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The Correlation between Rs1800795 Variant of *IL-6* and Sports Performance among Turkish Elite Athletes

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Abstract:

Background: *It has been reported that plasma levels of interleukin-6 (IL-6) increase during physical exercise and are involved in mediating endurance capacity. We compared allelic and genotypic frequencies of the IL-6 gene G174C variant (rs1800795) among elite athletes and non-athletic control subject.*

Materials Methods: *The study included 92 elite Turkish athletes and 100 non-athletes. Genomic DNA isolated and genotyped using polymerase chain reaction based-restriction fragment length polymorphism (PCR-RFLP) analysis for the IL-6 gene G174C variant.*

Results: *In this study, the allele distribution of IL-6 gene G174C variant exhibited statistically significant difference between the elite athletes and the controls (p=0.005). The G allele was more prevalent among the elite athletes than the control subjects. The genotype frequencies in the studied population were as follows: GG, GC, and CC in the controls were 40%, 45% and 15%, and in the elite athletes were 50%, 43.5%, and 6.5%, respectively. However, there was not any statistically significant difference in the genotype frequencies of the IL-6 G174C variant between the elite athletes and the control groups (p>0.05).*

Conclusion: *Our study suggests that a strong association exists between the IL-6 G174C variant and elite endurance performance in the Turkish population. Further studies in populations of different ethnic background are necessary to prove the association of IL-6 variant with sports performance.*

Keywords: *Interleukin-6 gene, G174C variant, elite athletes, sportperformance*.

1. INTRODUCTION

Physical performance is important for athletic activities. The musculoskeletal system and the central nervous system have been implicated to play a significant role in physical performance. Alteration in neurotransmitter levels, such as serotonin, and cytokines have been observed during the initial phases of fatigue(Davis, Bailey 1997).Giving recombinant human *interleukin-6* (rhIL-6) to an individual enhances the feeling of fatigue both during exercise(Robson-Ansley PJ 2004)and rest(Späth-Schwalbe E 1998)supporting this hypothesis. Current studies suggest that this protein has a crucial role in muscle repair and hypertrophy after exercise-induced damage (Ruiz 2010).

IL-6, a multifunctional pro-inflammatory and immunomodulatory cytokine, could define the individual variations in health and exercise-related phenotypes. It is secreted by monocytes, endothelial cells and fibroblasts and regulates immune response, the acute phase response and, inflammation. The human *IL-6* gene is mapped to chromosome 7p21 and consists of 5 exons and 4 introns (Karakus 2014). A functional G/C variant at position -174 (rs1800795) of the *IL-6* described firstly by Fischman et al. in the 5'flanking region of gene (Fishman 1998).This variability seems to be

functional, since it regulates transcriptional process and cytokine levels, and modulates inflammatory phenotype (Li 2015).It was demonstrated that G allele is associated with increased transcriptional response in vitro(Ruiz 2010). It was shown that the *IL-6* G174C variant is associated with numerous diseases and disease-related phenotype traits including non-small cell lung cancer (Bhat 2015), increased arterial stiffness (Sie 2008)polycystic ovary syndrome (Vural 2010) development of micro vascular complications in diabetic patients (Rudofsky 2009) and febrile seizures in children (Azab 2016). Also, it was reported that *IL-6* increases significantly in the circulation during exercise (Febbraio 2003). Therefore, we compared allelic and genotypic frequencies of the *IL-6* gene G174C variant (rs1800795) among elite athletes and non-athletic control subjects.

2. MATERIAL AND METHODS

2.1. Subjects

The study group consisted of 92 elite athletes [35 males and 25 females; mean age ± 23.68 ± 12.16 standard deviation (SD) years] and 100 (52 males and 48 females; mean age 24.9 ± 6.7 SD years) unrelated controls. Elite athletes were composed of subjects who played in an active team group for at least 2 years. Control group consisted of subjects who do not have any chronic disease and who do not perform any active sports. Informed written consent was obtained from each participant. The study was performed according to the Declaration of Helsinki and was approved by the local Clinical Research Ethical Committee.

