



Collagen Gene Variants and Anterior Cruciate Ligament Rupture in the Korean Population

Ki-Hoon Seong^{1,†} MS, Kwang-Jun Kim² PhD, Hee-Jung Park¹ MS, Byung-Hoon Lee³ MD, Eunwook Chang^{1,†} PhD, Dong-Ho Park^{1,4} PhD

¹Department of Kinesiology, Inha University, Incheon; ²Department of Sports Science, Korea Institute of Sports Science, Seoul; ³Department of Orthopaedic Surgery, College of Medicine, Gachon University, Incheon; ⁴Department of Biomedical Science, Program in Biomedical Science and Engineering, Inha University, Incheon, Korea

PURPOSE: Anterior cruciate ligament rupture (ACLR) is a common knee ligament injury that occurs in sports. The precise etiology of ACLR remains unknown. Previous studies in various ethnic groups have confirmed an association between genetic variants and ACLR; however, no such research has been conducted in Koreans. This study aimed to investigate whether certain single nucleotide polymorphisms (SNPs), namely COL3A1 rs1800255, COL5A1 rs12722, COL12A1 rs970547, and COL5A1 rs13946, are associated with ACLR in the Korean population.

METHODS: This study involved 60 ACLR patients (ACL group, average age 29.9 ± 10.9 years) and 328 control subjects (CON group, average age 23.8 ± 4.1 years). All the participants were genotyped for COL3A1 rs1800255, COL5A1 rs12722, COL12A1 rs970547, and COL5A1 rs13946.

RESULTS: No significant genotypic differences were found for COL3A1 rs1800255 ($p = .565$), COL5A1 rs12722 ($p = .779$), COL12A1 rs970547 ($p = .193$), or COL5A1 rs13946 ($p = .356$). Furthermore, no significant differences were observed between the homozygous and dominant models for each SNP or between the haplotypes of COL5A1 rs12722 and rs13946 ($p = .118$). However, a significant association with ACLR was observed for the genotype combinations COL3A1 rs1800255 and COL5A1 rs12722 ($p = .02$).

CONCLUSIONS: The results of this study indicate that specific genotypes (SNPs) COL3A1 rs1800255 and COL5A1 rs12722 may influence the occurrence of ACLR. Considering the results and limitations of this study, future research should focus on increasing the sample size, particularly by including both male and female patients of diverse ages, to further validate these findings.

Key words: SNP, Genotype, Collagen, Anterior cruciate ligament, Rupture

INTRODUCTION

Anterior cruciate ligament (ACL) tears are common knee ligament injuries that occur frequently during sports activities [1-3]. The precise etiology of ACLR remains unknown. Numerous external and internal risk factors, including genetic factors, have been identified. If a parent or sibling has experienced an ACL tear, the risk of ACLR appears to more than double [4,5].

The ACL, one of the four major ligaments in the knee, is defined as the collagen tissue that spans the joint and is anchored to the bones at

both ends [6]. Ligaments are composed of fibroblasts surrounded by a cellular matrix; the fibroblasts play a role in matrix synthesis and constitute a small proportion of the ligaments overall. Ligaments and tendons assist in connecting forces and facilitating joint strength in the musculoskeletal system [7]. The primary component of the ligaments is collagen, with Type I collagen accounting for 85% of the total collagen—the remaining 15% consists of Types III, VI, V, XI, and XIV collagens [8]. Collagen represents 75% of the dry weight of the ACL, with the remaining weight comprising proteoglycans, elastin, various proteins, and glycoproteins [6]. The genes COL3A1 and COL5A1 encode the $\alpha 1$ chains of

Corresponding author: Dong-Ho Park **Tel** +82-32-860-8182 **Fax** +82-32-860-8188 **E-mail** dparkosu@inha.ac.kr

[†] Ki-Hoon Seong and Eunwook Chang contributed equally as first authors.

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Type III and V collagens, respectively, and polymorphisms within these genes have been identified in several studies as associated with the risk of ACLR [9,10].

