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COL1A1 rs1800012 Polymorphism Associated with Anterior Cruciate Ligament Injuries: A Meta-Analysis

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Abstract

Purpose: To evaluate the relationship between the alpha 1 chain of collagen type I gene (COL1A1) polymorphism and the anterior cruciate ligament (ACL) rupture risk.

Methods: The PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched from their earliest entries through January 15, 2016. Methodological quality of each included studies was assessed using the Newcastle-Ottawa Scale (NOS). The relevant data were analyzed using Stata 12.0 software. The PRISMA checklist was used as protocol of the meta-analysis and the guideline was followed. The odds ratio (OR) and its 95% confidence interval (95%CI) were used to assess the strength of the association.

Results: A total of 4 studies (1361 people comprised 580 with ACL rupture and 781 without it) were found to be eligible for meta-analysis. In the present meta-analysis, a significantly decreased risk of ACL ruptures was detected in recessive model comparison (TT *vs.* GT+GG: OR= 0.174, 95%CI: 0.061~0.497; $P_{heterogeneity}$< 0.05), homozygous model (TT *vs.* GG: OR=0.188, 95%CI: 0.066~0.536; $P_{heterogeneity}$< 0.05) and heterozygous model (TT *vs.* GT: OR=0.142, 95% CI: 0.048~0.416; $P_{heterogeneity}$< 0.05) when all eligible studies were pooled. While, no significant association was found in allele model (T *vs.* G: OR=0.979, 95%CI: 0.796~1.205; $P_{heterogeneity}$< 0.05) or dominant model (TT+GT *vs.* GG: OR=1.133, 95%CI: 0.897~1.432; $P_{heterogeneity}$< 0.05). No heterogeneity or publication bias was detected in all comparisons and subgroup analysis was not necessary.

Conclusion: The combined analysis suggests that COL1A1 G-T haplotype may be protective against ACL injury.

Keywords: COL1A1; Polymorphism; Anterior cruciate ligament; Rupture; Meta-Analysis

Abbreviations

COL1A1: Alpha 1 Chain of Collagen Type I gene; ACL: Anterior Cruciate Ligament; NOS: Newcastle-Ottawa Scale; OR: Odds Ratio; CI: Confidence Interval; T: Thymine; G: Guanine; TT: TT Genotype; GT: GT Genotype; GG: GG Genotype; SNP: Single Nucleotide Polymorphisms; HWE: Hardy-Weinberg Equilibrium

Introduction

Injuries to the Anterior Cruciate Ligament (ACL) of the knee are common in populations with regular physical activities and often result in joint effusion, muscle weakness, altered movement and reduced functional performance. Severe ACL injury may even increase the risk of early-onset post-traumatic osteoarthritis regardless of the treatment administered [1]. Most ACL injuries in sports occur during a non-contact episode, typically during deceleration, lateral pivoting, or landing tasks that are associated with high loads on the knee joint [2]. Although these injuries have been well described at a clinical level, the biological mechanisms causing these injuries are poorly understood. Interestingly, Flynn et al. [3] reported a familial predisposition toward the ACL tearing by a case control study. Harner et al. [4] also found there was significant difference in the incidence rate of ACL injury in the family history of the experimental group compared with the control group. Recent years, more and more studies have suggested that genetic elements should be considered as an intrinsic risk factor for ACL rupture [5-8].

Collagen type I is the main component of ACL, which accounts for about 85% of collagen, and the rest is made up of types III, VI, V, XI and XIV [9]. It is a heterotrimer consisting of two alpha 1

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chains and one alpha 2 chain, which are encoded by the corresponding genes, respectively [10]. The gene that encodes for the alpha 1 chain of collagen type I (COL1A1) is located on chromosome 17q21 [6]. Single nucleotide polymorphisms (SNPs) in the collagen type I (COL1A1) gene have been shown to be associated with several complex connective tissue disorders, such as shoulder dislocations, Achilles tendon ruptures and Achilles tendinopathy [6,11,12]. Both ligaments and tendons are collagenous bands of fibrils mainly consisting of collagen type I. The guanine (G) to thymine (T) substitution in an intronic Sp1 binding site (rs1800012), resulting in increased affinity for the transcription factor Sp1, and increased COL1A1 expression, has been one of the most extensively investigated polymorphisms within this gene [6]. In addition, the TT genotype was shown to be under represented within individuals with ACL ruptures within four independent studies in a South African, Polish and Swedish cohort [11,13-15].

Though, a number of reports have been conducted to investigate the association between the SNP and the risks of ACL rupture in diverse population, the results were mixed and inconclusive. Also, traditionally we believe that all kinds of sports and activities lead to the ACL injury, and genetic factors are not related to the risk of it. Up to now, there is no meta-analysis investigating the association between them. Therefore, we performed a meta-analysis to evaluate the association between the COL1A1 polymorphism and ACL rupture risks.

