4	54.2±4.6	61.6±5.7
1 km-CCSTA (s)	185.2±19.8	208.2±12.1	173.7±10.5
Number of faster subgroup athletes	17	5	10
Number of slower subgroup athletes	13	5	10

Table 2. Genotype distribution of IL-6 rs1800795 and PPAR-A rs4253778 polymorphisms.

Polymorphisms	Genotypes	Athletes (n=30)	Female athletes (n=10)	Male athletes (n=20)
	GG	13 (43.33 %)	4 (40 %)	9 (45 %)
***IL-6* rs1800795**	GC	17 (56.66 %)	6 (60 %)	11 (55 %)
	CC	0 (0 %)	0 (0 %)	0 (0 %)
***PPAR-A* rs4253778**	GG	20 (66.66 %)	6 (60 %)	14 (70 %)
	GC	7 (33.33 %)	2 (20 %)	5 (25 %)
	CC	3 (10 %)	2 (20 %)	1 (5 %)

Table 3. Allele distribution of *IL-6* rs1800795 and *PPARA* rs4253778 polymorphisms.

IL-6* *rs1800795	***PPARA* *rs4253778***		**Athletes (n=30)**	**Female athletes (n=10)**	**Male athletes (n=20)**
		Total	43	14	29
G	**-**	Faster subgroup	23 (38.33 %)	7 (35 %)	10 (25 %)
		Slower subgroup	20 (33.33 %)	7 (35 %)	19 (47.5 %)
		Total	17	6	11
C	**-**	Faster subgroup	11(18.33 %)	3 (15 %)	8 (20 %)
		Slower subgroup	7 (11.66 %)	3 (15 %)	3 (7.5 %)
p- value			p= 0.5656	p=1.0000	p=0.0398*
		Total	47	14	33
-	**G**	Faster subgroup	27 (45 %)	8 (40 %)	18 (45 %)
		Slower subgroup	20 (33.33 %)	6 (30 %)	15 (37.5 %)
		Total	13	6	7
-	**C**	Faster subgroup	7 (11.66 %)	2 (10 %)	2 (5 %)
		Slower subgroup	6 (10 %)	4 (20 %)	5 (12.5 %)
p-value			p=1.0000	p=0.6285	p=0.4075

Table 4. Distribution of genotypes of *IL-6* rs1800795 and *PPAR-A* rs4253778 polymorphisms between faster and slower athletes.

Polymorphisms	Genotypes	Athletes Faster (n=17)	Athletes Slower (n=13)	p-value
***IL-6* rs1800795**	**GG** n=13 (43.33 %)	n=6 (20 %)	n=7 (23.33 %)	p= 0.4601
(n=30)	**GC** n=17 (56.66 %)	n=11 (36.66 %)	n=6 (20 %)	
	CC n=0 (0 %)	n=0 (0 %)	n=0 (0 %)	
***PPAR-alfa* rs4253778**	**GG** n=20(66.66 %)	n=11 (36.66 %)	n=9 (30 %)	p= 0.5197
(n=30)	**GC** n=7 (33.33 %)	n=5 (16.66 %)	n=2 (6.66 %)	
	CC n=3 (10 %)	n=1 (3.33 %)	n=2 (6.66 %)	

faster and slower subgroups (Table 4).

For females, genotypes did not show a significant difference between faster and slower athletes in both polymorphisms (Table 5).

For male athletes, the distribution of *IL-6* rs1800795 polymorphism genotypes between faster and slower subgroups showed a significant difference (Table 6). The *IL-6* rs1800795 polymorphism' GC genotype was detected at a significantly higher rate in the faster subgroup (p=0.0098). The GC genotype, which was 15% in the slower subgroup, was observed as 40% in the faster subgroup (Table 6).

Values of 1 km-CCSTA and differences of genotypes of *IL-6* rs1800795 and *PPARA* rs4253778 polymorphisms for athletes, female athletes, and male athletes are shown in Tables 7, 8 and 9; respectively.

Although the genotypes did not show a statistically significant difference between faster and slower athletes in both polymorphisms (Table 7). The GC genotype of the *IL-6* rs1800795 polymorphism completed 1km earlier than the 1 km-CCSTA of the group with 3.7±22.9 seconds, and the GG genotype of the *PPARA* rs4253778 polymorphism completed the 1km early with 2.5±18.9 seconds (Table 7). These polymorphisms had a time advantage in completing 1km.

Although the genotypes of female athletes did not show a statistically significant difference between faster and slower subgroups in any of the *IL-6* rs1800795 and *PPARA* rs4253778 polymorphisms (Table 8), some of the

Table 5. Distribution of genotypes of *IL-6* rs1800795 and *PPARA* rs4253778 polymorphisms between faster and slower female athletes.

