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ORIGINAL RESEARCH

Genetic factors and anterior cruciate ligament injury risk in professional football players: *COL3A1* (rs1800255) and *COL5A1* (rs12722) polymorphisms

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Abstract

This study was conducted to investigate the genotype and allele distributions of COL3A1 (rs1800255) and COL5A1 (rs12722) polymorphisms of professional footballers who have suffered at least 2 anterior cruciate ligament (ACL) injuries non-contact and professional footballers who have never had a ligament injury. The research group consists of 108 professional men's football players [ACL group (n=45), Control group (n=63)] with at least 10 years of football background. The results ACL and control groups were compared by Chi-square or Fischer's exact test. There were no significant differences noted neither in terms of genotype distribution of COL3A1 (rs1800255) nor A-allele frequency distribution between control (CON) and ACL group. A highly significant difference in the allele distribution was noted for COL5A1 (rs12722) with the T-allele significantly less frequent in CON than ACL. The TT genotype compared to the C alleles (TC + CC) showed significant relationship between the TT genotype and ACL injury potential in the dominant model. However, it was not showing significance in the recessive (TT + TC vs. CC). In conclusion, it can be said that professional football players who have the COL5A1 rs12722 C allele have about 2 times lower risk of anterior cruciate ligament injury. In the COL3A1 rs1800255 polymorphism, there is no relationship between the groups in terms of genotypes and allele distribution.

Keywords: ACL, COL3A1, COL5A1, gene, football, polymorphism.

Introduction

Football is an intermittent team sport with a load and rest cycle featuring high physiological demands. It is known that professional football players cover a distance of approximately eight to twelve kilometers during a single match, approximately 20% of which is exerted at maximal or near-maximal velocity (Bishop et al., 2011; Stolen et al., 2005). Short accelerations such as tackling and jumping are frequently performed during a match (Bangsbo 1994; Zois et al., 2011). When the highly taxing demands of football are taken into consideration, it is often expected for players to experience injuries (Agel et al., 2007; Dvorak & Junge, 2000). Anterior cruciate ligament (ACL) injury is accepted as one of the most severe sports injuries (Brooks et al., 2005). Football players are typically at high risk, especially when involved in actions of sudden

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deceleration and change of direction. Although ACL injury exerts a low incidence in sedentary individuals (1 in 10,000 persons) (Marshall et al., 2007), individuals who regularly engage in sports may exhibit a 10-fold higher incidence (Parkkari et al., 2008).

The ACL is one of the four major ligaments of the knee. Ligaments are defined as dense bands of collagenous tissue that span a joint and are anchored to bone at either end (Frank, 2004). Collagen is the main component of ligaments. Collagen type I makes up 85% of all collagens, whereas the remainder is made up of III, VI, V, XI, and XIV collagens (Szumilo, 2014). Collagen type III is a product of the *COL3A1* gene, which produces the pro-α1 chains of Type III collagen (O'Connel et al., 2013). The *COL3A1* gene is located on chromosome 2q31 (Fujiwara et al., 2010). Collagen type III is a significant fibrillar collagen for tendons, which is thought to play an important role in wound healing and fibrillogenesis (Banos et al., 2008; Liu et al., 1995). It is localized with collagen type I during tendon formation and may form heterotypic fibrils in some cases (Banos et al., 2008). Collagen type III plays an important role in regulating the strength and flexibility of the tissues in which it is expressed. In a study with skiers, it was determined that those with the AA genotype were exposed to approximately 5-fold higher risk of ACL injury compared to those with the AG+GG genotype (Stępień-Słodkowska et al., 2015). The *COL5A1* gene, localized on chromosome 9q34.3, encodes the alpha-1(V) chain of Type V collagen. The *COL5A1* gene supports many tissues in the body, such as tendons, ligaments, and muscles, while playing a crucial role in the regulation of the size and configuration of other collagens (Birk et al., 1990). Single-nucleotide polymorphisms (SNPs) *COL5A1* rs12722 (T/C) and COL12A1 rs970547 (A/G) were determined to modulate the risk of ACL injury in women (Posthumus et al., 2010; Posthumus et al., 2009). In other available studies, *COL5A1* (Mokone et al., 2006; September et al., 2009) and MMP3 (matrix metalloproteinase 3) (Raleigh et al., 2009) genes were reported to associate with sports-related Achilles tendinopathy.

