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Araştırma Makalesi

Ön Çapraz Bağ Ameliyatı Olan Futbolcularda Genetik Sakatlık Duyarlılığında COL12A1 Gen Polimorfizmi Profillerinin Araştırılması

Investigation of COL12A1 Gene Polymorphism Profile in Genetic Injury Susceptibility in Football Players Having Anterior Cruciate Ligament Surgery

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ÖZET

Amaç: Futbolda tekrarlayan travmalar, aşırı yüklenmeler, dönme, kayma hareketleri, kas zayıflıkları, aşırı antrenman yoğunluğu ve süresi, hatalı antrenman gibi risk faktörleri sporcularda adeta ön çapraz bağ yaralanmalarına davetiye çıkarır. Bu bağlamda futbolcuların performanslarını artırmak ve sakatlıklardan kaçınmak için gen profillerinin belirlenmesinin hem performans hem de sporcu sağlığı açısından sahaya ciddi katkı sağlayacağı düşünülmektedir. Moleküler mekanizmaların etiyolojisi tam olarak anlaşılamamış olsa da genetik faktörler, MMP'ler gibi onarım sürecinde yer alan genler veya apoptoz sürecinin bileşenleri dahil olmak üzere birçok risk faktörü ön çapraz bağ yırtıkları ile ilişkilidir. Bu çalışmada çapraz bağ cerrahisi geçiren futbolcularda COL12A1 gen polimorfizminin ön çapraz bağ yaralanması ile ilişkisi araştırıldı.

Materyal ve Metot: Ön çapraz bağ ameliyatı olan (ÖÇB) olan 41 hasta ve yaş-cinsiyet uyumlu 65 sağlıklı birey COL12A1 A/G polimorfizmi açısından araştırıldı. COL12A1 A/G'nin genotiplemesi, PCR-RFLP kullanılarak belirlendi. Verilerin istatistiksel analizi Epi ve Arlequin yazılım programı ile yapıldı. $p < 0,05$ değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Çalışma bulgularımız, hasta ve kontrol grupları arasında COL12A1 polimorfizminin allel sıklığı ve genotip dağılımı açısından anlamlı bir fark olmadığını gösterdi ($p=0,880$).

Sonuç: Bu çalışmanın bulguları COL12A1 (rs970547)'in Türk toplumunda ön çapraz bağ yaralanmalarına yatkınlıkla ilişkili olmadığını ortaya koydu.

Anahtar Kelimeler: Futbolcu; kollajen; ön çapraz bağ yaralanmaları; PCR; RFLP.

ABSTRACT

Aim: Risk factors such as repetitive traumas, overloads, turning, sliding movements, muscle weakness, excessive training intensity and duration, and faulty training in football invite anterior cruciate ligament injuries in athletes. In this context, it is thought that determining the gene profiles of football players to increase their performance and avoid injuries will make a serious contribution to the field in terms of both performance and athlete health. Although the etiology of the molecular mechanisms is not fully understood, many risk factors are associated with anterior cruciate ligament tears, including genetic factors, genes involved in the repair process such as MMPs, or components of the apoptosis pathway. In this study, the relationship between COL12A1 gene polymorphism and anterior cruciate ligament injury in football players who underwent cruciate ligament surgery was investigated.

Materials and Methods: 41 patients who had Anterior cruciate ligament (ACL) surgery and 65 age-sex-matched healthy individuals were investigated for COL12A1 A/G polymorphism. Genotyping of COL12A1 A/G was determined using PCR-RFLP. Statistical analysis of the data was done with Epi Information Software and Arlequin Software. A value of $p < 0.05$ was considered statistically significant.

Results: Our study findings showed that there was no significant difference between the patient and control groups in terms of allele frequency and genotype distribution of the COL12A1 polymorphism ($p=0.880$).

Conclusion: The findings of this study suggested that COL12A1 (rs970547) was not associated with susceptibility to anterior cruciate ligament injuries in the Turkish population.

Keywords: Anterior cruciate ligament injuries; collagen; footballer; PCR; RFLP.

