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# The Relationship between *COL5A1* rs12722 Polymorphism and Flexion-Extension Lumbar Spine Range of Motion and Soft Tissue Injuries

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**SUMMARY**

**Background.** Genetics may play a critical role in soft tissue injuries by influencing the level of range of motion. To this end, the aim of the study was to investigate the relationship between the *COL5A1* rs12722 gene polymorphism and flexion-extension lumbar spine range of motion and soft tissue injuries

**Methods.** A total of 100 male athletes from elite level bodybuilding, wrestling, artistic gymnastics and football sports branches were included in the present study. Blood samples were taken from athletes to analyze the *COL5A1* rs12722 gene polymorphism. Then, with the help of a goniometer, flexion-extension lumbar spine range of motion levels of the athletes were measured. ANOVA, Pearson Chi-Square and Fisher Freeman Halton exact tests were used in the statistical analysis.

**Results.** As a result, it was seen that 30% of the athletes had CC, 46% had CT and 24% had TT genotype. In terms of allele distribution, 53% of athletes had the C allele and 47% had the T allele. There was a statistically significant difference between the *COL5A1* rs12722 and flexion lumbar spine range of motion ($p < 0.05$). On the other hand, there was no statistically significant difference in the other sub-dimensions ($p > 0.05$).

**Conclusions.** In the study, it was concluded that the CC genotype and C allele of the *COL5A1* rs12722 polymorphism may be associated with the increased level of range of motion in lumbar spine flexion. In conclusion, due to the increased level of movement, athletes may be significantly protected from soft tissue injuries.

**KEY WORDS**

*COL5A1* rs12722 *polymorphism; lumbar spine; range of motion; soft tissue injury; sports.*

## INTRODUCTION

Sporting performance is a complex phenomenon that is influenced by many factors. There are many factors that have an impact on this phenomenon. Genetics, which is a candidate to be one of these factors, may have a critical impact on athlete performance. Genetics is a multifactorial trait that involves athletic performance (1). Genetic traits possessed by athletes may have a key role for success in sports. When the success of the athletes was examined, it was observed that some of them could achieve the desired success with 3,000 hours of work and some with 10,000 hours of work. This may indicate that genetics may be an important marker in determining sporting success (2).

Athletes' hereditary conditions such as skeletal-muscle, respiratory, cardiovascular system efficiency and susceptibility to injuries may be critical in maintaining a healthy sports life. Sports injuries occur when the body's endurance limits are exceeded. The negativities caused by sports injuries may sometimes turn into an irreversible situation for athletes. Identifying the hereditary characteristics that cause

sports injuries can make great contributions to athletes and their coaches in terms of protection from injuries. Another dimension of sports injuries is their effects on the economies of the countries. The English Premier Football League is an example of this situation. In the Premier League, an average of £74.7 million was spent on sports injuries in a season, including medical fees and insurance costs (3). In this case, the abilities and physical development of the athletes may decline, and they may face an irreversible situation.

The injuries that athletes encounter during sports performance are mostly soft tissue injuries (4). Damage to tissues such as tendons, ligaments, muscles, etc., is known as soft tissue injuries. Although many factors are effective on soft tissue injuries, there may also be genetic factors that affect these injuries. To date, regarding soft tissue injuries in sports, *COL5A1*, *COL1A1*, *COL12A1*, *MMP1*, *MMP3*, *IGF2*, *EMILIN1*, *ESR1*, *SMAD6*, *TTN* and *TIMP2* gene variants have been identified (5-8). The *COL5A1* gene, which is assumed to be effective on collagen tissues, may be of great importance in soft tissue injuries.

The *COL5A1* gene has important effects on type V collagens (9). The *COL5A1* gene is responsible for the production of type V collagen which is called the Pro-a1 (V) chain. Collagens are rope-like procollagen structures consisting of three chains each. The combination of the two chains forms type V collagen. Three-stranded procollagen structures form mature collagen structures with the help of enzymes. These collagens turn into a thin and long structure with the help of type I collagen. Type V collagen regulates the range of these fibrils, that is, their thickness (10). The most common forms of type V collagen are heterotype chains consisting of 1 alpha 2 propeptide and 2 alpha 1 propeptide encoded by *COL5A1* and *COL5A2*, respectively (11).