Previous studies on collagen gene polymorphism have focused on athletes or individuals with ACL injury versus control groups from the general population. The key factor that distinguishes the present study from available literature is that both the control group and the study group consisted of professional football players with at least 10 years of background. Considering the much higher risk of ACL injury among athletes who are constantly involved in high-intensity activities due to the nature of football, the genetic difference between the players with and without ACL injury is believed to provide valuable insight. Based on this perspective, the study was carried out to determine the association between *COL3A1* and *COL5A1* genes and anterior cruciate ligament injury in professional football players.

Methods

Study Design

This was a case-control study designed with a sample group of professional football players.

Participants

One hundred and eigth professional male football players (ACL-CON) with at least 10 years of football background were included in the study. The entire study sample consisted of forty different teams competing in the Turkish Professional Football Leagues (Super League, 1st League, 2nd League, 3rd League).

Athletes who were deemed inappropriate to donate blood due to personal reasons and general health conditions, those who carried health risks, and those who did not qualify for either the study or the control group were not included in the study. All participating athletes were provided detailed information about the research and were asked to sign a form to verify voluntary participation. The study was carried out in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from Tokat Gaziosmanpaşa University Clinical Research Ethics Committee with the decision dated 28/01/2021 and numbered 21-KAEK-028.

Genetic Analysis

Blood samples obtained from athletes were analyzed in Tokat Gaziosmanpaşa University Faculty of Medicine Biochemistry Laboratory. Genomic DNA (gDNA) was isolated from peripheral blood using GeneAll DNA isolation kit. The *COL5A1* rs12722 (C414T) and *COL3A1* rs1800255 (Ala531Thr) gene polymorphisms were analyzed by using polymerase chain reaction (PCR)-based restriction fragment length polymorphism (RFLP) method. The primers used for *COL5A1* polymorphism were F: 5'-GAAGACGGTTCTGGAGATCG-3', R: 5'-GAAGGCACCTGCAGAATGAC-3', and for *COL3A1* polymorphism F: 5′ AAG TATACA AAT TTC TAG ATT G 3′, R: 5′ ATA AAT GAT CAG AAG GAA ATC

A 3′. PCR was performed in a total volume of 25 µL containing 2 µl gDNA, 0.8 nmole/µL of each primer, 1.5 µL MgCl2 (25mM), 2.5 µL 10× PCR buffer, 0.3 µL dNTP (25mM), and 1 Unıte Taq polymerase (Thermo).

The following conditions were used to amplify the region of interest: 94°C for 3 minutes, followed by 30 cycles of denaturation at 94°C for 30 seconds, annealing at 59°C for 30 seconds, extension at 72°C for 120 seconds, and a final extension step at 72°C for 10 minutes. The restriction endonuclease was used BstU1 to distinguish *COL5A1* rs12722 polymorphism.

94°C for 3 min followed by 30 cycles of denaturation at 94°C for 30 seconds, annealing at 50°C for 30 seconds, extension at 72°C for 60 seconds, and a final extension step at 72°C for 10 minutes. The restriction endonuclease used was Alu I to distinguish *COL3A1* rs1800255 polymorphism. The products of this reaction were separated on 3% agarose gels containing ethidium bromide. BstU1 digestion generated the following fragments: 351 bp and 316 bp for T allel, 316 bp, 271 bp and 80 bp for C allel. Alu I digestion generated the following fragments: 208 bp and 86 bp for A allel, 113 bp, 95 bp and 86 bp for G allel.

Data Analyses

Statistical analyzes were carried out using Open Epi Info Software Version 3.2.2 (CDC, Atlanta GA, USA). Our results patients and control groups were compared by Chi-square or Fischer's exact test. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated when Chi-square or Fisher's exact test was significant. Chi-square test was used to test for quality of fitness of genotypic distributions and Hardy-Weinberg equilibrium using Arlequin Software ver. 2000 (University of Geneva, Switzerland).

