



**SPORMETRE**  
The Journal of Physical Education and Sport Sciences  
Beden Eğitimi ve Spor Bilimleri Dergisi



DOI: 10.33689/spormetre.1487161

Geliş Tarihi (Received): 20.05.2024

Kabul Tarihi (Accepted): 25.06.2024

Online Yayın Tarihi (Published): 30.06.2024

**DETERMINATION OF THE GENETIC PROFILE OF *MCT1 (SLC16A1)* GENE A/T POLYMORPHISM AND *GDF5* GENE T/C POLYMORPHISM RELATED TO CONNECTIVE TISSUE AND MUSCLE INJURY RISK IN YOUNG ATHLETES\***

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**Abstract:** In this study, *MCT1 (SLC16A1)* gene A/T polymorphism related to muscle injury and *GDF5* T/C polymorphism related to connective tissue damage in young athletes were studied and it was investigated whether there was a difference in allele distribution in the athlete group related to connective tissue and muscle injury compared to the control group. Whether the allele distributions of the experimental and control groups were in balance was tested using the Hardy-Weinberg equation. Differences between groups were analyzed with Chi square Test. The confidence interval was determined as 95% (p<0.05). As a result of the research, no significant difference was found between the control group and athletes in terms of *SLC16A1* gene A/T polymorphism (rs1049434). A significant difference was found between the athletes and the control group in terms of *GDF5* gene T/C polymorphism (rs143383). CC and TC genotypes in athletes were more common than TT genotypes in individuals in the control group. This situation is in favor of athletes. As a result of the genotypes determined by studying the *SLC16A1* and *GDF5* gene polymorphisms in elite athlete groups within the scope of the research, coaches and club sports physicians can be informed and strategies can be developed to plan training to prevent injuries and to intervene in case of possible injury.

**Key Words:** Gene, Polymorphism, Injury, *SLC16A1 (MCT1)*, *GDF5*

**GENÇ ATLETLERDE BAĞ DOKUSU VE KAS YARALANMA RİSKİ İLE İLGİLİ *MCT1 (SLC16A1)* GENİ A/T POLİMORFİZMİ VE *GDF5* GENİ T/C POLİMORFİZMİNE AİT GENETİK PROFİLİN BELİRLENMESİ**

**Öz:** Bu araştırmada, genç atletlerde kas yaralanması ile ilgili *MCT1 (SLC16A1)* geni A/T polimorfizmi ve bağ doku hasarı ile ilgili *GDF5* T/C polimorfizmi çalışılarak bağ doku ve kas yaralanması ile ilgili sporcu grubunda kontrol grubuna göre alel dağılımında bir farklılık bulunup bulunmadığı araştırılmıştır. Deney ve kontrol grubuna ait alel dağılımlarının dengede olup olmadığı Hardy-Weinberg eşitliği kullanılarak test edilmiştir. Gruplar arasındaki farklılık Chi square Testi ile analiz edilmiştir. Güven aralığı %95 olarak belirlenmiştir (p<0,05). Araştırmanın sonucunda *SLC16A1* geni A/T polimorfizmi (rs1049434) açısından kontrol grubu ve sporcular arasında anlamlı bir fark bulunmamıştır. *GDF5* geni T/C polimorfizmi (rs143383) açısından sporcular ile kontrol grubu arasında anlamlı bir fark bulunmuştur. Sporculardaki CC ve TC genotipi kontrol grubunda bulunan bireylerdeki TT genotipinden daha sık görülmüştür. Bu durum sporcuların lehinedir. Araştırma kapsamında çalışılan *SLC16A1* ve *GDF5* gen polimorfizmleri elit sporcu gruplarında çalışılarak belirlenen genotipler sonucunda antrenörler ve kulüp spor hekimleri bilgilendirilip yaralanmanın engellenmesine yönelik antrenmanlar planlanması ve olası yaralanma durumunda müdahale için stratejiler geliştirilebilir.

**Anahtar Kelimeler:** Gen, Polimorfizm, Yaralanma, *SLC16A1 (MCT1)*, *GDF5*

\* Bu makale Ankara Üniversitesi Sağlık Bilimleri Enstitüsü'nde tamamlanan "Genç Atletlerin Bazı Genetik Faktörleri ile Fiziksel Uygunluk Parametreleri Arasındaki İlişkinin İncelenmesi" başlıklı tez çalışmasından üretilmiştir.

