REVIEW

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Investigation of The Relationship Between *COL5A1* rs12722 Polymorphism and Non-Contact Soft Tissue Injuries: A Systematic Review

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SUMMARY

Background. The increasing popularity of sport and the desire of athletes to exceed their performance limits have significantly increased both the number of injuries and the losses related to these injuries. Soft tissues are under the influence of many internal and external factors. Of these factors, genetics can have a considerable impact on soft tissue injuries. For this purpose, many gene polymorphisms have been detected in some studies. One of these polymorphisms, the *COL5A1* rs12722 polymorphism may have a critical role on soft tissues. The aim of this study was to investigate the relationship between *COL5A1* rs12722 polymorphism and non-contact soft tissue injuries.

Methods. The study was designed as a systematic review, and PRISMA 2020 statement was used to selection of the studies. PubMed and PubMed Central in NCBI, Web of Science and Google Scholar internet databases were scanned. ROBIN-I, including Cochrane handbook, Robvis tools, were used to determine the risk level of bias.

Results. As a result, 9 case-control studies were found to meet the criteria. However, there is a significant risk of bias in studies investigating the relationship between *COL5A1* rs12722 polymorphism and non-contact soft tissue injuries. When the results were examined, statistically significant results were found in 2 of the 9 studies, but not in 7 studies.

Conclusions. *COL5A1* rs12722 polymorphism may be an important regulator on soft tissues. To this end, clinical applications describing the mechanism of non-contact soft tissue injuries with individuals from larger populations may make important contributions to this field.

Study registration. Prospero ID: 1064082.

KEY WORDS

COL5A1 rs12722 polymorphism; genetic; non-contact soft tissue injuries; performance; sport.

INTRODUCTION

Sports injuries are a type of sports-specific injury whose incidence is increasing day by day depending on the type of sports branch. The increasing popularity of sports and exceeding performance limits have significantly increased both the number of injuries and the losses related to these injuries, recently. This is not only physical and physiological negativity for the athlete, but also a situation that causes high financial burdens (1).

Structures such as tendons, ligaments, meniscus, muscles, *etc.*, consisting of tissues other than bones of the body, are defined as soft tissues. Damage to the structural integrity of these tissues is described as soft tissue injuries and the frequency of such injuries is increasing day by day (2). Many factors have important effects on soft tissue injuries. Age, gender, nerve-muscle compatibility, psychological state, physical fitness, heredity, *etc.* are intrinsic factors. Additionally, nutrition, ergogenic supports, sports area, climate, spectators, materials, *etc.* are also external factors. Recent research has proven that heredity may have a significant impact on soft tissue injuries (3, 4).

Sports injuries are expressed in different situations according to the way they occur. Considering the effects of internal and external factors, they are classified as contact and

Table I. Some genes and their location associated with non-contact injuries.

Gene	Explanation	Function	rsNCBI
ELN	Elastin	Tissue repair- Muscle building	rs228936
TTN	Titin	Strenght transfer	rs2742327
SOX15	SRY-Box Transcription Factor 15	Muscle regeneration	rs4227
IGF2	Insulin Like Growth Factor 2	Muscle damage	rs3213221
CCL2	C-C Motif Chemokine Ligand 2	Response to muscle damage	rs2857656
TNC	Tenascin C	Tendinopathy	rs2104772
COL1A1	Collagen Type I Alpha 1 Chain	Ligament ruptures	rs1800012
COL5A1	Collagen Type V Alpha 1 Chain	Ligament ruptures- Tendinopathy	rs12722

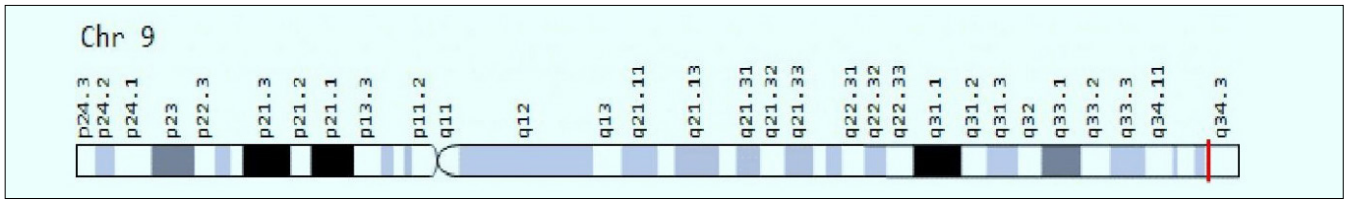


Figure 1. Location of the *COL5A1* gene on chromosome.

non-contact. Many factors may cause important effects on non-contact injuries. These may be listed as anatomical, neuromuscular, biomechanical, hormonal, genetic (5). Non-contact injuries have negative consequences for some athletes, when environmental factors provide similar effects (6, 7). To this end, genetics factors may play a critical role in sports injuries (8). It is known that some SNP's (single nucleotide polymorphisms) show a significant effect on non-contact sports injuries (9) (**table I**).