Polymorphisms	Genotypes	Female athletes Faster subgroup (n=5)	Female athletes Slower subgroup (n=5)	p- value
***IL-6* rs1800795 (n=10)**	**GG** n=4 (40 %)	n=2 (20 %)	n=2 (20 %)	p= 1.000
	GC n=6 (60 %)	n=3 (30 %)	n=3 (30 %)	
	CC n=0 (0 %)	n=0 (0 %)	n=0 (0 %)	
***PPARA* rs4253778 (n=10)**	**GG** n=6 (60 %)	n=3 (30 %)	n=3 (30 %)	p= 0.1353
	GC n=2 (20 %)	n=2 (20 %)	n=0 (0 %)	
	CC n=2 (20 %)	n=0 (0 %)	n=2 (20 %)	

Table 6. Distribution of genotypes of *IL-6* rs1800795 and *PPARA* rs4253778 polymorphisms between faster and slower male athletes.

Polymorphisms	Genotypes	Male athletes Faster Subgroup (n=10)	Male athletes Slower Subgroup (n=10)	p- value
***IL-6* rs1800795 (n=20)**	**GG** n=9 (45 %)	n=1 (5 %)	n=8 (40 %)	p= 0.0098**
	GC n=11(55 %)	n=8 (40 %)	n=3 (15 %)	
	CC n=0 (0 %)	n=0 (0 %)	n=0 (0 %)	
***PPARA* rs4253778 (n=20)**	**GG** n=14(70 %)	n=8 (40 %)	n=6 (30 %)	p= 0.4758
	GC n=5 (25 %)	n=2 (10 %)	n=3 (15 %)	
	CC n=1 (5 %)	n=0 (0 %)	n=1 (5 %)	

Table 7. Values of 1km-CCSTA and of *IL-6* rs1800795 and *PPARA* rs4253778 polymorphisms of the athletes (s: second).

Polymorphisms	Genotypes	Athletes Average 1km-CCSTA (s)	The differences in genotypes' 1km-CCSTA	Genotypes' time advantage status
***IL-6* rs1800795 (n=30)**	**GG** n=13(43.33 %)	189.9±15.4	4.7±15.4	Slower than average
	GC n=17(56.66 %)	181.5±22.3	-3.7±22.9	Faster than average
	CC n=0(0 %)	-	-	-
***PPAR-alfa* rs4253778 (n=30)**	**GG** n=20 (66.66 %)	182.7±18.9	-2.5±18.9	Faster than average
	GC n=7 (33.33 %)	183.9±17.9	-1.3±17.9	Faster than average
	CC n=3(10 %)	204.3±26.3	19.1±26.3	Slower than average

genotypes completed the 1km distance earlier from the others. The GG genotype of the *IL-6* rs1800795 polymorphism completed 1km distance earlier than the the avarage of the group with 1.0±16.1 seconds, and the GC genotype of the *PPAR*-A rs4253778 polymorphism completed the 1km distance earlier with 3.0±3.2 seconds (Table 8). These polymorphisms had a time advantage in completing 1km distance.

In male athletes the GC genotype of *IL-6* rs1800795 polymorphism was found to be significantly higher in the faster subgroup (p=0.0098). This genotype completed 1km 7.1±7.3 seconds earlier than the group's 1km-CCSTA and is the time-advantaged genotype of the male athletes (Table 9).

Table 8. Values of 1km-CCSTA and differences of genotypes of *IL-6* rs1800795 and *PPARA* rs4253778 polymorphisms for female athletes (s: second).

Polymorphisms	Genotypes	Female athletes Average 1 km-CCSTA (s)	The differences of genotypes' 1km CCSTA(s)	Genotypes' time advantage status
***IL-6* rs1800795 (n=10)**	**GG** n=4 (40 %)	207.3±16.1	-1.0±16.1	Faster than average
	GC n=6 (60 %)	208.8±10.3	0.6±10.3	Slower than average
	CC n=0 (0 %)	-	-	-
***PPARA* rs4253778 (n=10)**	**GG** n=6 (60 %)	205.6±13.3	-2.6±13.3	Faster than average
	GC n=2 (20 %)	205.3±3.2	-3.0±3.2	Faster than average
	CC n=2 (20 %)	218.8±11.7	10.6±11.7	Slower than average

Table 9. Values of 1km-CCSTA and differences of genotypes of *IL-6* rs1800795 and *PPAR*A rs4253778 polymorphisms for male athletes (s: second).