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## INTRODUCTION

Sports genetics began in the early 2000s with the discovery of genetic markers associated with sports performance. This field aims to develop molecular methods for understanding the genome function and organization of athletes, identifying talent, planning personalized exercise programs, optimizing nutrition, and minimizing the risk of injury. The first genes studied in this context were the *angiotensin-converting enzyme (ACE)*, *adenosine monophosphate deaminase 1 (AMPD1)*,  *$\alpha$ -actinin 3 (ACTN3)* and *peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC1a)* (Jones et al., 2002; Rubio et al., 2005; Yang et al., 2003). Studies have shown that both genetic and epigenetic factors influence athletic performance, as well as significantly impacting related phenotypes such as aerobic capacity, strength, coordination, flexibility, height, muscle mass, and personality traits. In particular, research on single nucleotide polymorphisms (SNPs) has made significant contributions to this field. An athlete's ability to perform is affected by environmental factors, psychology and genetics. Since sports performance is a polygenic trait, genetic influence is critical. Factors affecting endurance capacity, muscle performance, tendon-ligament formation and physiological condition for training, such as heart rate during exercise, anthropometry, cardiac morphology, metabolism, blood pressure and body composition, are directly related to genetics. Additionally, genetic variations play an important role in susceptibility to tendon and connective tissue injuries.

Regardless of age range, athletes are susceptible to injuries involving soft tissue, bone, tendon, ligament, and nerves due to direct trauma or repetitive stress (Longo et al., 2008; Longo et al., 2010). Athletics, which engages large muscle groups, tends to have a higher incidence of injuries compared to other sports. The knee joint is the most commonly injured joint in athletics. Overuse of tendons can lead to pain and a pathological condition known as "tendinopathy," which causes significant disability (Ames et al., 2008; Maffulli, 1998; Maffulli et al., 2009). Injuries such as medial collateral ligament tears, meniscus tears, and anterior cruciate ligament tears are frequent. When muscles, tendons, and ligaments are damaged, the blood vessels in the affected area rupture, leading to bleeding, swelling, and tenderness due to the accumulation of blood in the surrounding tissues. This bleeding and the resulting swelling and increased pressure can delay the healing process, resulting in prolonged recovery times (Peterson & Renstrom, 2019). Given the frequent occurrence of connective tissue and muscle damage in athletics, research on preventing these injuries is crucial. Studies have explored the relationship between single nucleotide polymorphisms (SNPs) and the susceptibility to sports injuries, as well as their impact on sports activity and performance (Lippi et al., 2010).

The *MCT* gene family, which facilitates the removal of lactate from the body, plays an active role in muscle injuries. The expression of these genes results in the removal of lactate and protons from muscle fibers, their mixing into the blood, and subsequent excretion (Halestrap & Wilson, 2012; Massidda et al., 2015). Certain variations in these genes have been linked to direct muscle injury. For example, the *Collagen type I alpha 1* gene (*COL1A1*), which is particularly associated with sports injuries, has been associated with cruciate ligament ruptures. *Collagen type V alpha 1* gene (*COL5A1*) has been associated with achilles tendon injuries and anterior cruciate ligament ruptures. *Tenascin C* gene (*TNC*) is also associated with achilles tendon injuries, and studies on this gene show that individuals with O blood group have a higher risk of such injuries. Other genes studied in relation to sports injuries include *Matrix metalloproteinase 3 (MMP3)*, *Transforming growth factor beta 1 (TGFB1)*, and *Growth/differentiation factor-5 (GDF-5)*. The *SLC16A1 (MCT1)* gene, located at 1p13.2-p12 on chromosome 1, is particularly important for lactate transport. Defects in this gene can lead to deficiencies in lactate transport, resulting in lactate accumulation and muscle injury in

athletes. Two common single nucleotide polymorphisms (SNPs) in the *SLC16A1* gene have been associated with exercise and heat exposure, as well as reduced erythrocyte lactate transport (Cuperio et al., 2010; Merezhinskaya et al., 2000). The presence of the T allele, which reduces the erythrocyte lactate transport rate, has been linked to high blood lactate levels. Low blood lactate transport causes lactate accumulation, leading to muscle injuries and negatively affecting aerobic and endurance athletes (La Montagna et al., 2020).