A study by Stepien-Slodkowska et al. [11], in which Polish recreational skiers were the study population, demonstrated an association between the COL3A1 rs1800255 polymorphism and ACLR. Skiers with the AA genotype were found to have an almost five-fold higher probability of ACL injury than those with the AG+GG genotype. In a study by Posthumus et al. [10] investigating COL5A1 rs12722(T/C) and COL12A1 rs970547(A/G) single nucleotide polymorphisms (SNPs) in relation to ACLR, the group of 216 study participants included 129 females clinically diagnosed with ACLR (including 38 females with the AA genotype of COL12A1) and 83 females with no history of ACL injury. The results of the study revealed a statically significant correlation of the COL12A1 SNP—with a high frequency of the AA genotype—with ACL injury risk only in females ($p = .048$) and not in males ($p = .359$). In addition, in a study by Zhao et al. [12] involving 101 Han Chinese individuals with ACL injuries, no significant differences in ACLR risk were found in study subjects with COL5A1 rs12722 or rs13946. However, the A allele and AA genotype of COL12A1 rs970547 in males were associated with a higher risk of ACL injury. When examining these previous results, it becomes evident that differences may exist not only with regard to race, but also sex (male/female). Recently published studies have explored ACLR in diverse racial populations; however, studies targeting the Korean population are currently lacking.

Accordingly, the objective of this study was to investigate—in a Korean study population—the possible association between ACLR and the SNPs COL3A1 rs1800255, COL5A1 rs12722, COL12A1 rs970547, and COL5A1 rs13946, which have been previously suggested to be related to ACLR.

METHODS

1. Participants

The clinical study followed the Declaration of Helsinki. The Institutional Review Board and Ethical Committee of Inha University (Incheon, Korea) approved the study (approval no. 2000824-6A).

This study was conducted with a group of Koreans, including individuals diagnosed with ACLR (“ACLR” group, $n = 60$) and a control group (“CON” group, $n = 328$) with no history of ACLR. In the ACL group, 55 patients underwent ACLR surgery and the other 5 did not. All partici-

Table 1. Characteristics of the participants

Parameter		ACL ($n = 60$)	CON ($n = 328$)
Sex ^a	Male	50 (83.3)	190 (57.9)
	Female	10 (16.7)	138 (42.1)
Age (yr) ^a		29.9 ± 10.91	23.8 ± 4.08
Height (cm) ^a		173.1 ± 6.83	171.1 ± 9.04
Weight (kg) ^a		74.8 ± 13.2	67.9 ± 12.8
BMI (kg/m ²) ^a		24.9 ± 3.49	23 ± 2.94
Family history ^b	Yes	4 (6.67)	20 (6.12)
	No	56 (93.33)	308 (93.88)

CON, Control group; ACL, Anterior cruciate ligament rupture group; BMI, body mass index.

^aData are presented as mean and SD; ^bData are shown in frequencies and percentages.

pants were recruited from local hospitals, sports centers, universities, and similar institutions. An identical sample size between the two groups could increase statistical power; however, there were limitations in recruiting patients diagnosed with ACL injuries. Additionally, 143 was determined to be the total sample size needed to investigate the frequency difference of each SNP's genotype between the two groups, with an effect size of 0.3, a power of 0.8, and an α level set below 0.05. The purpose and content of the study were explained to all the participants, and their consent was obtained before conducting the research. The characteristics of the participants are presented in Table 1.

2. Body measurements and family history

Height, weight, body fat percentage, and body mass index (BMI) were measured to assess body composition. Height and weight were measured using a TBF-2002 measurement device (Tantia Co., Japan), with the participants wearing short sleeves and shorts. Weight was measured with an accuracy of 0.01 kg, and height was measured with an accuracy of 0.1 cm. The BMI of each participant was calculated as weight (kg) divided by the square of height (m). Family histories were assessed through a questionnaire.

3. DNA extraction and SNP genotyping

Approximately 200 μ L of whole blood was collected from the individual's fingertips using a capillary tube (HCH-41B2501, Kimble Chase, USA). Genomic DNA was extracted using the AccuPrep Genomic DNA Extraction Kit (K-3032, Bioneer, Korea), following the manufacturer's instructions. The DNA was quantified using a NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific, USA). COL3A1 (rs1800255), COL5A1 (rs12722), and COL12A1 (rs970547) were analyzed using a SNaP-

shot* Multiplex System (Thermo Fisher Scientific) and COL5A1 (rs13946) was analyzed using a TaqMan SNP Genotyping Assay (Thermo Fisher Scientific).

4. Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows version 25.0. The characteristics of the participants between the two groups were presented as means and standard deviations.