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INTRODUCTION

Football is the most popular sport in the world today. Football, which is a complex contact sport, is played more aggressively and faster than other branches (1). Depending on the fast game flow, the players must have high endurance in order to perform the movements such as repetitive sprinting, jumping, stealing, hitting the ball and changing direction (2). The risk of injury to the players during football matches is also high due to the physiological demands required during the performance of these movements, body contact and physical interaction during bilateral struggles (3). As a result of the studies, it is stated that the risk of injury in football is higher than in other sports branches (4, 5). When the studies on injuries in football were examined, the types of injuries, the regions where the injuries occurred, and the severity of the injuries were evaluated (6, 7). The effect of individual factors on the occurrence of injury was also examined separately (8, 9). In a study conducted on Turkish national team football players, it was stated that injuries mostly occur in the lower extremities, especially in the thighbone and knees (10). It is also supported by various studies that knee injuries are very common in football (5, 11).

It can be said that one of the most important injuries that make it difficult for football players to return to the field and prevent them from playing football for a long time is anterior cruciate ligament injuries (12). The anterior cruciate ligament (ACL), which plays a role in the stabilization of the knee joint, is the connective tissue originating from the intercondylar region (anteromedial surface) and connecting to the lateral condyle of the thigh bone, and consists of two components: anteromedial and posterolateral bundles (13-15). Anterior cruciate ligament injuries, which frequently require reconstruction, are among the most common knee ligament injuries and are also the most common soft connective tissue injury in the knee (12). Damage typically occurs during activities that involve stopping rapidly, jumping and landing abnormally, sudden changes in direction of motion, a direct blow to the side of the knee, or slowing down while running (16).

The incidence of ACL, which is the most common ligament to be damaged (teared) in the knee, is between 100,000-200,000 in the USA. Although there is no difference in terms of demographic factors (age, gender) in ACL ruptures, it is suggested that the risk of ACLs increases in women. Some studies attribute the high prevalence of the anterior cruciate ligament in women to the weakness of the posterior cruciate ligaments, and preferably to the use of the quadriceps muscle group during deceleration, to the increase in the valgus angle of the knee, and to estrogen (13). Although its etiology is not clear; many risk factors associated with anterior cruciate ligament injuries have been identified. In the formation of anterior cruciate ligament injuries, genetic factors as well as anatomical, hormonal, biomechanical and neuromuscular factors have been associated with anterior cruciate ligament rupture (17, 18). Studies of sports genetics on injuries that occur frequently in sports have become widespread, and studies in the fields of identifying genes that affect athletic performance, elucidating their mechanisms of action and determining their sensitivity to athletic performance have also become widespread (19, 20). Genomic DNA profiling for athletic performance and sports injuries is thought to lead to an understanding of genetic advantages and genetic barriers to be overcome in the future (21). Genetic risk factors include proteins such as DNA repair genes, apoptosis genes, collagen proteins and matrix metalloproteinases (22). DNA sequence variants in many genes encoding collagen, which is thought to be a genetic risk factor for anterior cruciate ligament injuries, have been associated with anterior cruciate ligament ruptures (23). Due to the multi fascicular structure of the ACL, it is thought that collagen plays a role in the tensile strength of the connective tissue and its polymorphisms are effective in ACL ruptures (24). Recent studies have emphasized the importance of COL5A1, COL1A1, COL12A1 and COL14A1 genes in Achilles tendon problems and anterior cruciate ligament injuries (25, 26).

As a result, the biological mechanisms that cause non-contact soft tissue injuries in the movement system have not been elucidated yet. There is strong evidence that genetic factors are associated with susceptibility to sports injuries and may play an important role in the healing process, and many studies have confirmed the influence of genetic factors (27). In this context, it is thought that determining the gene profiles of the football players in order to increase their performance and avoid injuries will make a serious contribution to the field in terms of both performance and athlete health. Understanding the etiology of ACL injuries, determining the mechanism and risk factors correctly are important in terms of preventing injuries. From this point of view, in this study, the possible role of COL12A1 gene polymorphism in anterior cruciate ligament injury in football players who play active football in professional leagues and have undergone anterior cruciate ligament surgery was investigated.

MATERIALS AND METHODS

Working group

The study group of the research was composed of 41 football players who were over the age of 18 and had at least one anterior cruciate ligament surgery in the 2020-2021 seasons in Turkish Professional Football Leagues (Tokatspor Football Club, Erbaaspor Football Club, Çaykur Rize Sports Club and Of Sports Club). The control group consisted of football players who actively played football in the Turkish Professional Football Leagues in the 2020-2021 seasons, were over the age of 18, had at least 5 years of football history and had not undergone surgery due to injury before. According to the power analysis, the sample size was determined as at least 40 people in each group (80% power, 5% margin of error and

0.3 effect size). The G-power 3.1.9.6 program was used for the sample size. For the study, the remaining blood from the blood samples taken during routine screenings was used with the consent and knowledge of the participants. Ethics committee approval was obtained from Tokat Gaziosmanpaşa University Clinical Research Ethics Committee with the number 21-KAEK-028. The entire study was carried out by Tokat Gaziosmanpaşa University Faculty of Medicine, Department of Medical Biology.