The *GDF5* gene encodes the *Growth and Differentiation Factor 5* protein, which plays a crucial role in the growth and development of bone, muscle, and tendon structures. This gene is located on chromosome 20 at position q11.22. The *GDF5* gene T/C polymorphism (rs143383) has three variants: CC, CT, and TT. Individuals carrying the T allele produce less *GDF5* protein, which has been associated with diseases such as osteoarthritis (Southam et al., 2007; Miyamoto et al., 2007; Evangelou et al., 2009). Research has indicated that athletes with the TT genotype of the *GDF5* gene experience a higher incidence of ankle, knee, and overall injuries compared to others (McCabe & Collins, 2018).

In this research, it was investigated whether there was a difference in allele distribution in the athlete group regarding connective tissue and muscle injury compared to the control group by studying the *MCT1* (*SLC16A1*) gene A/T polymorphism related to muscle injury and *GDF5* T/C polymorphism related to connective tissue damage in young athletes.

## **MATERIALS AND METHODS**

### **Research Model**

This study was designed as a case-control type. In the study, the representation rates of *MCT1* (*SLC16A1*) gene A/T polymorphism related to muscle injury and *GDF5* T/C polymorphism related to connective tissue damage of sedentary individuals in the same age range as the athlete group were evaluated.

### **Population and Sample of the Study**

The population of the research consists of young athletes in the 12-16 age group who run middle distance in athletics and sedentary people in the same age range. The sample group consists of 15 athletes who regularly participate in competitions and training and 15 sedentary people who do not do physical activity other than their daily work. The athlete group consists of athletes who are preparing to participate in the Turkish Youth Championship to be held in 2022 on behalf of Gümüşhane province.

### **Anthropometric Measurements**

It is important to determine the body composition of athletes to evaluate their health status. Anthropometric measurements, body fat and muscle ratios, body mass index (BMI) and Bioelectrical Impedance Analysis (BIA) were determined for body composition.

### **Data Collection**

Since the participants were to undergo an invasive procedure (blood sampling), this was clearly stated in the Parent Consent Form and Child Consent Form, and the participants were informed about the possible complications that may occur under the control of the healthcare team at the beginning. The materials used for blood sampling were sterile and used specifically for one person, and no adverse health effects were caused. Support was received from health personnel and athlete coaches during all tests.

### Single Nucleotide Polymorphisms Investigated

In the study, *SLC16A1* A/T, *GDF5* T/C polymorphisms were analyzed and the SNPs analyzed are given in Table 1.

**Table 1.** SNPs analyzed in the study

Gene	Polymorphism	SNP Code
<i>SLC16A1</i>	A/T	rs1049434
<i>GDF5</i>	T/C	rs143383

### Primer Design

For the 2 polymorphisms studied, 2 pairs of polymerase chain reaction (PCR) primers were designed. Primers designed using Primer 3 Plus and NCBI Primer Blast programs. (*SLC16A1\_F*;TCCCAAGCCTCTTTAGCAACA,*SLC16A1\_R*;TCCCATCAATGAACAACCTGGTATG,*GDF5\_F*;TTCTTCAGCATCTCTCCTCGG,*GDF5\_R*;GTGCCTCTGGTTTGGCAG).

### Inclusion and Exclusion Criteria

Health controls of the athletes were performed and individuals who were healthy as a result of biochemical tests, who regularly participated in training and who had no injuries were included in the study. In addition, control groups of the same age range were voluntarily selected for genetic test comparison. The control group also consisted of individuals who did not perform any physical activity other than their daily habits and were found to be healthy as a result of health controls.

### Data Evaluation

For sequencing, the Foundation Data Collection program was used to input the samples to be sequenced. Samples were analyzed using Miseq Reporter software and IGV 2.3 software developed by Broad Institute. Analysis of the sequenced samples was performed using the Sequencing Analysis program.

In the study, the distribution of polymorphisms in the experimental and control groups was analyzed using the Hardy-Weinberg equation. AA, AT, TT were tested for the *SLC16A1* gene and TT, TC, CC were tested for the *GDF5* gene. The difference between groups in allele distributions was analyzed by Chi square Test. The minimum confidence interval was set at 95%, ( $p < 0.05$ ). SPSS 24.0 program was used in the analysis process of all data.

### Ethical Aspect

Ethical rules were followed while selecting the experimental and control groups. Since blood samples were to be taken while selecting the group, a Parental Consent Form and a Child Consent Form were prepared for the underage athlete and control group, and permission was obtained from both the families and the children constituting the athlete and control group. Approval was obtained from Gümüşhane University Ethics Committee for the research (Decision No: E-95674917-108.99-101079, Decision Date: 22/06/2022). Permission was obtained from Gümüşhane Provincial Directorate of Youth and Sports to work with licensed athletes.