2.2. Genotype Analysis

Total 192 subjects between the age group of 13-32 years were included in the present study. 2 ml of venous blood obtained from each subjects. Genomic DNA was extracted from whole blood samples using a commercial DNA isolation kit (SigmaAldrich, Taufkirchen, Germany). The*IL-6* G174Cvariant was analyzed as previously described by Tseng et al. (2002) using forward (f) 5'- TTG TCA AGA CAT GCC AAA GTG CGG-3' and reverse (r) 5'- GTG CAA TGT GAC GTC CCT TAG CAT-3' primers. The amplification conditions consisted of an initialmelting step of 5 min at 94 C;followed by 40 cycles of 30 s at 94 C, 30 s at 56 C and 1 minat 72 C. Thenthe PCR products were digested with FastDigestBsrL-I restriction endonuclease (Fermentas) at 37^{o}C for 30 minandanalyzed on a 3% agarose gel stainedwithethidiumbromide. Twofragments (139 and 17 bp) for G all ele and three fragments (117, 22 and 17 bp) for C all ele were determined. Second PCR was performed to confirm samples whose results were unclear.

2.3. Statistical Analysis

All statistical analyses were performed using computer SPSS Statistical Program Version 20.0 and Openepi 3.01 software package program. Continuous data were given as mean±SD (standart deviation) and (minmax). Chi^2 test was used to significance of differences in the allele frequency and genotypedistribution between the two study groups. Hardy-Weinberg equilibrium test was performed for both study groups. Oddsratio (OR) and 95% confidence intervals (CIs) were calculated. *p*valuep<0,05was considered statistically significant.

3. RESULTS

Table 1 summarizes the distribution of physical characteristics in athletes and control groups. The elite athletes comprised 92 athletes (age ranging between 13 and 30). The control group included 100 non-athletes (age ranging between 18 and 30).

Demographic variables and base line characteristics of elite athletes are presented Table 2.

Allelic and genotypic distributions of *IL-6* G174C variant in elite athletes and controls are given in Table 3. The genotype frequencies in the studied population were as follows: GG, GC, and CC in the controls were 40%, 45% and 15%, and in the elite athletes group were 50%, 43.5%, and 6.5%, respectively. There was not any statistically significant difference in the genotype frequencies of the *IL-6* G174C variant between elite athletes and control groups (*p>0.05*).

The *IL-6* gene G allele was present in 71.1% of the elite athletes and 62.5% of the control group, while C allele frequency was 28.3% in the elite athletes and 37.5% in the control group. In this study, the allele distribution of *IL-6* gene G174C variant showed statistically significant difference between the elite athletes and the controls (*p=0.005*). The G allele was more prevalent among the elite athletes than the control subjects.

4. DISCUSSION

Physical performance is a complex condition. It is influenced by several variables including genetic, environmental and lifestyle factors. Numerous genes have been reported to have crucial role in athletic performance. Cytokines make up a large group of polypeptides or proteins, which play a unifying and modulator role as universal intercellular messengers. Several studies analyzed alterations in the circulating levels of cytokines after exercise. It has been shown that *IL-6* acts as pro- and anti-inflammatory factor in response to numerous physiological activities such as exercise(Fischer 2006).

Factors involved in *IL-6* release at the time of exercise have been studied widely. Early research on the *IL-6* kinetics showed that arduous and prolonged physical activity elevated the levels of serum *IL-6* and other cytokines (Northoff 1991) leading to deterioration of the immune system(Fischer 2006). Factors that influence the plasma levels of *IL-6* include magnitude, duration, and the muscle mass involved in endurance exercise (Ostrowski 1998).Efflux of *IL-6* into blood can increase up to 100-fold during an arduous exercise (18).(Pedersen 2003).During ultra-endurance activities (150 km races, triathlons and marathons) plasma *IL-6* levels increase 50-fold or more from baseline and this correlate to several immunity factors(Wallberg 2011).