The fact that collagen is structurally flexible and has a wide range of motion may protect athletes against soft tissue injuries. Flexibility is the ability of the muscle to contract, extend, be stimulated, transmit, and to expand the joints at an optimal level during movement (12). The joint range of motion, which has similar characteristics to flexibility, is an important skill in the development of physical fitness and sporting ability (13). Regardless of the sports branch, improving joint range of motion may provide a number of benefits. These may be listed as improving athletic performance, protection from injuries and adaptation to activities (14, 15).

The joint range of motion level may be a trait controlled by hereditary factors. To this end, it is a trait that is influenced by both multifactorial phenotypes and genetic factors (16). For this reason, the *COL5A1* gene polymorphism may be an important biomarker in joint range of motion and soft tissue injuries (17-19, 21). The *COL5A1* gene is localized on the 9q34.3 long arm of chromosome 9 (**figure 1**).

In the study, male athletes from football, bodybuilding, gymnastics and wrestling branches were examined. This may explain due to have a higher injury rate male athletes than female athletes in these sports branches (22). The aim of the study was to investigate the relationship between the *COL5A1* rs12722 gene polymorphism and flexion-extension lumbar spine range of motion and soft tissue injuries. We think that the results of the study will make valuable contributions to sports science.

## MATERIALS AND METHODS

### The study group

The study group of the research consisted of a total of 100 athletes, 25 bodybuilders, 25 wrestlers, 25 artistic gymnasts and 25 footballers. Athletes were selected voluntarily and randomly for the study. The inclusion criteria for the study are presented in **table I**. The study was conducted in accordance with the Declaration of Helsinki. The study was approved by Ondokuz Mayıs University Clinical Research Ethics Committee, on February 26, 2021, with 2021/24 decision number. Additionally, permissions were obtained form the participants to be included in the study.

### The study design and data collection tools

The study was carried out in two parts. In the first part, the 10-question demographic information form was applied to the athletes by making the necessary explanations. Athletes were provided with the necessary time to answer each question.

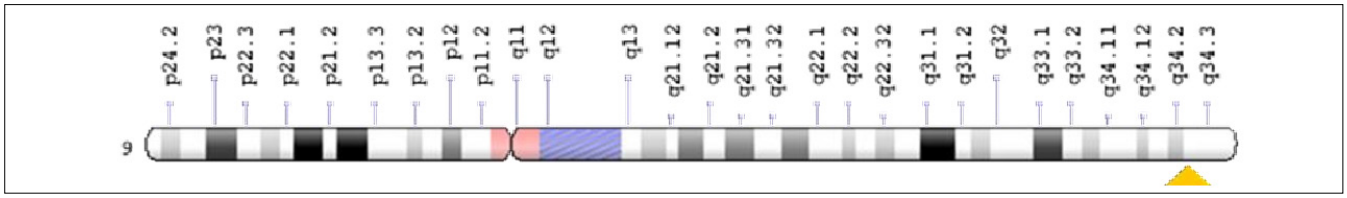


**Figure 1.** *COL5A1* gene in genomic location.

**Table I.** Criteria for study participation.

| Inclusion criteria |
|---|
| To be a male and Turkish athlete in the relevant sports branch over the age of 18. |
| To be active and regularly in elite level and related sports branches for at least 10 years. |
| To be a competitor at national and international level. |
| Not having any history of injury, especially in the lumbar spine region, before and during the measurements. |
| Not having any viral infectious diseases (COVID, hepatitis, diphtheria, dysentery, AIDS, tuberculosis, *etc.*), bacterial diseases and continuous treatment. |
| Not having any genetic disease due to soft tissue damage. For example, Ehlers-Danlos Syndrome, *etc.* |