COL1A1, *COL12A1*, *COL14A1*, *COL27A1*, *COL11A1*, *COL11A2*, *COL3A1*, *COL6A1* and *COL5A1* genes have been successfully studied for tendon and ligament injuries, so far. However, *COL5A1* gene polymorphisms are the most studied genetic structure in non-contact soft tissue injuries (10-11). The *COL5A1* gene is localized at q34.3 on the long arm of chromosome 9 (12) (**figure 1**).

The *COL5A1* gene codes for the alpha I chain of type V collagen (13). For this reason, the range of collagen structures is significantly regulated. While the *COL1A1* gene determines the length of collagen tissues, the *COL5A1* gene is, due to its heterodimer properties, responsible for the width of these structures. As the *COL5A1* gene regulates the width of collagen tissues, this gene may be an important regulator in non-contact soft tissue injuries. To this end, the *COL5A1* rs12722 polymorphism, due to C>T transition, may be important in chronic Achilles tendon pathology (14). For this purpose, Longo *et al*., (15) reported that tendon ruptures may occur not only in areas of external origin, but also in areas where there are no signs of ruptures. The effect of *COL5A1* rs12722 polymorphism on the structural formations of collagen tissues may be critical on this result (16). To this end, *COL5A1* rs12722 polymorphism may greatly protect athletes against non-contact injuries (17, 18).

In the literature, the abundance of studies on the relationship between *COL5A1* rs12722 polymorphism and non-contact injuries is remarkable. However, the role of *COL5A1* rs12722 polymorphism in non-contact injuries is still unclear in these studies. For this reason, the aim of this study was to investigate the relationship between *COL5A1* rs12722 polymorphism and non-contact soft tissue injuries. The results of the study will make valuable contributions to sports sciences.

MATERIALS AND METHODS

Protocol of the study

This systematic review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews

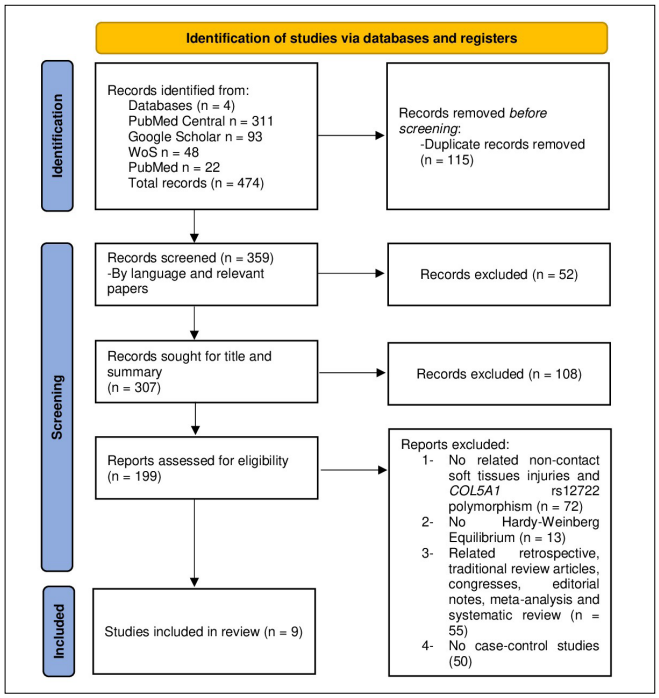


Figure 2. Desing of the studies used in the research according to PRISMA 2020.

and Meta-Analyses). In addition, the 2020 current version was preferred in the selection of studies suitable for PRISMA.

Eligibility criteria

The PICO algorithm was used to detail the main questions of this study and to guide the study (19). To this end, data on PICO are presented in **table II.**

The criteria for inclusion in the study are as follows: being a male or female individual, designing the studies as a case-control method, individuals in the case groups have a history of non-contact soft tissue injuries and their injuries need to be detected surgically the absence of any hereditary soft tissue disease in the participants (Ehlers Danlos Syndrome *etc.*). The exclusion criteria are as follows: not designing the studies as a case-control method, no history of non-contact soft tissue injuries in the case groups, inability to detect case group injuries surgically, participants have any hereditary soft tissue disease. Additionally, in the selection of the articles, the distribution of genes in the population was taken into account (20). For this reason, the Hardy Weinberg Equilibrium was given importance ($p > 0.05$). In the present study, retrospective, traditional review articles, congresses, editorial notes, meta-analysis and studies designed with systematic methods were not evaluated.