IL-6 is expressed in numerous tissues, such as adipose, skeletal muscle and hypothalamus, which all take a part in the regulation of body energy balance. In *IL-6* null mice, the deficiency of plasma *IL-6* was associated with obesity and low energy expenditure (Wallenius 2002).Some investigators also reported that *IL-6* acts as a hormone, and that is why it exerts biological actions during heavy physical activity. This hypothesis suggests that active muscle cells secrete *IL-6*, which in turn acts as a hormonal signal to liver or adipose tissue to activate glycogenolysis or lipolysis (Steensberg 2000).

Single nucleotid polymorphisms (SNPs) in the promoter region may change the function of genes and this could explain the individual responses to physical training (Macarthur 2005).The promoter of the *IL-6* gene is actively regulated at several sites, such as the multiple response element (-173 to 145) which acts by responding to *interleukin-1(IL-1), tumor necrosis factor-α (TNF-α)*, and other factors (Fishman 1998). Besides, the G to C change in position -174 of the *IL-6* gene leads to a potential site for the *transcriptional factor NF-1*, that can potentially repress the gene expression (Ruiz 2010).

G174C variation of *IL-6*, located in the gene promoter regions, can affect mRNA expression and protein levels. Alleles associated with decreased amount of *IL-6* expression can play a role in the low cytokine secretion during physical exertion, which can lead to low level of metabolism, decreased fat burning, and eventually, obesity. Individuals with G174C genotype have two fold *IL-6* plasma levels compared to as those who carry the homozygous CC allele (Białecka 2015).The impact of *IL-6* G174C variant on energy consumption may indicate the role of *IL-6* in obesity and type 2 diabetes. It was shown that the subjects bearing CC genotype are more resistant to insulin and have higher serum glucose concentration (Kubaszek 2003).

It was found that the *IL-6* G174C variant is related to high-density lipoprotein cholesterol levels (Halverstadt 2005) glucose tolerance (McKenzie 2004) and bone mass remodeling (Dhamrait 2003)in response to physical exercise. Ortlepp et al. reported a correlation between the C allele and maximal work capacity in Caucasian smokers (2003).Yamin et al. found a strong association between the C allele of the *IL-6* G174C variant and skeletal muscle damage after strenuous elbow flexion exercise in young adults (2008). Ruiz et al. showed that the elite power athletes, for whom muscle hypertrophy and strength is a essential phenotype trait, are more likely to have over expression of GG genotype and G allele, compared with elite endurance athletes and non-athletic control subjects (2010).

The majority of published data in sports genetics are obtained from studies performed among the European and North-American Caucasian populations. This study is the first to evaluate the *IL-6* G174C variant among the elite athletes in Turkish population. The earlier study suggesting that the C allele is underrepresented in Spanish power athletes (Ruiz 2010) is consistent with the previous finding reported by Yamin et al (2008), who implied a strong and dose-dependent correlation between the C allele/CC genotype and increased muscle damage in response to unusually strenuous exercise in non-athletes. In our study**,** there were both G and C allele in elite athletes Eider et al. and Ruiz et al. reported that the *IL-6* G174C variant GG genotype and G allele were significantly higher in the Polish power-oriented athletes and Caucasian (Spanish) descent, respectively (2013;2010).We also found that the G allele frequency between elite athletes and non-athletes controls was statistically different.

In this study, the *IL-6* G174C variant G allele was more prevalent among the elite athletes than the control subjects in Turkish population. However, there are studies reporting no association between the G allele of the *IL-6* G174C variant and power sports performance in the Israeli (Caucasian) population (Eynon 2011), and South African ironman triathlon (de Milander 2009). We believe that this difference of genotype and allele frequency may depend on ethnic background.

5. CONCLUSION

There is increasing evidence suggesting that athletic ability is at least partially determined by an athlete's genetic composition. As a result, our data suggest a positive correlation between the *IL-6* G allele and Turkish elite athletes endurance, however this finding should be confirmed by further studies conducted in groups with different ethnic origins.

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