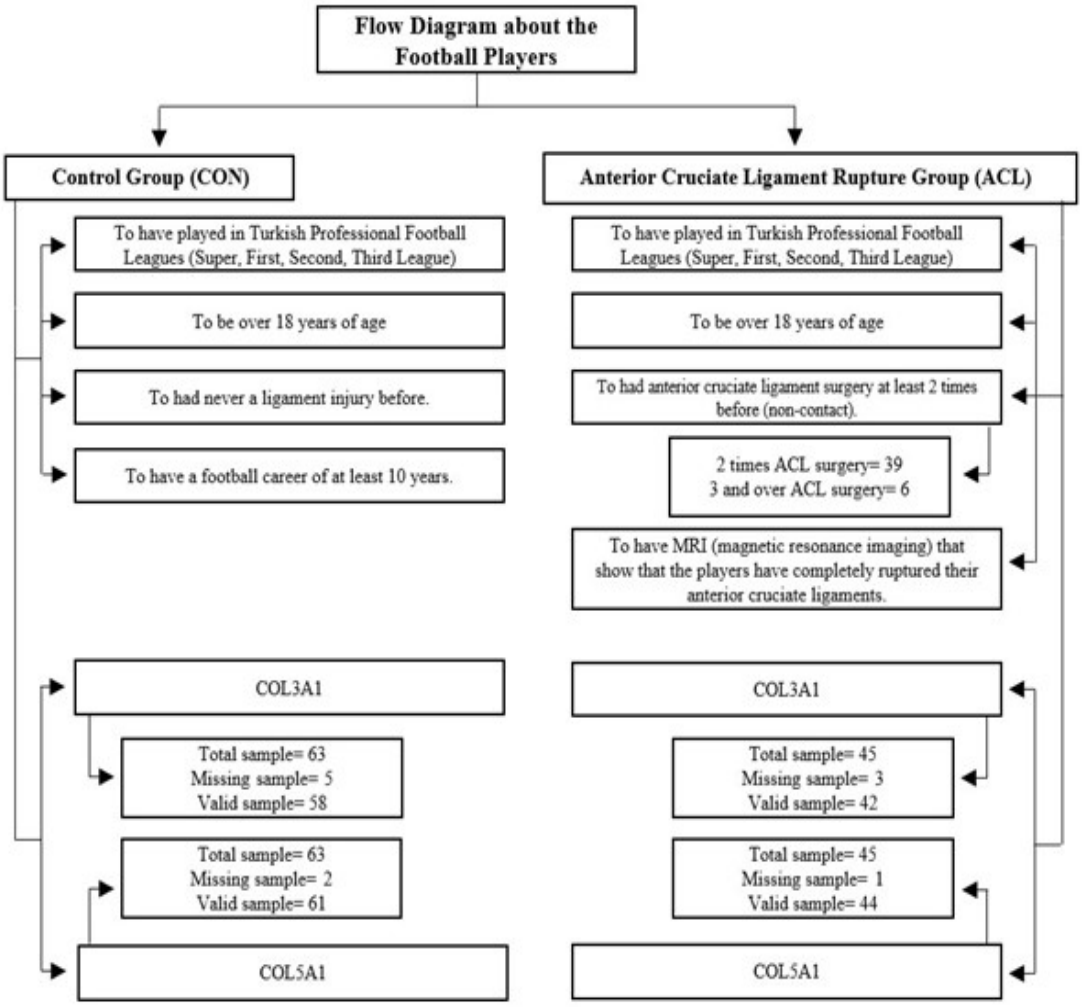

Figure 1. A flow diagram showing the inclusion criteria and valid polymorphism sample of the subjects.