Methods and Materials

Search strategy

The PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched from their earliest entries through January 15, 2016. The search strategy was (collagen type I alpha 1 [Title/Abstract]) or (COL1A1 [Title/Abstract]) or collagen I α1 [Title/Abstract]) or α1 chain of type I collagen

[Title/Abstract]) or "collagen type I, alpha 1 chain" [Supplementary Concept]) and ("Anterior Cruciate Ligament"[Mesh]) or "Ligaments"[Mesh]) or ("Posterior Cruciate Ligament"[Mesh] or "Collateral Ligaments "[Mesh]) and (polymorphism [Title/Abstract]) or polymorphisms [Title/Abstract]) or genetic risk factors [Title/Abstract]) or gene [Title/Abstract]) or gene variants [Title/Abstract]). The reference lists of these literatures and relevant articles from review literatures were also manually examined to further identify potentially relevant studies. No language restriction was imposed.

Inclusion criteria and exclusion criteria

Inclusion criteria were; (1) Evaluation of COL1A1 polymorphism and ACL injury; (2) A case-control or cohort design for human; (3) Sufficient published data were provided for the calculation of odds ratio with 95% confidence interval (CI); (4) Full-text manuscripts were included. Exclusion criteria included: (1) Duplication of the previous publications; (2) Abstract, comment, review and editorial; (3) Family-based studies of pedigrees; (4) Study with no detailed genotype data. When there were multiple publications from the same population, only the largest study was included. Study selection was achieved by two investigators independently, according to the inclusion and exclusion criteria by screening the title, abstract and full-text. Any dispute was solved by discussion.

Date extraction and assessment of methodological quality

After the consecutive procedures of screening of titles and abstracts, obtaining the full text of each article and reviewing them, articles that met the eligibility criteria and didn't meet the exclusion criteria's were selected to be included. The following data were extracted and collated independently by two authors (CB and ZXY) using a standardized data collection protocol (the PRISMA checklist, Table S1): the first author's name, published year, country origin, ethnicity, sample size, gender rate, patient age, numbers and genotypes of cases and control, source of controls (population-based and hospital-based), Hardy-Weinberg equilibrium (HWE) and genotyping method. The data of a published updated study involving the same cohort of patients was extracted synthetically. The corresponding authors were contacted when requisite data were unavailable in relevant articles. The methodological qualities of the included studies were assessed by two authors independently according to the Newcastle-Ottawa Scale (NOS), and three items were evaluated: patient selection, comparability of groups, and assessment of outcome. Trials with a score of 6 to 9 were considered as "high quality", no more than 5 were classified as "low quality". Disagreements were evaluated by the means of kappa text and were resolved by discussing with the corresponding author (CLB).

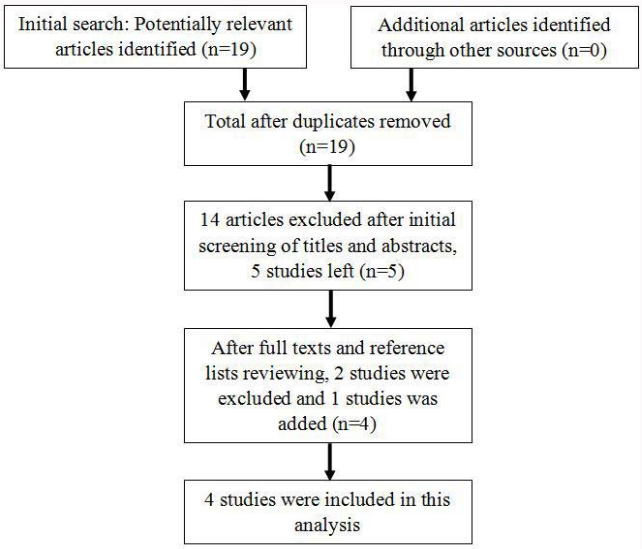

Figure 1: Flow diagram of the study selection process.

Statistical methods

We used the PRISMA checklist as protocol of the meta-analysis and followed the guideline [16]. The meta-analysis was conducted with Stata 12.0 software (Stata Corp, College Station, TX, USA). HWE was first assessed for each study using Chi-square test in control groups. $P< 0.05$ was considered representative of departure from HWE. For the meta-analysis, the odds ratio and its 95% confidence interval (95%CI) were used to estimate the strength of the association between the polymorphism of COL1A1 and the risk of sports injuries of the knee based on genotypes frequencies in cases and controls. A 95%CI without 1 for OR indicating a significant increased or reduced risk of sports injuries of the knee. The pooled ORs were performed for allelic comparison (T versus G), dominant model (TT+GT versus GG), recessive model (TT versus GT+GG), homozygote comparison (TT versus GG) and heterozygote comparison (TT versus GT), respectively. The significance of the pooled OR was determined by the Z-test. The statistical heterogeneity was tested with the Chi-square test and I2. If heterogeneity was low ($P >0.1$, $I2< 50\%$), a fixed-effect model

Table 1: Characteristics of studies included in the meta-analysis.