Search strategy

To define in detail the selection criteria of the data obtained, the PRISMA 2020 statement, developed by Page *et al.*, was used (21). In **figure 2**, the flowchart of the PRISMA technique is presented.

Selection and data collection

In the review, PubMed and PubMed Central in NCBI, Web of Science and Google Scholar internet databases were scanned. The keywords "soft tissue injuries in sports" OR "the relationship between sports and genetics and soft tissue injuries" OR "the relationship between *COL5A1* rs12722 polymorphism and soft tissue" OR "investigation the relationship between *COL5A1* rs12722 polymorphism and non-contact soft tissue injuries" were written, and the data obtained meticulously evaluated. In this present review, support was obtained from the NLM (National Library of Medicine) controlled Thesaurus MeSH (Medical Subject Headings), which is used to index PubMed articles. The data obtained from studies were evaluated by two indepen-

Table II. PICO description model

PICO	Description
Population	Individuals with non-contact soft tissue injuries and healthy individuals.
Intervention	To determine the genetic mechanism of non-contact soft tissue injuries and to interpret the results obtained in detail. In addition, applying different stretching exercise programs for soft tissues before the activity.
Comparator	To compare *COL5A1* rs12722 polymorphism with non-contact soft injuries and to determine soft tissue susceptibility.
Outcome	*COL5A1* rs12722 polymorphism may affect the sports performance status of athletes in non-contact soft tissue injuries.

dent researchers. The final decision on inclusion and exclusion was given within the content of the current study. The following rankings were carried out in data extraction and quality evaluation. The articles on the subject covered studies conducted between December 2009 and January 2024. For the review, a total of 474 articles were scanned according to many criteria. After the copies were removed, 359 articles were included in the language and relevance review. Then, the scan was done by title and summary. The 199 articles that met the criteria were eventually reduced to 9 articles based on 4 criteria (**figure 2**). The literature review of the study was conducted between April 15 and August 20, 2024. The data obtained from the articles were examined in detail. The articles that were suitable for the scope of the research were scanned according to the title and the necessary data were extracted. Articles that were not related to the research were excluded. In the present review, the data obtained from case-control studies were evaluated. The review included 3.333 individuals with soft tissue injuries and 3.195 healthy controls, and polymorphism and genotype data for the association of non-contact soft tissue injuries, and did not contain any restrictions such as ethnicity, gender, language, religion, cultural, *etc.*

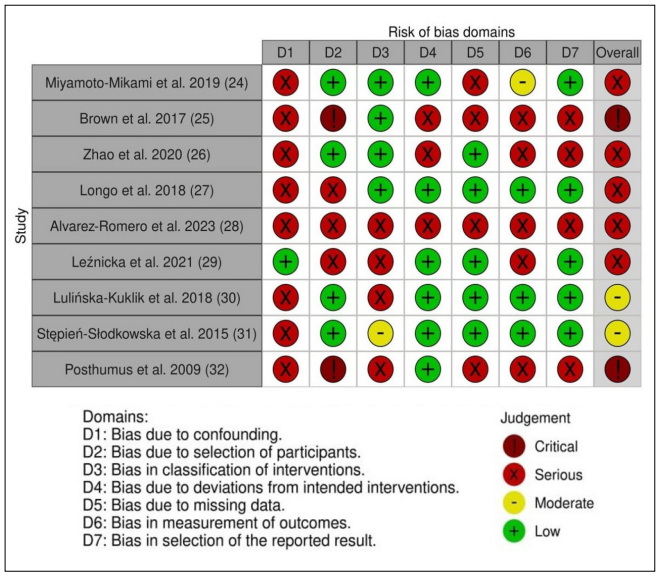


Figure 3. Traffic light plots of the domain-level judgements for each individual result.

Data items

The data obtained in the review were designed using table tools. To this end, first the data was identified. Then, these data were placed in tables with explanations. The tables contained article information, respectively. ROBINS-I bias risk assessments and explanations are presented in **table III**. In **table IV** it can be found: a- references, b- date of the articles, c- qualifications of the participants, d- results. Additionally, it is presented in **table V** respectively: a- references, b- country- ethnicity, c- genotype frequency case (%), d- genotype frequency control (%) ve, e- P-value (significance value). Additionaly, ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) tool, which estimated the effectiveness or safety in the reviews, was used to non-randomized studies of interventions (NRSI).