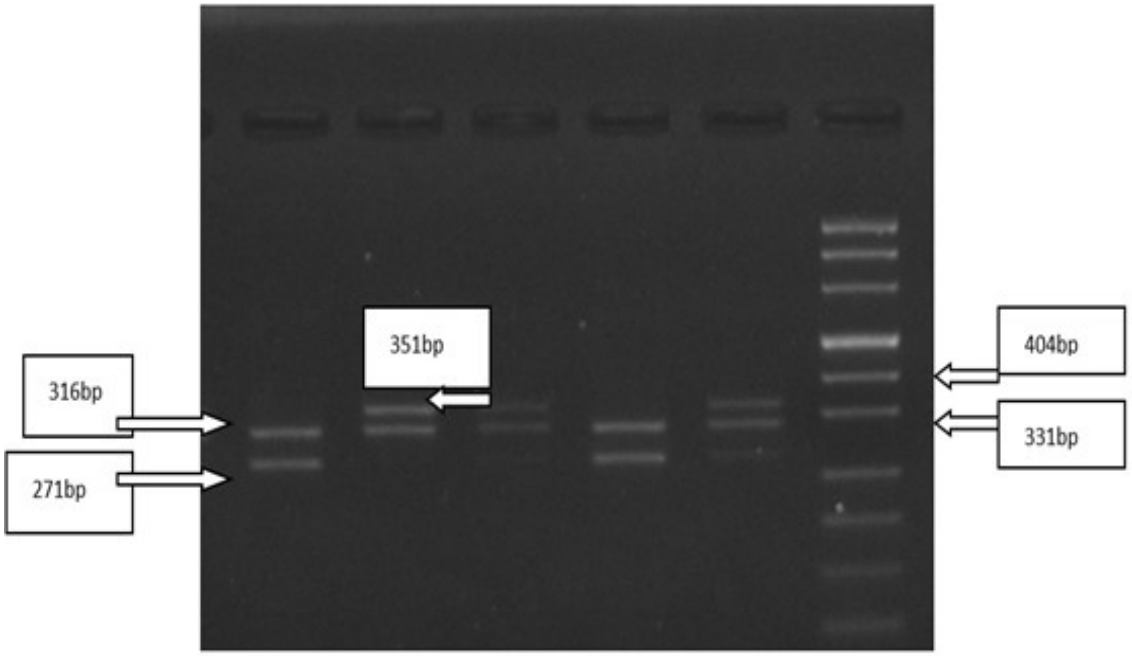

Figure 2. Gel image for *COL5A1* rs12722 polymorphism. The 667 bp PCR products were digested with BstUI restriction enzyme. Line 1 and 4 CC, Line 2, 3 and 5 TT, Line 6 Puc mix marker.

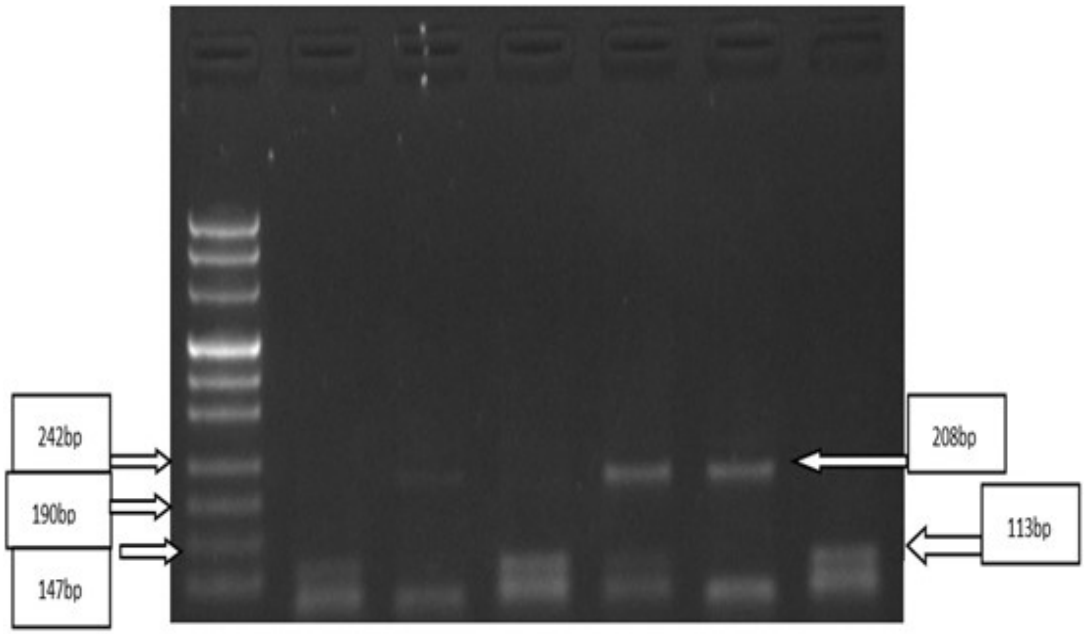

Figure 3. Gel image for *COL3A1* rs1800255 polymorphism. The 294 bp PCR products were digested with Alu I restriction enzyme. Line 1 Puc mix marker, Line 2,4,7 GG, Line 3,5 AG, Line 6 AA.

Results

The male professionel football players within the CON and ACL groups were matched for age, height, weight, body mass index (BMI) and experience (see Table 1). For the ACL group, age, experience, height, weight, and BMI were found respectively as 27.08±3.67 years, 14.00±3.41 years, 177.26±4.34 cm, 75.44±5.58 kg, 22.28±2.17 kg/m^2. On the other hand, age, experience, height, weight, and BMI of the CON group was determined as respectively 28.76±5.17 years, 16.60±4.42 years, 176.23±4.49 cm, 76.11±4.39 kg, 22.84±2.05 kg/m^2. There were no significant differences in the characteristics ($p>0.05$) between the CON and ACL groups except experience ($p<0.05$).