First author	Year	Country	Ethnicity	Sample size		Gender (M/F)		Age (years)		HWE	HWE	Genotyping Method
				Case	Control	Case	Control	Case	Control	Case	Control	
Ficek K et al. [13,15]	2013	Poland	Caucasian	91	143	91/0	143/0	23±3	24±5	0.201	0.587	TaqMan Pre-Designed SNP Genotyping Assay
Khoschnau S et al. [11]	2008	Sweden	Caucasian	234	325	??	0/325	??	??	>0.05	>0.05	solid-phase minisequencing
Posthumus M et al. [12,14]	2009	South Africa	Caucasian	117	130	81/36	97/33	29.0±11.2	37.7±10.0	0.219	0.075	nested PCR assay
Stepien-Slodkowska M et al. [15]	2013	Poland	Caucasian	138	183	138/0	183/0	27±2	26±3	0.2469	0.33	TaqMan Pre-Designed SNP Genotyping Assay

Notes: M: Male; F: Female; HWE: Hardy-Weinberg Equilibrium; SNP: Single Nucleotide Polymorphisms; PCR: Polymerase Chain Reaction

Table 2: Meta-analysis results of different model comparision.

Model	Comparison	OR	95% CI	*P* of chi-square	I^2	Selected model	*P* for overall effect
Recessive model	TT *vs.* GT+GG	0.174	0.061-0.497	0.529	0%	Fixed-effect model	< 0.05
Homozygous model	TT *vs.* GG	0.188	0.066-0.536	0.466	0%	Fixed-effect model	< 0.05
Heterozygous model	TT *vs.* GT	0.142	0.048-0.416	0.709	0%	Fixed-effect model	< 0.05
Allele model	T *vs.* G	0.979	0.796-1.205	0.215	33%	Fixed-effect model	< 0.05
Dominant model	TT+GT *vs.* GG	1.133	0.897-1.432	0.267	24%	Fixed-effect model	< 0.05

Notes: OR: Odds Ratio; CI: Confidence Interval; T: Thymine; G: Guanine; TT: TT Genotype; GT: GT Genotype; GG: GG Genotype

Table 3: Egger's linear regression test to measure the funnel plot asymmetric.

Index	T *vs.* G	TT+GT *vs.* GG	TT *vs.* GT+GG	TT *vs.* GG	TT *vs.* GT
a	-0.84	-0.54	-2.53	-2.74	-1.95
95% CI	-18.69~17.01	-17.36~16.28	-7.88~2.81	-8.43~2.94	-6.69~2.79

(using the Mantel-Haenszel method) was used [17]. If heterogeneity was significant (P< 0.1, I2 >50%), sensitivity analysis and subgroup analyses were conducted to find the source of the heterogeneity. If the heterogeneity could not be eliminated, a random-effect model (using the Der Simonian and Laird method) would be used when the result of meta-analysis had clinical homogeneity, or a descriptive analysis would be used [18]. Publication bias was detected with Begg's funnel plot and the Egger's linear regression test, a P< 0.05 was considered significant [19].

Results

Study characteristics

A total of 19 potential articles were identified and screened for the meta-analysis. 14 studies were screened off after reviewing the titles and abstracts. After obtaining the full text of each article, reviewing test and reference lists, 2 studies were excluded and 1 study was added. Finally, 4 studies were included for this meta-analysis (Figure 1). The cumulative sample size of 1361 people comprised 580 with ACL rupture and 781 without it. All studies were conducted in Caucasian populations. The main characteristics of the included studies were summarized in (Table 1) and the literature-exclusion procedures were depicted in (Figure 1). The methodological quality of the included studies was assessed with the NOS. All the quality scores for the individual studies were 8, which showed the high quality of the included studies. The results of Hardy-Weinberg equilibrium test for the distribution of the genotype in control population are shown in (Table 1). The genotypes distribution in the controls of all 4 studies was in agreement with HWE.