Risk of bias assessment

Risk analysis was performed to determine the bias possibilities of the articles used in the present review. For this purpose, ROBINS-I tools were used. The Cochrane Handbook was assessed for ROBINS-I. The Cochrane Handbook for Systematic Reviews of Interventions is the official guide that describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of healthcare interventions (22). ROBINS-I tool assesses risk

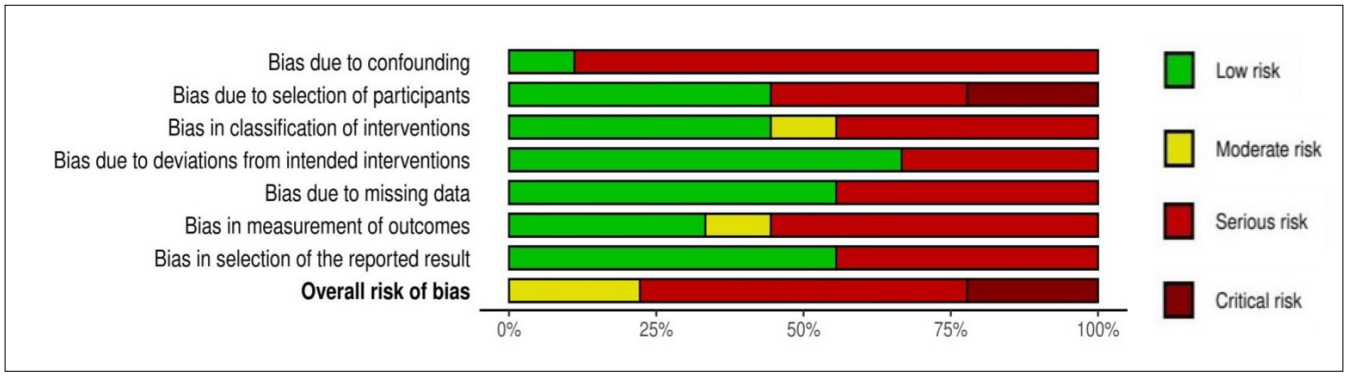


Figure 4. Weighted bar plots of the distribution of risk-of-bias judgements within each bias domain.

Table III. Outcome-level table with risk of bias assessments for ROBINS-I including judgements.

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Miyamoto-Mikami *et al.* 2019 (24)	**Serious**	**Low**	**Low**	**Low**	**Serious**	**Moderate**	**Low**	**Serious**
Rationale for judgement	They measured confounding variables. But used an analysis (Chi square) that does not allow for adjustment.	Selection into the study was based upon the outcome but this is unlikely to be related to the intervention.	The interventions were explained in detail and a detailed description was made.	It was found that there was a usual deviation between the intervention groups.	A decrease was detected in the data. However, no new analysis was carried out for the missing data.	The methods of outcome assessments were compared with the intervention groups. Different methods were used for evaluation measurements in different intervention groups. However, the outcome measures were not affected by the information of the interventions from the participants.	Protocol based on clinical knowledge there appears to be no selection based on outcome, intervention, multiple analyses, or different subgroups.	About 41% of the data is missing.
Brown *et al.* 2017 (25)	**Serious**	**Critical**	**Low**	**Serious**	**Serious**	**Serious**	**Serious**	**Critical**
Rationale for judgement	They measured confounding variables. But used an analysis (Chi square) that does not allow for adjustment.	They selected male rather than female individuals in *COL5A1* rs12722 TT and CT genotype analysis. There was no analysis looking at the effect of this selection bias.	The interventions were explained in detail, and a detailed description was made.	In the intergroup evaluation, deviations from the usual practices were detected. To this end, 87 individuals with Achilles tendon pathology and 25 individuals with Achilles tendon rupture may have influence on outcome assessment.	A decrease was detected in the data. Individuals who were found to be unable to meet the criteria were excluded from the study. However, no new analysis was carried out for the missing data.	The methods of outcome assessments were compared with the intervention groups. Outcome measures are likely to be influenced by the information of interventions received from their participants.	There is protocol based on clinical data. Depending on the findings, *COL5A1* and CASP8 genes were selectively reported from multiple measurements.	About 8% of the data is missing. There is an imbalance in the number of symptomatic groups. There is selective reporting.