Table 1
Characteristics of the Turkish professional football players within the CON and ACL.

Variables	ACL (n=45)	CON (n=63)	p
Age (year)	27.1±3.7	28.8±5.2	0.066
Experience (year)	14.0±3.4	16.6±4.4	0.001*
Height (cm)	177.3±4.3	176.2±4.5	0.237
Body Weight (kg)	75.4±5.6	76.1±4.4	0.487
BMI (kg/m^2)	22.3±2.2	22.8±2.1	0.178

** p<0.05; CON: Control group; ACL: Anterior cruciate ligament rupture group.*

Table 2
Genotype and minor allele frequency distributions of the *COL5A1* rs12722 C>T and *COL3A1* rs1800255 G>A variants in the control (CON) and anterior cruciate ligament rupture (ACL) groups of the Turkish professional football players.

Variables		ACL	CON	p	OR (95%CI)
COL3A1 (rs1800255)	n	n=42	n=58		
	AA	33.3 (14)	24.1 (14)	.527	
	AG	28.6 (12)	41.4 (24)	.370[d]	1.571 (0.652-3.786)
	GG	38.1 (16)	34.5 (20)	1.000[r]	0.860 (0.304-2.430)
	G	52.4 (44)	55.2 (64)	.662	1.119 (0.637-1.965)
	HWE p	0.751	0.27		
COL5A1 (rs12722)	n	44	61		
	TT	61.4 (27)	32.8 (20)	.001*	
	CT	22.7 (10)	49.2 (30)	.005[d]*	3.256 (1.450-7.309)
	CC	15.9 (7)	18.0 (11)	1.000[r]	0.860 (0.304-2.430)
	C	27.3 (24)	42.6 (52)	.029*	1.981 (1.097-3.576)
	HWE p	0.054	0.000*		

**: p<0.05; [d]: Dominant model; [r] : Recessive model; HWE: Hardy-Weinberg equilibrium; OR: Odd ratio; ACL: Anterior cruciate ligament group; CON: Control group.*

The genotype and allele frequency distribution for the *COL3A1* rs1800255 is presented in Tables 2. Hardy–Weinberg Equilibrium (HWE) was established for control and ACL group. There were no significant differences noted neither in terms of genotype distribution of AA, AG and GG (p=0.527) nor A-allele frequency distribution between CON and ACL group (OR=1.119 %95 CI=0.637-1.965; p=0.662). Two modes of inheritance of minor allele were included in the analysis: dominant (AA vs. AG + GG) and recessive (AG + AA vs. GG) but they failed to show any significance respectively (see Figure 4A-B) (OR=1.571 %95 CI=0.652-3.786; p=0.370), (OR=0.860; %95 CI=0.304-2.430; p=1.000).

The genotype and minor allele frequency distributions of *COL5A1* rs12722, together with the HWE p values, are shown in Table 2. A highly significant difference in the allele distribution was noted for *COL5A1* rs12722 with the C-allele significantly higher frequent in CON than ACL (p=0.029). Figure 4C showed that the TT genotype compared to the C alleles (CT + CC) showed significant relationship between the TT genotype and ACL injury potential in the dominant model (OR=3.256; %95 CI=1.450-7.309; p=0.005). However, it was not showing a significance in the recessive model (TT + CT vs. CC) (OR=0.860 %95 CI=0.304-2.430; p=1.000).