## Limitations

Since the financial expenses of the study were covered by the author and the number of athletes in Gümüşhane province is limited, the number of participants in the research group is small.

## DISCUSSION AND CONCLUSION

In this study, *SLC16A1* A/T and *GDF5* T/C polymorphisms were compared with the control group. In the study group, the allele distribution was tested for Hardy-Weinberg equilibrium and found to be in equilibrium.

**Table 2.** Demographic Data of Athletes and Control Group (n:30)

	Number (n)	Age (years)	Size (cm)	Weights (kg)
<b>Athletes</b>	15	13,60 ± 1,59	156,20 ± 7,20	44,80± 10,09
<b>Control Group</b>	15	13,73 ± 1,53	157,20 ± 9,36	48,33 ± 9,30

Athletes were statistically compared with the control group in terms of *SLC16A1* gene A/T polymorphism (rs1049434). As a result of statistical analysis, no significant difference was found between the athletes and the control group in terms of *SLC16A1* gene A/T polymorphism ( $p>0.05$ ). The frequency of AA genotype in athletes was not different from the control group. The differences found were not statistically significant. Genotype numbers and rates are shown in Table 3.

**Table 3.** *SLC16A1* gene A/T Polymorphism Number of Genotypes (n:30)

Genotype	Athletes (n = 15)	Control group (n=15)
AA	4 (%26,7)	6 (%40)
AT	8 (%53,3)	6 (%40)
TT	3 (%20)	3 (%20)
<b>Alel</b>		
A	16 (%53,33)	18 (%60)
T	14 (%46,66)	12 (%40)

$p < 0,05$

Athletes were statistically compared with the control group in terms of *GDF5* gene T/C polymorphism (rs143383). As a result of statistical analysis, a significant difference was found between the athletes and the control group in terms of *GDF5* gene T/C polymorphism ( $p < 0,05$ ). The frequency of CC and TC genotypes in athletes was found to be different from the control group. CC and TC genotypes in the athletes were found to be more frequent than TT genotype in the individuals in the control group. The differences found were statistically significant. Genotype numbers and ratios are shown in Table 4.

**Table 4.** *GDF5* gene T/C Polymorphism Number of Genotypes (n:30)

Genotype	Athletes (n = 15)	Control group (n=15)
TT	4 (%26,7)	3 (%20)
TC	7 (%46,7)	6 (%40)
CC	4 (%26,7)	6 (%40)
<b>Alel</b>		
T	15 (%50)	12 (%40)
C	15 (%50)	18 (%60)

$p < 0,05$

The analysis results of *SLC16A1* gene A/T polymorphism (rs1049434) and *GDF5* gene T/C polymorphism (rs143383), two genes studied related to injury, were examined. There was no significant difference between the athletes and the control group in terms of *SLC16A1* gene A/T polymorphism ( $p > 0.05$ ). When the studies in the literature are examined; La Montagna et al. (2020) studied *ACTN3*, *COL5A1*, *SLC16A1*, *VEGF* and *HFE* genes with the aim of developing personalized training programs with 30 professional football players, increasing athletic performance and minimizing injuries in professional athletes. In this study, it was determined that the AT variation of the *SLC16A1* gene was more represented in the athlete group. The *SLC16A1* gene has been mostly examined in the literature under the name *MCT1* gene. Studies have shown that carriers of the A1470T polymorphism in the *MCT1* gene exhibit a worse lactate transport capacity to less active muscle cells for oxidation and are responsible for subnormal lactate transport and therefore muscle injuries under environmental stress (Cuperio et al. 2010; Merezhinskaya et al., 2000). Fedotovskaya et al. (2014) reported that the frequency of the A allele and AA genotype was significantly higher in endurance-oriented athletes compared to the control group. Additionally, they found that male rowers with the T allele had higher average blood lactate concentrations. Again, Guilherme et al. (2021) examined the athletic condition and performance of athletes in their study and determined groups according to race. TT genotype carriers have been reported to accumulate less lactate in the blood in response to intense exertion. Based on all these studies, it can be concluded that if the increase in blood lactate level is not tolerated, the risk of injury increases accordingly. The T allele has an effect on blood lactate transport level. Sawczuk et al. (2015) touched upon the relationship of this gene with endurance performance and reported that TT genotype was represented at a higher rate in sprinters. Although the *MCT1* (*SLC16A1*) gene A/T polymorphism results in our study are not consistent with these studies, it is thought that the limitation of the sample group is the reason for this.