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Zhao *et al.* 2020 (26)	**Serious**	**Low**	**Low**	**Serious**	**Low**	**Serious**	**Serious**	**Serious**
Rationale for judgement	They measured confounding variables. But used an analysis (Chi square) that does not allow for adjustment.	Selection into the study was based upon the outcome but this is unlikely to be related to the intervention.	The interventions were explained in detail, and a detailed description was made.	In the intergroup evaluation, deviations from the usual practices were detected. The beta-fibrinogen gene was represented by 6 polymorphisms. This may affect the outcome.	No missing data has been identified.	The methods of outcome assessments were compared with the intervention groups. Outcome measures are likely to be influenced by the information of interventions received from their participants.	There is protocol based on clinical data. Depending on the findings, Beta-fibrinogen gene polymorphisms were selectively reported from multiple measurements.	Beta-fibrinogen gene polymorphisms were overrepresented.
Longo *et al.* 2018 (27)	**Serious**	**Serious**	**Low**	**Low**	**Low**	**Low**	**Low**	**Serious**
Rationale for judgement	confounding variables. But logistic regression was used for recessive and dominant models.	In the study, individuals of the Caucasian race constituted the case group. This can have an impact on outcome evaluation.	The interventions were explained in detail and a detailed description was made.	In the intended evaluation between the groups, it was seen that the differences represented a normal deviation.	No missing data has been identified.	The methods of outcome assessments were compared with the intervention groups. Outcome measures were not affected by the information of the interventions received from the participants.	Protocol based on clinical knowledge there appears to be no selection based on outcome, intervention, multiple analyses, or different subgroups.	The case group consisted of individuals of the Caucasian race.

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Alvarez-Romero *et al.* 2023 (28)	**Serious**	**Serious**	**Serious**	**Serious**	**Serious**	**Serious**	**Serious**	**Serious**
Rationale for judgement	They measured confounding variables. But used an analysis (Chi square) that does not allow for adjustment.	They did not select the intervention groups at a balanced level. The number of Japanese participants was higher than the others in both the control and case groups.	The interventions were not fully disclosed. 80 participants from the Australian control group did not engage in any sports activities.	In the intended evaluation between groups, deviations from practices were detected. Japanese individuals were more highly represented. This seems likely to affect the outcome.	No missing data has been identified. However, there are losses in the detection of the injury mechanism (contact, non-contact).	The methods of outcome assessments were compared with the intervention groups. Outcome measures are likely to be influenced by the information of interventions received from their participants.	There is protocol based on clinical data. Based on the findings, Japan individuals were selectively reported.	The number of Japanese individuals is greater than the number of other participants.
Leźnicka *et al.* 2021 (29)	**Low**	**Serious**	**Serious**	**Low**	**Low**	**Serious**	**Low**	**Serious**
Rationale for judgement	They measured confounding variables.	In the study, individuals of the Caucasian race constituted the case-control group.	The interventions were not fully disclosed. A total of 114 individuals were used in the case and control group.	It was found that there was a usual deviation between the intervention groups.	No missing data has been identified.	The methods of outcome assessments were compared with the intervention groups. Outcome measures are likely to be influenced by the information of interventions received from their participants.	Protocol based on clinical knowledge there appears to be no selection based on outcome, intervention, multiple analyses, or different subgroups.	The information from the individuals affected the outcome measurements.
Lulińska-Kuklik *et al.* 2018 (30)	**Serious**	**Low**	**Serious**	**Low**	**Low**	**Low**	**Low**	**Moderate**

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Rationale for judgement	They measured confounding variables. But used an analysis (Chi square) that does not allow for adjustment.	Selection into the study was based upon the outcome. but this is unlikely to be related to the intervention.	The interventions were explained in detail and a detailed description was made. However, the mechanism of injury to 134 athletes was not fully disclosed.	In the intended evaluation between the groups, it was seen that the differences represented a normal deviation.	No missing data has been identified.	The methods of outcome assessments were compared with the intervention groups. Outcome measures were not affected by the information of the interventions received from the participants.	Protocol based on clinical knowledge there appears to be no selection based on outcome, intervention, multiple analyses, or different subgroups.	The exact mechanism of injury to the case group was not disclosed.
Stępień-Słodkowska *et al.* 2015 (31)	**Serious**	**Low**	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Moderate**
Rationale for judgement	They measured confounding variables. But used an analysis (Chi square) that does not allow for adjustment.	Selection into the study was based upon the outcome. but this is unlikely to be related to the intervention.	The interventions were explained in detail and a detailed description was made. However, there is incomplete information in the interventions.	In the intended evaluation between the groups, it was seen that the differences represented a normal deviation.	No missing data has been identified.	The methods of outcome assessments were compared with the intervention groups. Outcome measures were not affected by the information of the interventions received from the participants.	Protocol based on clinical knowledge there appears to be no selection based on outcome, intervention, multiple analyses, or different subgroups.	There is incomplete information in the descriptions of the interventions.
Posthumus *et al.* 2009 (32)	**Serious**	**Critical**	**Serious**	**Low**	**Serious**	**Serious**	**Serious**	**Critical**
Rationale for judgement	They measured confounding variables. But used an analysis (Chi square) that does not allow for adjustment.	They found the exact mechanism of injury in 67 men and only 21 women in the study. There is no information about the other.	The interventions were explained in detail and a detailed description was made. But there is confusion in the cases of intervention.	Any deviations from intended intervention reflected usual practice.	No missing data has been identified. However, there are losses in the detection of the injury mechanism (contact, non-contact).	The methods of outcome assessments were compared with the intervention groups. Outcome measures are likely to be influenced by the information of interventions received from their participants.	There appears to be selection based on outcome. There is a selective evaluation in favor of female participants.	All biases can be considered critical. As there is a serious risk of bias in five areas.