Genotype and allele frequencies and distributions based on ACLR diagnosis were calculated for subjects diagnosed with ACLR and the general population. Depending on the sample size, either the chi-square test or Fisher's exact test was employed to examine the frequency differences in genotypes and alleles between the two groups (ACL group and CON

group). The reason is that the χ^2 test is appropriate when all expected frequencies in the cells are 5 or greater, whereas Fisher's exact test is used when any expected frequency is less than 5. The statistical significance level was set at less than 5% ($p < .05$).

RESULTS

1. Genotype and allele frequencies

Differences between the ACL and CON groups in terms of the frequency distributions of the studied SNPs—COL3A1 rs1800255, COL5A1 rs12722, COL12A1 rs970547, and COL5A1 rs13946—are shown in Table 2. The frequency distributions of alleles and genotypes did not show any significant differences between the ACL and CON groups (Table 2).

Table 2. Genotypic and allelic frequencies of the CON and ACL groups

Group		Allelic frequencies (%)		p^*	Genotypic frequencies (%)			p^*
COL3A1	rs1800255	G	A		GG	GA	AA	
	CON (n = 325)	506 (77.6)	146 (22.4)	.428	204 (62.8)	97 (29.8)	24 (7.4)	.565
	ACL (n = 59)	86 (72.9)	32 (27.1)		33 (55.9)	20 (33.9)	6 (10.2)	
COL5A1	rs12722	C	T		CC	CT	TT	
	CON (n = 327)	504 (76.8)	152 (23.2)	.799	191 (58.4)	121 (37)	15 (4.6)	.779
	ACL (n = 59)	93 (78.8)	25 (21.2)		37 (62.7)	19 (32.2)	3 (5.1)	
COL12A1	rs970547	G	A		GG	GA	AA	
	CON (n = 326)	206 (33)	438 (67)	.583	31 (9.5)	153 (46.9)	142 (43.6)	.193
	ACL (n = 59)	44 (36.7)	76 (63.3)		10 (16.9)	23 (39)	26 (44.1)	
COL5A1	rs13946	T	C		TT	CT	CC	
	CON (n = 306)	360 (58.8)	252 (41.2)	.682	105 (34.3)	150 (49)	51 (16.7)	.356
	ACL (n = 59)	74 (61.7)	46 (38.3)		25 (42.4)	23 (39)	11 (18.6)	

CON, Control group; ACL, Anterior cruciate ligament rupture group.

*Chi-square or Fisher's exact test. The level of significance (α) was set at 0.05.

Table 3. Genotype frequency analysis based on genetic models between control and ACL groups

SNPs	Group	Recessive model ^a		p^*	Dominant model ^a		p^*
COL3A1	rs1800255	GG+GA (%)	AA (%)		GG (%)	GA+AA (%)	
	CON (n = 325)	301 (92.6)	24 (7.4)	.434	204 (62.8)	121 (37.2)	.32
	ACL (n = 59)	53 (89.8)	6 (10.2)		33 (55.9)	26 (44.1)	
COL5A1	rs12722	CC+CT (%)	TT (%)		CC (%)	CT+TT (%)	
	CON (n = 327)	312 (95.3)	15 (4.6)	.745	191 (58.4)	136 (41.6)	.536
	ACL (n = 59)	56 (94.9)	3 (5.1)		37 (62.7)	22 (37.3)	
COL12A1	rs970547	GA+GG (%)	AA (%)		GG (%)	GA+AA (%)	
	CON (n = 326)	184 (56.4)	142 (43.6)	.942	31 (9.5)	295 (90.5)	.088
	ACL (n = 59)	33 (55.9)	26 (44.1)		10 (16.9)	49 (83.1)	
COL5A1	rs13946	TT+CT (%)	CC (%)		TT (%)	CT+CC (%)	
	CON (n = 306)	255 (83.3)	51 (16.7)	.711	105 (34.3)	201 (65.7)	.237
	ACL (n = 59)	48 (81.4)	11 (18.6)		25 (42.4)	34 (57.6)	

CON, Control group; ACL, Anterior cruciate ligament rupture group.

^aData are shown in frequencies and percentages.

*Chi-square or Fisher's exact test. The level of significance (α) was set at 0.05.