In our study, a significant difference was found in terms of *GDF5* gene T/C polymorphism ( $p < 0.05$ ). CC and TC genotypes were observed more frequently in athletes than the TT genotype in the control group. The presence of the TT genotype is associated with ankle and knee injuries and anterior cruciate ligament injuries. The low incidence of TT genotype in athletes is a very important result. This situation is in favor of the athletes in our study group. It is an indication that the athletes in the research group have a low risk of connective tissue injury. Foot and knee injuries are frequently encountered in sports branches that require endurance performance. McCabe et al. (2018) also stated in their research with football players that players with the TT genotype had a higher risk of injury. In the same study, it was determined that players with the TT genotype played fewer matches during the season than players with the CC and CT genotypes. Again, Maffulli et al. (2013), in their review study on the genetics of sports injuries and athletic performance, mentioned the effect of *GDF5* gene especially on connective tissue and tendon injuries. In another very recent study in 2023, genes were analyzed by race and it was reported that *GDF5* gene polymorphism played a role in Achilles tendon injuries (Collins & September, 2023). The study of injury genes and the training of athletes in this direction will be very beneficial for both performance and economically for the clubs.

## CONCLUSION AND SUGGESTIONS

Athletes were statistically compared with the control group in terms of *SLC16A1* gene A/T polymorphism (rs1049434). As a result of statistical analysis, no significant difference was found between the athletes and the control group in terms of *SLC16A1* gene A/T polymorphism ( $p > 0.05$ ). The frequency of AA genotype in athletes was not different from the control group.

Since the presence of the AA genotype indicates a high probability of injury as well as high endurance performance, especially in the athlete group, the individuals with AA genotype were informed about the risk of muscle injury and their coaches were informed about the attention to be paid to these individuals during training. All physical fitness parameter tests of one of these athletes were completed very successfully compared to the others, and it is important to inform this athlete because the injury of this athlete would negatively affect his/her sports life. In addition, since this gene shows lactate transport levels, it may also be included in studies as a determinant of endurance performance. This will contribute to the literature on both injury and performance evaluation.

Athletes were statistically compared with the control group in terms of *GDF5* gene T/C polymorphism (rs143383). As a result of the statistical analysis, a significant difference was found between the athletes and the control group in terms of *GDF5* gene T/C polymorphism ( $p < 0.05$ ). The frequency of CC and TC genotypes in athletes was found to be different compared to the control group. CC and TC genotypes were more common in athletes than the TT genotype in the control group. The presence of the TT genotype is associated with ankle and knee injuries and anterior cruciate ligament injuries. When the literature was examined, the presence of the T allele was also associated with osteoporosis. As a result of the research, it is a very important result that the TT genotype is less common in athletes. It is an indication that the athletes in the research group have a low risk of connective tissue injury. At the same time, it can be said that the likelihood of bone diseases such as osteoporosis is low. As a result of the research, athletes whose TT genotype was determined were warned about the risk of connective tissue injury and their coaches were informed about this.

Based on all these results, much more research is needed to conclude that the likelihood of injury can be precisely determined by genetic markers. Factors such as individuals' athletic performance, sports success, and injury risk are related to genetic markers as well as various parameters such as nutrition, environmental factors, and training duration. Confusing results occur in genetic studies as a result of low sample size, misclassification of athlete groups, failure to measure valid exercise performance characteristics, and lack of continuous follow-up of athlete groups. With further research, clearer and more detailed results can be obtained by increasing the number of sample groups for the genes examined within the scope of this study.

Within the scope of the research, it was determined that the polymorphism distributions of *SLC16A1* and *GDF5* genes, which are injury-related genes, were more representative in athletes than in the control group. These genes can be examined in larger sample groups and also in elite athlete groups. As a result of the determined genotypes, coaches and club sports physicians can be informed, injury prevention training programs can be prepared and precautions can be taken. By using genetic markers, strategies can be developed to take precautions before injuries occur.

### **Funding**

There is no funder.

### **Acknowledgments**

We would like to thank all the people and coaches who took part in our research. We would also like to thank the Genoks Genetic Diseases Evaluation Center, where we conducted our genetic analyses.

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