of bias in 7 domains. These may be listed as follows: bias due to confounding, bias due to selection of participants, bias in classification of interventions, bias due to deviation from intended intervention, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported results (**figure 3**). Finally, overall risk scores were used to assess total risk of bias. The weighted distribution of bias risk within each area was also shown (**figure 4**). For this study, traffic light plots and weighted plots bar tools in Robvis web application were used (23).

RESULTS

The study was conducted to investigate the relationship between *COL5A1* rs12722 polymorphism and non-contact soft tissue injuries. Regarding this relationship, studies with

Table IV. Descriptive features of studies on the relationship between *COL5A1* rs12722 polymorphism and non-contact soft tissue injuries.

References/ Year	Participations	Result
Miyamoto-Mikami *et al.* 2019 (24)	1,559 athletes from various sports branches and 363 healthy young adults.	There was no significant relationship between muscle injuries and *COL5A1* rs12722 polymorphism.
Brown *et al.* 2017 (25)	130 people with Achilles tendon pathology and 130 asymptomatic individuals.	There was no statistically significant relationship between Achilles tendon ruptures and *COL5A1* rs12722 polymorphism.
Zhao *et al.* 2020 (26)	101 sick individuals with ACL (anterior cruciate ligament) injury and 110 healthy individuals without ACL injury.	There was no statistically significant relationship between ACL injury and *COL5A1* rs12722 polymorphism.
Longo *et al.* 2018 (27)	93 individuals with a history of RC (rotator cuff) surgery and 206 individuals without RC injury.	There was no statistically significant relationship between rotator cuff injuries and *COL5A1* rs12722 polymorphism.
Alvarez-Romero *et al.* 2023 (28)	1,097 patient individuals with ACL and ligament injuries and 1715 healthy individuals without any history of soft tissue injuries.	A statistically significant relationship was found between ACL injury-ligament injuries and *COL5A1* rs12722 polymorphism.
Leźnicka *et al.* 2021 (29)	53 individuals with a history of injury and 61 individuals without any history of injury.	There was no statistically significant relationship between musculoskeletal injury susceptibility and *COL5A1* rs12722 polymorphism.
Lulińska-Kuklik *et al.* 2018 (30)	134 professional football players with ACL injuries and 211 amateur football players without ACL injuries.	There was no statistically significant relationship between ACL injury and *COL5A1* rs12722 polymorphism.
Stępień-Słodkowska *et al.* 2015 (31)	138 recreational skiers diagnosed with ACL injuries and 183 healthy skiers without ACL injuries	There was no statistically significant relationship between ACL injury and *COL5A1* rs12722 polymorphism.
Posthumus *et al.* 2009 (32)	129 individuals with ACL injury and 216 healthy individuals without any ACL injury	A statistically significant relationship was found between ACL injuries and *COL5A1* rs12722 polymorphism.

Table V. Statistical data of studies on the relationship between *COL5A1* rs12722 polymorphism and non-contact soft tissue injuries.

References/Year	Country	Ethnic	Genotype frequency (case) (%) CC-CT-TT	Genotype frequency (control) (%) CC-CT-TT	P-value
Miyamoto-Mikami *et al.* 2019 (24)	Japan	Asia	71.1-27.4-1.60	68.6-29.2-2.50	> 0.428
Brown *et al.* 2017 (25)	Africa-Australia	Africa-Australia	7-6-9	27-64-34	> 0.108
Zhao *et al.* 2020 (26)	Chinese	Asia	56-37-8	68-36-6	> 0.050
Longo *et al.* 2018 (27)	Italy	Caucasian	15.1-49.5-35.5	15-49-35.9	> 0.050
Alvarez-Romero *et al.* 2023 (28)	Australia-South Africa-Japan	Australia-Africa-Asia	78.1-21.9-0	67.6-29.2-3.1	< 0.036*
Leźnicka *et al.* 2021 (29)	Poland	Caucasian	37.5-37.1-48	62.5-62.9-52.1	> 0.050
Lulińska-Kuklik *et al.* 2018 (30)	Poland	West Europe	17-49-34	20-51-29	> 0.661
Stępień-Słodkowska *et al.* 2015 (31)	Poland	West Europa	17-48-35	21-50-28	> 0.467
Posthumus *et al.* 2009 (32)	Africa	Africa	2-19-16	2-38-23	< 0.006*

eligibility criteria were evaluated and the following results were achieved.