Table 4. Haplogenotype frequencies of rs12722 and rs13946 in the COL5A1 gene between Control and ACL Groups

COL5A1 Haplotypes		Frequency (%)		<i>p</i> *
rs12722	rs13946	CON	ACL	
CC / TT		37 (12.1)	12 (20.3)	.118
CT / CT		59 (19.3)	9 (15.3)	
TT / CC		0 (0)	0 (0)	

CON, Control group; ACL, Anterior cruciate ligament rupture group.

*Fisher's exact test. The level of significance (α) was set at 0.05.

2. Homozygous and dominant genotypes

In the statistical results for Homozygous and Dominant models of COL3A1 rs1800255, COL5A1 rs12722, COL12A1 rs970547, and COL5A1 rs13946, there was no significant difference in genotypes between the two groups, as shown in Table 3.

3. Genotype and allele frequencies

There was no significant difference in haplotype analysis between rs12722 and rs13946 of COL5A1 (Table 4).

4. Genotype and allele frequencies

In the group targeted for COL3A1 rs1800255 and COL5A1 rs12722, significant differences were observed only in the AA and TT groups ($p < .02$). No significant differences were observed between COL3A1 rs1800255 and COL12A1 rs970547, COL3A1 rs1800255 and COL5A1 rs13946, COL5A1 rs12722 and COL12A1 rs970547, or COL12A1 rs970547 and COL5A1 rs13946 (Table 5).

DISCUSSION

ACLR is commonly known as one of the most frequently occurring injuries in athletes [13]. If left untreated in the early stages, ACLR can lead to persistent instability of the knee, recurrent injuries, and serious consequences, such as removal of the intra-articular cartilage. Following ACL injury, the incidence of osteoarthritis can reach 80%, with early-onset arthritis occurring mostly in patients aged between 30 and 50 years. This results in knee pain and reduced quality of life [14,15].

In this study, the association between ACLR and each of the selected SNPs, namely COL3A1 rs1800255, COL5A1 rs12722, COL12A1 rs970547, and COL5A1 rs13946, was examined. The results showed that the individual genotypes or alternative alleles of these genes did not exhibit significant differences in ACLR. However, the results of the gene-gene interaction analysis, the COL3A1 rs1800255 and COL5A1 rs12722 AA-TT

Table 5. Gene-gene interaction analysis of genotypic frequency between control and ACL groups

SNP1	SNP2	CON	ACL	<i>p</i> *
COL3A1 rs1800255 COL5A1 rs12722				
	GG / CC	118 (36.4)	18 (30.5)	
	GA / CT	32 (9.9)	4 (6.8)	1.00
	AA / TT	0 (0)	2 (3.4)	.02
COL3A1 rs1800255 COL12A1 rs970547				
	GG / GG	18 (5.6)	4 (6.8)	
	GA / GA	50 (15.5)	11 (18.6)	1.00
	AA / AA	10 (3.1)	2 (3.4)	1.00
COL3A1 rs1800255 COL5A1 rs13946				
	GG / TT	61 (20.1)	15 (25.4)	
	GA / CT	51 (16.8)	10 (16.9)	.714
	AA / CC	3 (1)	1 (1.7)	.662
COL5A1 rs12722 COL12A1 rs970547				
	CC / GG	22 (6.8)	8 (13.6)	
	CT / GA	59 (18.2)	7 (11.9)	.067
	TT / AA	9 (2.8)	0 (0)	.160
COL12A1 rs970547 COL5A1 rs13946				
	GG / TT	12 (3.9)	5 (8.5)	
	GA / CT	72 (23.6)	11 (18.6)	.141
	AA / CC	5 (8.5)	5 (8.5)	.285

CON, Control group; ACL, Anterior cruciate ligament rupture group.

*Fisher's exact test. The level of significance (α) was set at 0.05.

genotypes showed a significant difference between the ACLR group and the control group. These findings suggest that, in the context of the Korean population, the interaction between genotypes may have a more significant impact on ACLR than individual genotypes.