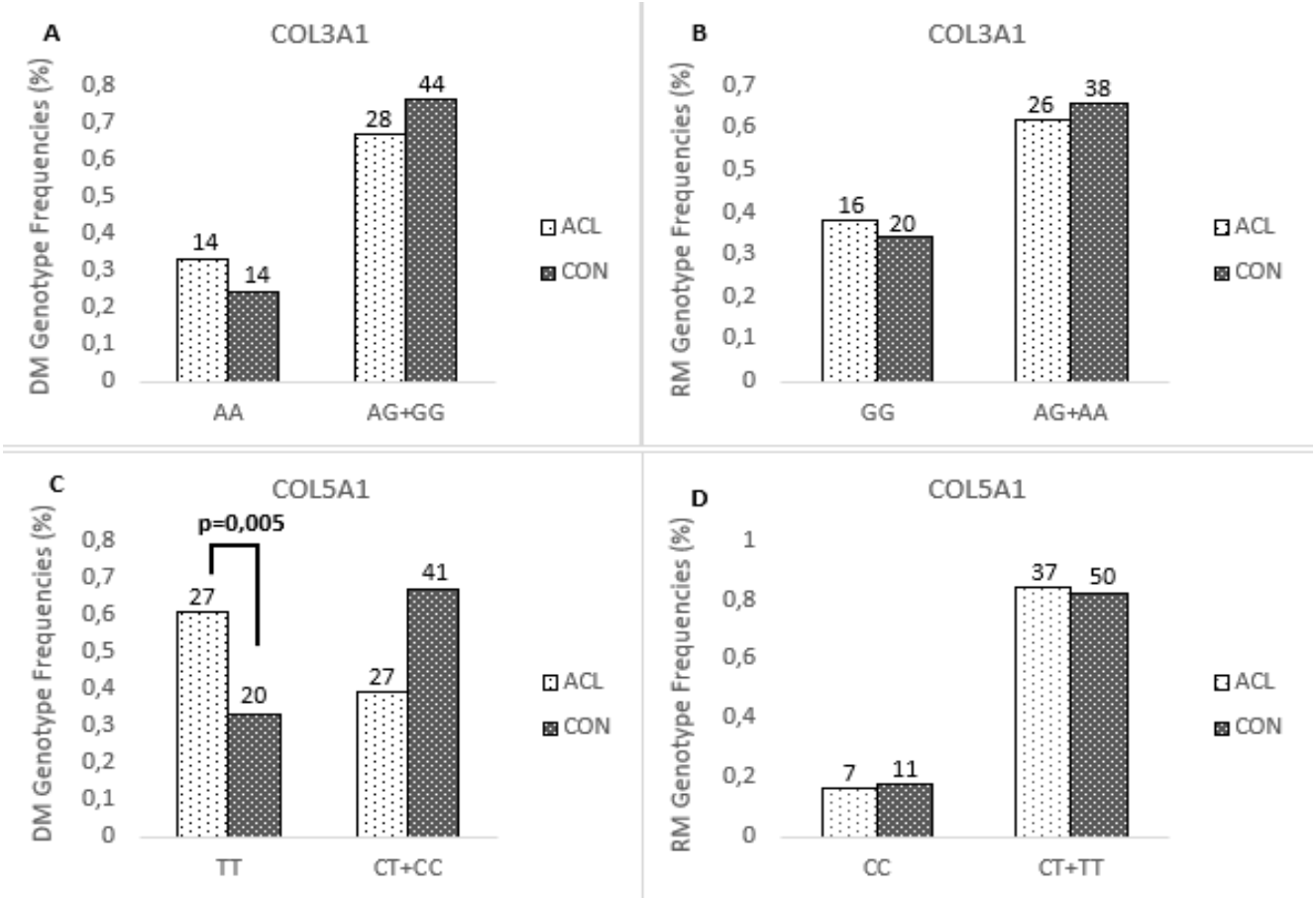

Figure 4. The genotype frequency distributions for *COL3A1* rs1800255 and *COL5A1* rs12722 in (A-C) dominant model, (B-D) recessive model. ACL: anterior cruciate ligament rupture group. CON: Control group. DM: dominant model. RM: recessive model.

Discussion

A significant differentiation of the T allele of the *COL5A1* rs12722 polymorphism in the ACL group constituted the primary finding of the study (p=0.001). Frequency of the TT genotype among the athletes in the ACL group was approximately 2-fold higher compared to the athletes in the CON group (66.36% - 32.78%, respectively). In addition, a significant difference was determined between the two groups in C-allele distribution (p=0.029). The secondary finding of the study was the lack of a significant difference between the CON and ACL groups in A-allele frequency for the *COL3A1* rs1800255 polymorphism (p>0.05).