Anthropometric characteristics of the athletes were measured at least twice, and the average of values were recorded. For height measurement, sensitivity ± 1 mm, device was used. Additionally, Xiaomi Mi Body Composition Scale 2 Model, sensitivity ± 50 g, digital scale was also used for weight measurement. Then, the athletes' Body Mass Indexes (B.M.I.) were calculated and recorded. Data obtained from athletes were presented by detailing in **table II.**

In the second part of the study, the flexion-extension lumbar spine range of motion levels of the participants were measured with a goniometer device. Before the measurements, the athletes were given general and special warm-up exercises, respectively. The athletes' flexion-extension lumbar spine range of motion levels were measured at least twice and the average results were recorded. The flexion-extension lumbar spine range of motion was measured by a manual goniometer with a length of 20 cm and a 360 degree rotation angle. Additionally, the goniometer measurements were performed by the test practitioner with the support of a doctor of physical therapy. This measurements were carried out with a similar technique and by the same person. The book, joint range of motion and muscle lenght testing, guided flexion-extension lumbar spine range of motion measurements (23).

## Genotyping

In the present study, blood samples were taken by EDTA tubes. DNA isolation procedures were performed using DNA isolation kit from 100 blood samples. The isolated DNA samples were taken to the PCR reaction process to amplify the *COL5A1 3'UTR* gene regions. For the

**Table II.** Participant characteristics in study.

| Variables | Groups | N | % |
|---|---|---|---|
| Age (years) | 18-22 | 60 | 60 |
| | 23-28 | 15 | 15 |
| | 29-34 | 7 | 7 |
| | 35-40 | 7 | 7 |
| | > 41 | 11 | 11 |
| Height (cm) | 160-165 | 6 | 5 |
| | 166-171 | 16 | 15 |
| | 172-177 | 38 | 37 |
| | 178-183 | 29 | 32 |
| | >184 | 11 | 11 |
| Weight (Kg) | 50-65 | 32 | 32 |
| | 66-85 | 46 | 47 |
| | 86-100 | 16 | 15 |
| | 101-115 | 4 | 4 |
| | >116 | 2 | 2 |
| Body Mass Index Kg/m$^2$) | 18.5 and under | 3 | 3 |
| | 19-24.9 | 57 | 57 |
| | 25-29.9 | 33 | 33 |
| | 30-34.9 | 3 | 3 |
| | >35 | 4 | 4 |
| Sports Branches | Bodybuilder | 25 | 25 |
| | Wrestler | 25 | 25 |
| | Artistic Gymnast | 25 | 25 |
| | Footballer | 25 | 25 |
| Soft tissue injury experienced for more than a month | Yes | 36 | 36 |
| | No | 64 | 64 |
| Soft tissue injury experienced for every year | Yes | 14 | 14 |
| | No | 86 | 86 |
| **Total** | | **100** | **100** |

*COL5A1* rs12722 (BstUI) region, *5'GAAGACGGTCTTGGAGACTG-3'* was used as the forward primary and *5'-GAAGGCACCTGCAGAATGAC-3'* was used as the reverse primer. New England M0285L Taq 5x Master Mix was used in the PCR reaction. Reaction conditions were prepared as master mix 5 µl., forward primer 0.5 µl, reverse primary 0.5 µl, DNA 3 µl, ddH2O 16 µl total 25 µl. PCR reactions were performed as 3-minute denaturation at 94 °C, 1 minute at 94 °C, 1 minute at 53 °C, 1 minute 35 cycle at 72 °C and 8 minute elongation reaction at 72 °C. The