Polymorphisms	Genotypes	Male athletes average 1km-CCSTA (s)	The differences of genotypes' 1km-CCSTA(s)	Genotypes' time advantage status
***IL-6* rs1800795 (n=20)**	**GG** n=9 (45 %)	182.2±6.7	8.5±6.7	Slower than average
	GC n=11 (55 %)	166.6±7.3	-7.1±7.3	Faster than average
	CC n=0 (0 %)	-	-	-
***PPARA* rs4253778 (n=20)**	**GG** n=14 (70 %)	172.9±10.5	-0.8±10.5	Faster than average
	GC n=5 (25 %)	175.3±12.5	1.6±12.5	Slower than average
	CC n=1 (5 %)	175.5±0.0	1.8±0.0	Slower than average

Discussion

In the present study, the distributions of *IL-6* rs1800795 and *PPAR-A* rs4253778 polymorphisms in national cross-country skiing runners were investigated to evaluate potential genetic effects on the speed component of athletic performance.

When the of *IL-6* rs1800795 polymorphisms in terms of endurance performance is evaluated, it may be speculated that IL-6 molecules can increase the speed of glucose and fat use by the muscles, but high levels of secretion of IL-6, a versatile cytokine, can overstimulate the immune system and this can cause excessive inflammation.

Therefore, genotypes with an average expression power, which can be less affected by the destructive effect of excessively increased cytokine amount, may be more advantageous in sports that require endurance. For this reason, in *IL-6* rs1800795 polymorphism, the GC genotype may be more suitable for endurance sports than GG genotype. The *IL-6* rs1800795 GC genotype (p=0.0098), which is intensely found in the fast subgroup of male athletes in this study, supported the hypothesis.

Some studies established the association between the G allele of the *IL-6* rs1800795 polymorphism and increased power performance (23, 10). In addition, in studies examining the relationship between the *IL-6* rs1800795 polymorphism and the resistance phenotype in the literature, there was a significant relationship between the G allele and the resistance phenotype (24), as well as a significant relationship between the C allele and the resistance phenotype (25).

When the *PPAR-A* rs4253778 polymorphisms in terms of endurance performance is evaluated, it can be said that PPARA, whose production increases in the fasting state, can meet the ATP requirement of the cell by taking part in fatty acid oxidation. Therefore, athletic endurance can increase in direct proportion to *PPAR-A* activity and the amount of receptors produced. For this reason, the G allele and GG genotype, which have higher expression power, may be more advantageous for endurance sports and therefore for cross-country skiing. In this study, the *PPAR-A* rs4253778 polymorphism GG genotype was not dense enough to give significant statistical results in the faster subgroup of any group, but this may have occurred as a result of the *IL-6* rs1800795 GG genotype suppressing the *PPAR-A*. However, considering the velocity data, it can be said that the *PPAR-A* rs4253778 polymorphism GG is advantageous.

According to the literature review, in some of the studies

investigating the distribution of the *PPAR-A* rs4253778 polymorphism in power athletes, the C allele was significantly associated with the power phenotype (26, 27, 28), while in some, the G allele was significantly associated with the power phenotype (29, 30). In addition, when the distribution of this polymorphism in resistant-type athletes was investigated, it was stated in some studies that there was a significant relationship between the G allele and the endurance phenotype (22, 26, 31, 32, 33, 34). In a meta-analysis study in which five studies were evaluated, it was reported that there was a significantly higher rate of G allele and GG genotype among endurance athletes than among controls (35).

According to the findings from this study, the *IL-6* rs1800795 GC and *PPAR-A* rs4253778 GG genotypes support the endurance phenotype, but more studies are needed in this area due to the small number of athletes in the study group and the different findings in the literature. In future studies, the presence of biochemical data as well as PCR data will reveal more information about both gene activity and inter-gene relationships. In order to reach a consensus on genotypes that support resistance, it will be very meaningful to re-evaluate the findings obtained from this study together with the findings of other investigators within the framework of meta-analyses.

The main limitation of the current study is the low number of athletes. There are not enough numbers of athletes dealing with cross-country skiing when compared with other sports. That's the main reason that we can not find enough athletes for the study. And the lowe numbers of the athketes may be the reason for the insignificant results. The second limitation could be the lack of biochemical analysis of serum IL-6 levels. Despite these limitations, we suggest the results of our study to guide further studies.

Conclusion

The general findings from this study are that "*IL-6* GC and *PPARA* GG" genotypes can support endurance and cross-country skiing performance. The fact that this genotypes is more successful than the o "*IL-6* GG and *PPARA* GG" genotypes may be because the *IL-6* gene suppresses *PPARA*.

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Interest conflict

The authors declare no conflict of interest within the publication of the study.

Consent for publications

The authors read and proved the final manuscript for publication.

Disclosure statement (declaration of interest statement)

No potential conflict of interest was reported by the authors.

Authors' Contribution

DK, KU designed the study, KU and BTA supervised the experimental works, and reviewed and edited the final version of the manuscript; ÖK and MFB obtained the athlete sample and data, TP conducted the laboratory works, DK and BTA wrote and editing the manuscript drafts.

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Ethics approval and consent to participate

The study design was approved by the Ethics Committee of Uskudar University for clearance since it involved human participants. The authors ensured that this work was carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All participants obtained informed consent before participating in the present study

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