Assessment of the risk of bias

Risk analysis was performed in 9 studies with appropriate criteria to reduce possible bias. In **figure 3**, the risk of bias level assessments of individual results was presented as a traffic light. Accordingly, in the measurement of the outcomes, it was determined that 5 studies were at risk of serious bias (25, 26, 28, 29, 32). In the selection of the reported results, it was seen that 4 studies had a serious risk of bias (25, 26, 28, 32). 2 studies were moderately represented in terms of overall risks of bias (30, 31). Additionally, in overall bias, 5 studies had serious (25, 26-29) scores and 2 studies had critical (25, 32) scores.

The research started with a total of 474 articles and was reduced to 9 articles with the desired qualifications. In the present study, case-control studies on the relationship between *COL5A1* rs12722 polymorphism and non-contact soft tissue injuries were reviewed, and the results were summarized in **table IV**.

In the literature review, it is concluded that the alleles and genotypes in the *COL5A1* rs12722 polymorphism may be important regulators in non-contact soft tissue injuries. However, when the results obtained from the present study were examined, there were not many results that supported this situation. To this end, Miyamoto-Mikami *et al.* (24) concluded that no significant relationship was found between *COL5A1* rs12722 polymorphism and muscle injuries. In another study, by Leźnicka *et al.* (29), it is found that there was not a significant relationship between *COL5A1* rs12722 polymorphism and musculoskeletal injury susceptibility.

Another soft tissue injury as important as muscle injuries is ACL injury, the prevalence of which is increasing day by day. ACL injuries mostly occur in the knee area. ACL injuries are the most frequently studied type of soft tissue injury in orthopedic literature and create a high financial burden (33-35). Surgical operations after ACL injuries have been steadily increasing in the last 20 years. This increase was from 17.6 % in 1990 to 50.9 % in 2009 (36).

Many internal and external factors may be effective on ACL injuries. However, recent studies have shown that genet-

ic factors may have significant effects on these injuries. To this end, in the study by Alvarez-Romero *et al.* (28), it was reported that between *COL5A1* rs12722 polymorphism and ACL injuries may exist a statistically significant relationship. In another study by Posthumus *et al.* (32), it was found that there was a statistically significant relationship between *COL5A1* rs12722 polymorphism and ACL injuries. However, as this study was conducted on female individuals, the results may need to be carefully examined. Contrary to these results, Zhao *et al.* (26) concluded that there was not a statistically significant relationship between *COL5A1* rs12722 polymorphism and ACL injuries. In the studies by Lulińska-Kuklik *et al.* (30) and Stępień-Słodkowska *et al.* (31) it was reported that there was not a statistically significant relationship between *COL5A1* rs12722 polymorphism and ACL injury.

Tendons are dense collagen structures that connect muscles to bones, and provide range of motion to the joint (37). Tendon injuries are soft tissue injuries that occur when muscles are exposed to a load greater than they can handle. For this reason, the Achilles tendon, the largest and strongest tendon in the body, has a wide prevalence of injuries (38). This may vary from 11% to 37% in per 100,000 patients (39). In the study, which is about *COL5A1* rs12722 polymorphism and Achilles tendon ruptures, by Brown *et al.* (25), it was found that a statistically significant relationship between *COL5A1* rs12722 polymorphism and Achilles tendon ruptures did not exist.

The shoulder, which is the area of the upper extremity with a wide range of motion, is a very sensitive area against injuries. To this end, it is a common problem that soft tissues such as muscles and tendons in the shoulder joint degenerate as a result of mechanical factors. RC injuries may be a major risk factor on this condition in the shoulder. Although many factors are effective in RC injuries, sports activities are shown as one of the most important factors (40-42). Longo *et al.* (27) examined the relationship between *COL5A1* rs12722 polymorphism and RC injuries. However, they did not find a statistically significant relationship. This result suggests that the ability to control the functional movements of the shoulder and the stabilization of multiple tissue units may improve the sensitivity of this region to injuries (43). As a result, more work on the subject is needed. Some statistical data related to the results obtained from the study are presented in **table V**.