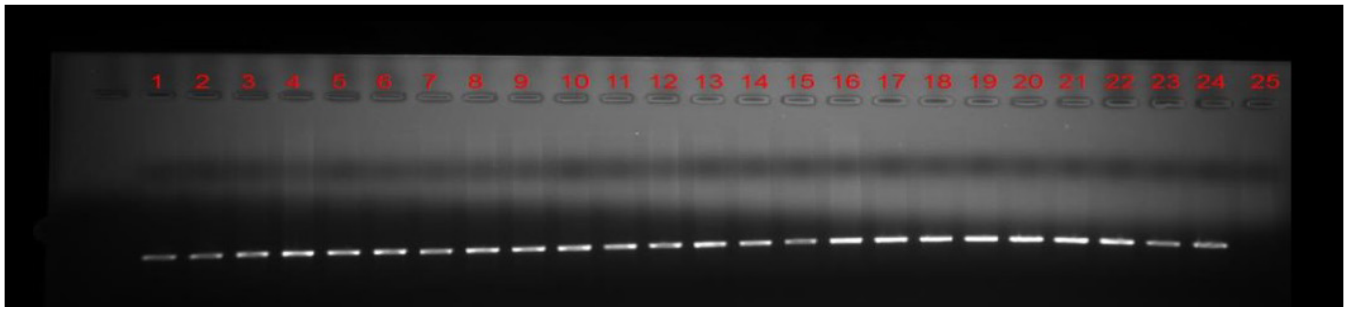


**Figure 2.** Gel electrophoresis image of *COL5A1* rs12722 polymorphism.

products obtained after PCR were processed in 2% agarose gel at 90 volts and 90 minutes. The Sanger Method was used for sequencing. (24). The sequence PCR program was performed in 25 cycles of 1 minute at 96° C, 10 seconds at 96 °C, 5 second at 50 °C and 4 minute at 60 °C. The samples were loaded into the ABI 3130 genetic analyser device and one-way sequencing was performed.

The gel electrophoresis image of the *COL5A1* rs12722 polymorphism was shown in **figure 2**.

### Statistical evaluation

SPSS 22.0 package statistical program was used in the analysis of the data. In more than two group comparisons, the ANOVA test was used. Chi-square and Fisher Freeman halton exact tests were used to determine whether there is a relationship between categorical independent variables. The statistical significance level was determined as $p < 0.05$. The Hardy-Weinberg Equilibrium was considered in the distribution of genes within the population (25). The data obtained from genotyping and another measuremets were presented in the results.

**Table III.** Genotype and allele distribution of the *COL5A1* rs12722 polymorphism.

| %/n | Genotype | | | Allele | |
|---|---|---|---|---|---|
| | CC | CT | TT | C | T |
| Total % | 30% | 46% | 24% | 53% | 47% |
| Total n | 30 | 46 | 24 | 106 | 94 |

## RESULTS

The findings obtained from the present study were shown below as both genotype and allele distribution. In order to facilitate the statistical process, the flexion-extension lumbar spine range of motion scores of the athletes were standardized and the average of their lower and upper performance ranges was taken as flexion <120/≥120, extansion <60/≥60.

According to **table III**, 30% of the athletes had CC, 46% had CT and 24% had TT genotype. Additionally, 53% of athletes had C allele and 47% had T allele.

According to **table IV**, there was no statistically significant difference between genotypes of the *COL5A1* rs12722 polymorphism and the anthropometric test results ($p > 0.05$).

According to **table V**, *COL5A1* rs12722 polymorphism CC, TT, and CT genotypes were in the Hardy-Weinberg Equi-

**Table IV.** Test result of the *COL5A1* rs12722 polymorphism and anthropometric variables.

| Anthropometric Variables | Genotype | | | | |
|---|---|---|---|---|---|
| | CC | CT | TT | f | p |
| Height | 174.85±5.94 | 177.95±7.01 | 175.84±5.83 | 2.28 | 0.10 |
| Weight | 73.35±11.09 | 77.93±17.30 | 76.91±12.53 | 0.92 | 0.40 |
| BMI | 24.17±3.92 | 24.60±4.17 | 25±4.15 | 0.27 | 0.76 |

*P-value < 0.05.