ACL ruptures are feared and commonly encountered injuries among athletes from all branches. They may occur during both recreational and competitive athletic activities (Tifford and Jackson, 2001). In a study that examined the *COL3A1* rs1800255 gene polymorphism of Polish male skiers and healthy recreational skiers with a history of ACL rupture, skiers with the AA genotype were found to have an almost 5 times higher risk of injury than skiers with the AG+GG genotype (Stępień-Słodkowska et al., 2015). In the present study, no significant difference was found among professional male football players. In the study conducted with a sample group of South African and Polish participants, they stated that there was no significant relationship between the *COL3A1* rs1800255 polymorphism and an ACL tear in the South African cohort. In the same study, the incidence of *COL3A1* rs1800255 AA genotype in the Polish cohort was found to be higher in the ACL group compared to the control group (O'Connell et al., 2015). The study with Norwegian and Finnish elite female athletes competing in team sports reported that the six selected collagen gene polymorphisms (COL1A1 rs1800012-rs1107946, *COL3A1* rs1800255, *COL5A1* rs12722-rs13946, COL12A1 rs970547) exhibited no correlation with the risk of ACL injury (Sivertsen et al., 2019).

Several available studies reported a significant correlation between *COL5A1* variants and different injuries. In a study that examined the relationship between *COL5A1* rs12722 and rs13946 polymorphisms and ACL injuries in professional male football players, it was found that genotype and allele distributions in

both polymorphisms were not associated with ACL injury. Haplotype analysis of the participants showed that the control group exhibited a higher representation tendency of the C-C haplotype under the dominant model (Lulińska-Kuklik et al., 2018). In this study, the *COL5A1* rs12722 C-allele exhibited a higher representation in the control group. In a study with team sports athletes exposed to a high risk of injury, it was reported no relationship between *COL5A1* rs12722 polymorphism and ACL rupture (Sivertsen et al., 2019). In the study conducted with sedentary Chinese participants revealed no correlation between the control group and the ACL group for *COL5A1* rs12722 polymorphism (Zhao et al., 2020). In the research that examined a control group engaging in recreational sports and an experimental group with a history of ACL injury, reporting that the *COL5A1* rs12772 C/C genotype was associated with a reduced risk of ACL ruptures in female participants (Posthumus et al., 2009). A study conducted with populations from Australia, South Africa, and Japan reported the *COL5A1* rs12722 C allele and the CC genotype were associated with an increased risk of ACL injury among female participants in the South African cohort versus the control group. No correlation was found in the South African and Australian cohorts (Alvarez-Romero et al., 2021). In a study recruiting elite rugby athletes, reported a lower risk of tendon and ligament injury in athletes with the C allele (Heffernan et al., 2017). The study in which the relationship between collagen gene variants and ACL injury was investigated, reported a significant association between *COL5A1* rs12722 and COL12A1 rs970547 polymorphisms and ACL ruptures in females (O'Connell et al., 2015). The study with skiers investigated the correlation between *COL5A1* variants (rs12722- rs13946) and ACL injury. When the allele combinations are examined, a higher *COL5A1* C-T haplotype frequency may be interpreted as the contributing factor to lower ACL injury risk in the control group (Stępień-Słodkowska et al., 2015). Another study found an age-related increase was reported for the *COL5A1* rs12722 CC genotype of male participants while no such finding was detected for female participants (Posthumus et al., 2010).

Finally, the findings of the present study indicate that professional football players with the *COL5A1* rs12722 C allele have an approximately two-fold lower risk of anterior cruciate ligament injury. There is no correlation between the groups in genotype distribution and allele frequency for the *COL3A1* rs1800255 polymorphism. These results are thought to be of significance to provide insight into potential ACL injury among athletes in a branch that includes a wide variety of physical demands and a high risk of injury, such as football.

This study suggests that in football, which is a game with a high contact level, it is possible to obtain information about the predisposition of athletes to ACL rupture with *COL5A1* gene polymorphism. In addition, it is recommended that prospective studies investigating the relationship between ACL injury and genetic predisposition in football players are carried out with larger cohorts from different races and gender.

Conclusion

This study suggests that in football, which is a game with a high contact level, it is possible to obtain information about the predisposition of athletes to ACL rupture with *COL5A1* gene polymorphism. In addition, it is recommended that prospective studies investigating the relationship between ACL injury and genetic predisposition in football players are carried out with larger cohorts from different races and gender.

Authors' Contribution

Study Design: GI, HIC, AB; Data Collection: GI, HIC, AB, NB, SS; Statistical Analysis: GI, HIC; Manuscript Preparation: NA, GI; Funds Collection: NB.

Ethical Approval

The study was approved by the Tokat Gaziosmanpasa University Ethical Committee (2021/02) and it was carried out in accordance with the Code of Ethics of the World Medical Association also known as a declaration of Helsinki.

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Conflict of Interest

The authors hereby declare that there was no conflict of interest in conducting this research.

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