Meta-analysis results

We observed a significantly decreased risk of ACL ruptures in recessive model comparison (TT *vs.* GT+GG: OR=0.174, 95%CI: 0.061~0.497; $P_{heterogeneity}$< 0.05, Table 2), homozygous model (TT *vs.* GG: OR=0.188, 95%CI: 0.066~0.536; $P_{heterogeneity}$ < 0.05, Table 2) and heterozygous model (TT *vs.* GT: OR=0.142, 95%CI: 0.048~0.416; $P_{heterogeneity}$< 0.05, Table 2) when all eligible studies were pooled. While, no significant association was found in allele model (T *vs.* G: OR=0.979, 95%CI: 0.796~1.205; $P_{heterogeneity}$< 0.05, Table 2) or dominant model (TT+GT *vs.* GG: OR=1.133, 95%CI: 0.897~1.432; $P_{heterogeneity}$< 0.05, Table 2). As no heterogeneity was detected in all comparisons and the ethnicity of all studies was Caucasian, subgroup analysis was not necessary.

Evaluation of publication bias

The results of Egger's linear regression test were shown in (Table 3). No obvious asymmetry was detected by the shape of the funnel plots for all genetic models in the meta-analysis. Egger's test was used to provide statistical evidence of funnel plot symmetry. The intercept a still did not show any significant evidence of publication bias for any of the genetic models.

Discussion

In this meta-analysis, four eligible case-control studies including 580 cases and 781 controls for COL1A1 rs1800012 were analyzed. We demonstrated that COL1A1 rs1800012 polymorphism was associated with a statistically decreased risk of ACL rupture in recessive, homozygous and heterozygous models. This association was significant in Caucasians, however, an opposite result was not found in other ethnicity.

ACL injury is known to be a type of sports related injury, and its incidence is associated with the sports activity, such as football, skiing, basketball and tennis, and thus apparently environmental factors can contribute significantly to its incidence. However, the role of genetics in sport research increases with every passing year [20-23]. In 2008, Khoschnau et al. [11] found that a substantially decreased risk of these injuries associated with collagen type I α1 Sp1 polymorphism in Sweden. In 2009, Posthumus et al. [14] reported that the TT genotype of the COL1A1 Sp1 binding site polymorphism was significantly

under-represented in South African participants with ACL ruptures. In 2013, Stępien-Słodkowska et al. [15] showed that the risk of ACL ruptures was around 1.43 times lower in carriers of a minor allele G as compared to carriers of the allele T. Ficek et al. [13] also found that higher frequency of the COL1A1 G-T haplotype was associated with reduced risk of ACL injury in a group of professional soccer players in Poland. Previous research has indicated that the Sp1 polymorphism is a functional variant that affects DNA binding affinity, collagen transcription and collagen protein production, leading to disruption of the normal 2:1 ratio of collagen type 1 alpha 1 and alpha 2 chains [23,24]. We speculate that the increased production of collagen type I (mRNA and protein) also increases the tensile strength of tendons and ligaments. As type I collagen is the most important structural component of ligaments, it is reasonable that rs1800012 (G-T) may contribute to decrease the incidence of ACL injury.

The current genetic research result might be appealing for genetic tests could help to detect at-risk athletes and general population and enable implementation of preventive measures, which provided a new edge in sports medicine. Goodlin et al. [25] conducted a pilot study and found customized warm-up protocols that targeted proper landing and cutting form, core strength, and hamstring strength could reduce the risk of sustaining ACL tear in these genetically predisposed athletes. This pilot program showed that recent genetic research provided valuable information to help reduce sports injuries. There are increasing genetic studies for health and disease that can be mined to provide useful information to athletes about their individual risk for relevant injuries [26]. Although more and more reports have been published over the past few years regarding different polymorphisms associated with ACL tear, there is still a lack of deep study in terms of the molecular mechanisms and gene-gene interaction [27]. It is necessary to further clarify the association of these polymorphisms with ACL tear and other musculoskeletal injuries in the future.

Our meta-analysis has several strengths. First of all, this is the first meta-analysis focused on the association between COL1A1 polymorphism and the risk to ACL rupture. In addition, all the included studies had high qualities according to the methodological quality assessment. Moreover, no publication bias was identified by either Begg's funnel plot or Egger's regression test. Finally, no limitation was made in literature search, thus selection bias was well controlled.

In spite of the considerable efforts to explore the possible relationship between the COL1A1 polymorphism and ACL rupture risk, some limitations should be considered. Firstly, the number of included studies for COL1A1 rs1800012 polymorphism limited further analysis due to shortage of original studies. Secondly, the included studies were carried out in Caucasians. Absence of data from other ethnics makes a more comprehensive evaluation of the association between the COL1A1 polymorphism and ACL rupture risk not possible.

In conclusion, despite the limitation, this meta-analysis suggests that COL1A1 G-T haplotype may be protective against ACL injury. Knowledge of the role of individual genes in the processes occurring in the human body can also be used in sport rehabilitation and injury prevention. Precise determination of genotypes at risk for acute or chronic diseases related to sport will probably allow changes in individual training plans to greatly minimize the risk of injury. In the future, well designed studies with larger sample size and more ethnic groups should be considered to further clarify the association.

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