**Table V.** Test result of the *COL5A1* rs12722 polymorphism and sports branches.

| Sports Branches | Genotype | | | $X^2$ | HWE | P-value | Allele | | $X^2$ | P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| | CC | TT | CT | | | | C | T | | |
| Body Building | 4 (13.3%) | 5 (0.8%) | 16 (34.8%) | | | | 24 (22.6%) | 26 (27.7%) | | |
| Wrestling | 8 (26.7%) | 9 (37.5%) | 8 (17.4%) | | | | 24 (22.6%) | 26 (27.7%) | | |
| Artistic Gymnastic | 10 (33.3%) | 4 (16.7%) | 11 (23.9%) | 7.73 | 0.78 | 0.25 | 31 (29.2%) | 19 (20.2%) | 2.65 | 0.44 |
| Soccer | 8 (26.7%) | 6 (25%) | 11 (23.9%) | | | | 27 (25.5%) | 23 (24.5%) | | |
| **Total** | **30 (30%)** | **24 (24%)** | **46 (46%)** | | | | **106 (53%)** | **94 (47%)** | | |

*P-value < 0.05.

**Table VI.** Test result of extension lumbar spine range of motion and *COL5A1* rs12722 polymorphism.

| Extension | Genotype | | | $X^2$ | P-value | Allele | | $X^2$ | P-value |
|---|---|---|---|---|---|---|---|---|---|
| | CC | TT | CT | | | C | T | | |
| < 60 | 16 (53.3%) | 15 (62.5%) | 32 (69.6%) | | | 64 (60.4%) | 62 (66%) | | |
| ≥ 60 | 14 (46.7%) | 9 (37.5%) | 14 (30.4%) | 2.05 | 0.35 | 42 (39.6%) | 32 (34%) | 0.66 | 0.41 |
| **Total** | **30 (30%)** | **24 (24%)** | **46 (46%)** | | | **106 (53%)** | **94 (47%)** | | |

*P-value < 0.05.

librium (p > 0.78). There was no statistically significant difference between the bodybuilding, wrestling, artistic gymnastics and football sports branches and genotype and allele distribution of the *COL5A1* rs12722 polymorphism (p > 0.05). It was observed that bodybuilder athletes had the highest genotype (CT genotype) distribution ratio. The highest allele distribution was found in artistic gymnasts (C allele).

According to **table VI**, there was no statistically significant difference between extension lumbar spine range of motion and the *COL5A1* rs12722 polymorphism (p>0.05). The highest genotype distribution was athletes with CT genotype and < 60 extension lumbar spine range of motion. The highest allele distribution was athletes with T allele and < 60 extension lumbar spine range of motion.

According to **table VII**, there was a statistically significant difference between flexion lumbar spine range of motion and the *COL5A1* rs12722 polymorphism (p < 0.05). These differences were found in both genotype and allele distribution. The highest genotype distribution was athletes with TT genotype and < 120 flexion lumbar spine range of motion. The highest allele distribution was athletes with T allele and < 120 flexion lumbar spine range of motion.

## DISCUSSION

In the study, the *COL5A1* rs12722 polymorphism, which was thought to be an important risk factor on soft tissue injuries, was examined in detail. The obtained results were discussed and evaluated together with the scientific data in the relevant literature.

**Table VII.** Test result of flexion lumbar spine range of motion and *COL5A1* rs12722 polymorphism.

| Flexion | Genotype | | | $X^2$ | P-value | Allele | | $X^2$ | P-value |
|---|---|---|---|---|---|---|---|---|---|
| | CC | TT | CT | | | C | T | | |
| < 120 | 14 (46.7%) | 20 (83.3%) | 26 (56.5%) | | | 54 (50.9%) | 66 (70.2%) | | |
| ≥ 120 | 16 (53.3%) | 4 (16.7%) | 20 (43.5%) | 7.89 | 0.019* | 52 (49.1%) | 28 (29.8%) | 7.70 | 0.005* |
| **Total** | **30 (30%)** | **24 (24%)** | **46 (46%)** | | | **106 (53%)** | **94 (47%)** | | |

*P-value < 0.05.

There was no significant difference between the sports branches and genotype and allele distribution of the *COL5A1* rs12722 polymorphism ($p > 0.05$). When the genotype and allele distribution results of the *COL5A1* rs12722 polymorphism were examined, it was seen that the athletes had the most CT genotype and C allele. Bodybuilders had the highest genotype percentage for CT genotype of the *COL5A1* rs12722 polymorphism. Gymnasts also had the highest allele percentage for C alelle of the *COL5A1* rs12722 polymorphism. Bodybuilders and gymnasts had the lowest genotype count of the *COL5A1* rs12722 polymorphism. For this purpose, in study by Tringali *et al.* (26) was found that, when the rhythmic gymnasts were examined in terms of the *COL5A1* rs12722 polymorphism distribution, 4 of the 42 athletes had CC genotypes, 13 had TT genotypes and 25 had CT genotypes. According to these results, the *COL5A1* rs12722 polymorphism genotype distribution was not consistent with the present study.