Methods

Genomic Analysis

In the study, blood samples were collected from football players (41 people) who had anterior cruciate ligament surgery and from the control group (65 people) who did not have cruciate ligament surgery. DNA was extracted from a peripheral blood sample using the Biobasic Genomic DNA Kit according to the manufacturer's instructions. Variation in the collagen gene COL12A1 (rs970547) was analyzed by a polymerase chain reaction (PCR) based restriction fragment length polymorphism (RFLP) method.

The reaction was carried out by preparing a PCR reaction mixture with the components and ratios given in Table 1 to be 25–50 ng of genomic DNA. PCR primers 5'-GAGAATCCAGAACAGCTCCACCAG-3' and 5'-CATGGCTAGTATGGGACAG-3' were synthesized by the commercial company. The PCR program, restriction product length and restriction enzyme applied in the study are given in Table 2.

Table 1. PCR components used in the detection of COL12A1 polymorphism.

	PCR compenents	µl/Tube
1.	distilled water	17,0 µl
2.	10X PCR buffer	2,5 µl
3.	$MgCl_2$ (25mM)	1,5 µl
4.	dNTP Mix (12,5mM)	0,3 µl
5.	Primers (F-R) (10pmol/ µl)	0,8 µl
6.	Taq DNA Polymerase (5 u/µl)	0,1 µl
7.	Genomic DNA	2 µl
	Total volume	25 µl

Table 2. The PCR program, restriction product length and restriction enzyme used in the detection of COL12A1 polymorphism.

Program	COL12A1		Restriction Enzyme
Initial Denaturation	94°C	3 minutes.	Alu I
Denaturation	94 °C	30 seconds	
Annealing	59 °C	30 seconds	
Extension	72 °C	120 seconds	
Termination	72 °C	10 minutes.	
The number of cycles	30 cycles		
Product Length	615 bp		AA =460,139,16 GG=599,16

Statistical Analysis

Statistical analysis of the data was performed using Epi Info Software version 3.2.2 (CDC, Atlanta, GA). The distribution of COL12A1 gene polymorphisms in football players who underwent anterior cruciate ligament surgery and control groups was compared with the $\chi 2$ or Fisher test. A value of $p< 0.05$ was considered statistically significant. Genotype distribution and Hardy-Weinberg equivalence were tested with the Arlequin Software 2000 (University of Geneva, Switzerland) program.

RESULTS

There was no statistically significant difference between groups in terms of COL12A1 A/G polymorphism genotype and allelic distribution. Both patients and controls were in Hardy-Weinberg equilibrium with COL12A1 A/G genotypes distribution ($p > 0.05$). Although the overall genotype distributions of COL12A1 A/G polymorphism are different from patient and control groups, these differences was not statistically significant (p=0.880). In this study the collagen gene COL12A1 variant was genotyped in football players who have had anterior cruciate ligament surgery and control groups. The genotype frequencies of COL12A1 are shown in Table 3. COL12A1 rs970547 polymorphism gel image is given in Figure1.

Figure 1. Agarose gel image of the COL12A1 (rs970547) polymorphism. The 615 bp PCR product was digested with the AluI restriction enzyme.Well 1=GG, well 2=AA, well 4=AG, well 6=Marker

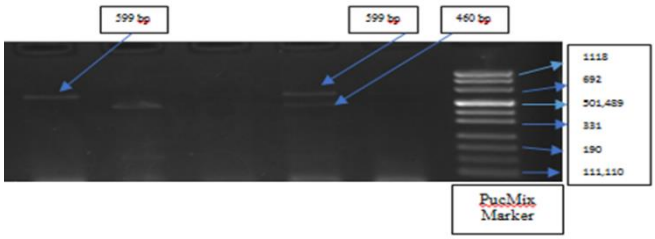

Table 3. COL12A1 polymorphism statistical analysis results.