DISCUSSION

In this study, the relationship between *COL5A1* rs12722 polymorphism and non-contact soft tissue injuries was examined in detail together with the results of the study in the literature. When the results of the bias risk analysis of the obtained results were examined, it was determined that 5 studies had a serious risk of bias in the outcome measurements (25, 26, 28, 29, 32). Additionally, in the selective reporting of the results, it was determined that 4 studies had a serious risk of bias (25, 26, 28, 32). Only 2 studies were found to have a moderate level of bias risk analysis in general risk areas (30, 31). When these results are examined, it may be concluded that there is a serious risk of bias in outcome measurements and selective reporting in case-control studies examining the relationship between *COL5A1* rs1 rs12722 polymorphism and non-contact soft tissue injuries. This may be due to the unilateral selection of the individuals included in the study or the design of the study. To this end, Youn *et al.* (44) found that, in studies examining the relationship between sports and genes, there were studies that examine individuals from certain races rather than different ethnic groups. Therefore, these studies may be sensitive to the risk of bias. Additionally, it may be necessary to make the study design meticulous.

In the present study, no statistically significant differences were found in 7 of the data obtained from the study (24-27, 29-31). On the other hand, it was observed that there was a statistically significant relationship between the 2 studies. Examining results of 2 studies, it was found that these were about ACL and ligament injuries. To this end, in the studies by Alvarez-Romero *et al.* (28) and Posthumus *et al.* (32), it was found that *COL5A1* rs12722 CC genotype showed a statistically significant association compared to CT and TT genotypes. This may be related to the amount of protein encoded by the *COL5A1* rs 12722 polymorphism. Examining the literature, it was found that the *COL5A1* rs12722 CC genotype created a collagen structure that was more resistant to non-contact soft tissue injuries compared to CT and TT genotypes. For this purpose, in the study by Heffernan *et al.* (45) it was found that the *COL5A1* rs12722 CC genotype and the C allele may be protective against soft tissue injuries. This may occur due to the sparse sequence of the amount of collagen synthesized by the *COL5A1* rs12722 CC genotype and C allele. As a result soft tissues may reach a wide range of motion level. Petrillo *et al.* (46) reported that the *COL5A1* rs12722 CC genotype showed higher range of motion scores in passive external rotation compared to the TT and CT genotypes. In similar study by Lim *et al.* (47), it was found that the *COL5A1* rs12722 CC genotype may related to the increased level of range of motion. In another study by Kubo *et al.* (48), it was found that the *COL5A1*

rs12722 CC genotype had significant effects on the range of motion of the tendon. Examining the data obtained from the present studies, it may be concluded that the *COL5A1* rs12722 CC genotype may develop a protective mechanism against injuries that may occur in soft tissues. Contrary to this result, the TT genotype and the T allele due to the intense amount of collagen may be more susceptible to injuries in terms of muscle stiffness (24). To this end, McCabe and Collins (49) concluded that the *COL5A1* rs12722 TT genotype may be a genetic structure associated with sports injuries. In another study by Jacob *et al.* (50), it was found that between the *COL5A1* rs12722 TT genotype and the total number of muscle injuries statistically significant differences may exist. According to these results, *COL5A1* rs12722 CC genotype and C allele may contribute positively to sports performance. For this reason, Dines *et al.* (51) reported that the *COL5A1* rs12722 C allele may be a biological structure supporting sports performance.

In the study, the results of studies on Asian, African, Australian, Western European and Caucasian races were examined. In addition, the study showed an increase in the number of studies conducted on individuals belonging to certain races. This may be explained by the high number of studies involving individuals of the Caucasian race. As a result of this, studies with certain races may cause biases (44). For this reason, including individuals from different ethnic groups in studies on *COL5A1* rs12722 polymorphism may significantly reduce the biases that may arise.

CONCLUSIONS

Examining the data obtained from the present studies, it may be concluded that *COL5A1* rs12722 polymorphism may have a important effect on soft tissue injuries. However, the effect of *COL5A1* rs12722 polymorphism on non-contact soft tissue injuries is still controversial. For this reason, there is a significant risk of bias in studies investigating the relationship between *COL5A1* rs12722 polymorphism and non-contact soft tissue injuries. This was reported in the present study.

When **table IV** and **V** were examined, statistically significant differences were found in 2 studies. However, it should be noted that the participants in these studies are female individuals. The sex-related effect of genetics on this outcome may be an important reason. This result needs to be carefully evaluated. *COL5A1* rs12722 polymorphism may be an important regulator on soft tissues. To this end, clinical applications describing the mechanism of non-contact soft tissue injuries with individuals from larger populations may make important contributions to this field. Additionally, these practices may also significantly reduce the bias risks of studies. But completely eliminate it. As a result, determining the non-contact injury susceptibility of the athletes and organizing the training programs according to these results may make significant contributions to coaches, sports clinicians, and athletes.

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CONFLICT OF INTERESTS

The author declare no conflict of interests.

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