In the present study, there was no significant difference between the *COL5A1* rs12722 polymorphism and extension lumbar spine range of motion ($p > 0.05$). The fact that the spine has a mechanism that may protect the lumbar spine region from excessive extension may be effective on this result. Additionally, the spine's anatomy during the backward movements of the athletes may also have an effect on the extension lumbar spine range of motion measurement scores. This issue has to more research. According to the chi-square results, significant differences were found between *COL5A1* rs12722 polymorphism and flexion lumbar spine range of motion ($p < 0.05$). To this end, Petrillo *et al.* (27) concluded in their study that the *COL5A1* rs12722 polymorphism CC genotype showed significant differences, in the passive external rotation, compared to the TT and CT genotypes. Collins *et al.* (28) concluded in their study that the *COL5A1* rs12722 polymorphism may be a genetic marker related to range of motion. In another study by Brown *et al.* (29) it was found that the *COL5A1* rs12722 polymorphism may be related to range of motion. Lim *et al.* (30) reported that the COL5A1 CC genotype, in passive straight leg lift, had differed significantly compared to the CT and TT genotypes. These results should support that the *COL5A1* rs12722 CC genotype may be associated with an increased level of range of motion. As CC genotype and the C allele of the *COL5A1* rs12722 polymorphism produce irregular and sparse collagen, the collagens - which is encoded by this genotype and allele - may prevent athletes from soft tissue injuries. On the contrary, the fact that the TT genotype and the T allele produce denser and more regular collagen may affect the mechanical properties of connective tissues, stimulating a decrease in level of range of motion (31). For this reason, the genotype and allele of the *COL5A1* rs12722 polymorphism may regulator structural integrity of soft tissues. To this end, Dines *et al.* (32) reported that the C allele of the *COL5A1* rs12722 polymorphism may provide resistance to injury in runners. In another study, Hefferman *et al.* (33) reported that the the C alleles and CC genotypes of the *COL5A1* rs12722 and rs3196378 polymorphisms had an inherited resistance in soft tissue injuries.

In the literature review, the studies were also found in which there was no relationship between the *COL5A1* polymorphism and joint range of motion. For this purpose, Bertuzzi *et al.* (34) concluded in their study that the *COL5A1* rs12722 polymorphism had no effect on the level of range of motion. Posthumus *et al.* (35) reported that there was no significant difference between the MMP3 rs679620 and the *COL5A1* rs12722 polymorphisms and range of motion. O'connell *et al.* (36) reported there were no significant differences between *COL3A1* rs1800255, *COL6A1* rs35796750 and *COL12A1* rs970547 gene variants and range of motion.

A mutation in the *COL5A1* gene polymorphism can have significant effects on both the range of motion and the level of flexibility. This is supported by clinical data. Classic Ehlers-Danlos syndrome (EDS) is an inherited connective tissue disease which is associated with joint hypermobility and excessive skin elasticity. In conclusion, it seems likely that the *COL5A1* gene may cause soft tissue injuries by affecting the level of range of motion.

## CONCLUSIONS

The present study concluded that the CC genotype and C allele of the *COL5A1* rs12722 polymorphism may be associated with the increased level of range of motion in lumbar spine flexion. As a result, due to the increased level range of motion, athletes may be significantly protected from soft tissue injuries. This may be explained by the fact that genetics has an indirect rather than direct effect on the range of motion.

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## DATA AVAILABILITY

Data are available under reasonable request to the corresponding author.

## CONTRIBUTIONS

SK: writing – original draft, data curation, conceptualization. ME: project administration, conceptualization.

## ACKNOWLEDGEMENTS

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## CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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