COL12A1 polymorphism	Patient n=41	Control n=65	p
Genotype (rs970547)			
AA	19 [% 46	28 [% 43]	0.880
AG	14 [% 34]	25 [% 38,5]	
GG	8 [% 20]	12 [% 18,5]	
Allele frequency			
A	52 [% 63,5]	81 [% 62,3]	0.828
G	30 [% 36,5]	49 [% 37,7]	

DISCUSSION

ACL is a feared condition that is most commonly observed in young people, especially in players playing sports that require sudden movement and has negative physical and psychological effects in the long term. This is important in

terms of negatively affecting the long-term active sports lives of athletes (28). Many risk factors for ACL injuries have been identified, including BMI (Body Mass Index), female gender, decreased lower extremity strength, increased joint laxity, genetics, family history, and altered trunk and knee biomechanics (29). The main treatment option for ACL injuries is surgery and the healing process is time-consuming. However, recurrent ruptures and degenerative joint injuries such as osteoarthritis and meniscal tears are common after surgery (24). ACL injuries continue to be an important burden and problem for both sports clubs and athletes. To determine the treatment and prevention interventions for ACL injuries, the effect of factors such as gender, anatomical, genetic, hormonal, and neuromuscular should be better understood (30, 31, 32).

Many studies have been conducted on the role of genetic polymorphisms in ACL tears and its effectiveness has been proven. One of the genes thought to play a role in ACL injuries is collagen (24). For example; Beckley et al. reported that the COL3A1 polymorphism was not significantly associated with knee laxity measurements in a study they conducted with African professional athletes (33). However, in a study conducted with Polish skiers, it was revealed that there is a relationship between COL3A1 rs1800255 polymorphism and ACL ruptures (34). In a study, it was reported that the maximum knee extensor tendon elongation and tension measurement values of the CC genotype were higher than those of the CT or TT genotypes in individuals with the COL5A1 rs12722 polymorphism (35).

Collagen XII, a member of the collagen family, is a heterodimer located on chromosome 6 and encoded by the COL12A1 gene. Studies have shown that COL12A1 is expressed at high levels in tendons and ligaments. In addition, mutations in COL12A1 have been associated with the absence of tendon reflexes and hypermobile distal joints (36).

In this study, the possible relationship between injury exposure and COL12A1 (rs970547) gene polymorphism in professional male football players with anterior cruciate ligament injury and a history of surgery was investigated. According to our findings, there was no statistically significant difference between this polymorphism and anterior cruciate ligament injuries. There are conflicting results between populations in the literature between COL12A1 and the risk of ACL injury (36). Posthumus et al. analyzed the rs240736 and rs970547 polymorphisms of COL12A1 in their study comparing anterior cruciate ligament rupture (142 individuals) and healthy controls in a South African population and found that the AA genotype in the rs240736 polymorphism increased the risk of rupture by 2.4 times in female participants with anterior cruciate ligament injury. It has been reported that it has no effect on men (37). In the Caucasian population, O'Connell et al. and Ficek et al. found similar results to that of Posthumus et al. It was stated that the AA genotype of COL12A1 (rs970547) increased the risk of ACL injury in women, but there was no such relationship in men (38, 39). However, in the study of John et al., and Kang et al., they were shown that both the AA genotype and the frequency of the A allele were associated with a significantly higher risk of ACL injury in the entire population (19, 40). In addition, the COL12A1 gene rs970547 and rs240736 are associated with ACL on Chinese men. According to these results, AA genotype may cause an increased risk of ACL (41).

Our study results suggest that COL12A1 gene polymorphism is not an effective factor in susceptibility to anterior cruciate ligament injuries in the Turkish population. However, since our study is the first to investigate the relationship between COL12A1 polymorphism and anterior cruciate ligament injuries in the Turkish population, and our relatively low number of patients and controls, our results need to be confirmed by other studies.

Authors' Contributions

All authors contributed to the design and design of the study to review, read, and approve the final version of the manuscript. Material preparation and analysis were done by Kubra SAHIN, Nihan BOZKURT, Sadegul SAVKIN. The first version of the manuscript was written by Kubra SAHIN.

Compliance with Ethical Standards

All authors have no conflicts of interest with the submission. Our study was approved by the local Ethics Committee of Gaziosmanpasa University, Turkey (Number: 21-KAEK-028), conducted in line with the principles of the Declaration of Helsinki. All patients were obtained full written informed consent for this research.

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