In previous studies conducted in different populations, 321 male Polish recreational skiers (138 ACL group vs. 183 control group) showed an association between the COL3A1(rs1800255) AA genotype and ACLR [16]. The COL3A1 (rs1800255) AA genotype, on the other hand, did not significantly associated with ACLR in a research involving 108 professional men's football players (45 ACL group vs. 63 control group) of the same ethnicity. Additionally, a study [17] examining the relationship between COL5A1 polymorphisms and ACLR in Australian (362 ACL group vs. 80 control group), South African (235 ACL group vs. 232 control group), and Japanese individuals (500 ACL group vs. 1403 control group) found that the CC genotype was only associated with ACLR in the Japanese population. In contrast, Chinese individuals (101 ACL group vs. 110 control group) demonstrated an association between the COL12A1 rs970547 genotype and ACLR, whereas the COL5A1 rs12722 and rs13946 genotypes were not related to ACLR [12]. Italian individuals (86 ACL group vs. 96 control group) did not show any association between the COL5A1 rs13946 and COL12A1 rs970547 genotypes or

ACLR [18]. These diverse results suggest the importance of race and region, as different outcomes have been observed based on ethnicity or residence [13,17,19]. Furthermore, the statistical power is greatly impacted by the sample size of the ACL group because the distribution of genotypes for each SNP is not equal. Thus, it is crucial to secure above 100 samples. This study differs from earlier research in that it identified substantial differences only in gene-gene interactions, but no differences in the frequency distribution of genotypes for each SNP linked to ACLR. This result may be due to the relatively small individual effects of the SNPs associated with ACLR examined in this study, which manifested as gene-gene interaction effects with vulnerable genotypes between genes. Alternatively, the reduced statistical power resulting from the small sample size mentioned earlier could also have contributed to this outcome.

A family history of ACLR has been reported in some studies, suggesting the possibility of genetic factors influencing knee injuries and other musculoskeletal tissue damages [20,21]. Genetic factors are also reported to influence injuries to the Achilles tendon and shoulder rotator cuff [20]. Female twins were shown to have several functional factors that increase the risk of ACLR, including an increased intraarticular knee angle, decreased knee flexion angle, and increased overall joint laxity, all of which increase the likelihood of ACLR [20]. Recently, Magnusson et al. [22] investigated the heritability and family risk of ACL rupture in 88,414 identical and fraternal twins at least 17 years old. ACL rupture had a high overall heritability of 69%, rising from 60% at age 17 to 80% at age 60. The heritability and familial risk of ACL rupture were comparable for men and women. These findings contradict previous studies [10,12,20] that indicate sex-specific genetic variations in ACLR. Despite the high genetic influence, the ACL group in this study showed a family history similar to the Con group, which presents a result contrary to that of Magnusson et al. [22]. The primary causes of this discrepancy might be that our study is cross-sectional rather than longitudinal like Magnusson et al.'s, it isn't a twin study that could evaluate genetic influence, the participants are young, and the sample size is relatively small. Especially, the age of onset may be later even if there is a genetic vulnerability, which could explain the variations from these previous studies [10,12,20-22].

This examination of the association between ACLR and Koreans yielded results that differ from those of previous studies conducted in different ethnicities. This discrepancy can be attributed to differences in study populations. However, one major limitation of this study is the small sample size, which can reduce statistical power when subdivided

into specific subgroups. Furthermore, it was difficult to examine gender differences in this study due to the small number of female ACLR patients. Considering the results and limitations of this study, future research should focus on increasing the sample size, particularly in diverse age groups (20-30s and 50-60s) and both sexes (male and female), to further validate these findings.

CONCLUSION

In this study, individuals of Korean descent in their 20s and 30s with the AA genotype of COL3A1 rs1800255 and the TT genotype of COL5A1 rs12722 were found to be more susceptible to ACLR. These results suggest that the association between genetic diversity and ACLR may vary depending on the race and region. The causes of ACLR may involve not only genetic factors, but also various environmental factors and lifestyle patterns, leading to diverse outcomes.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Conceptualization: KH Seong, E Chang, KJ Kim, BH Lee; Data curation: KH Seong, E Chang, HJ Park, KJ Kim, BH Lee; Methodology: HJ Park; Writing - original draft: KH Seong; Writing - review & editing: E Chang.

ORCID

Ki-Hoon Seong	https://orcid.org/0009-0005-0704-9039
Kwang-Jun Kim	https://orcid.org/0009-0003-9827-245X
Hee-Jung Park	https://orcid.org/0009-0008-9496-2193
Byung-Hoon Lee	https://orcid.org/0000-0002-1548-5691
Eunwook Chang	https://orcid.org/0000-0001-5876-9275
Dong-Ho Park	https://orcid.org/0000-0003-1863-0652

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