

Genetic risk factors for anterior cruciate ligament ruptures: *COL1A1* gene variant

M Posthumus,¹ A V September,¹ M Keegan,¹ D O'Cuinneagain,³ W Van der Merwe,³ M P Schweltnus,¹ M Collins^{1,2}

¹UCT/MRC Research Unit for Exercise Science and Sports Medicine, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa; ²UCT/MRC Research Unit for Exercise Science and Sports Medicine, South African Medical Research Council, Cape Town, South Africa; ³UCT/MRC Research Unit for Exercise Science and Sports Medicine of the Sports Science Orthopaedic Clinic, Cape Town, South Africa

Correspondence to: Professor M Collins, UCT/MRC Research Unit for Exercise Science and Sports Medicine, PO Box 115, Newlands 7725, Cape Town, South Africa; malcolm.collins@uct.ac.za

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ABSTRACT

Background: Anterior cruciate ligament (ACL) ruptures are considered the most severe injury sustained in sports. Although various intrinsic and extrinsic risk factors have been identified, the exact aetiology of the injury is not yet fully understood. Recently, the gene encoding for the $\alpha 1$ chain of type I collagen (*COL1A1*) has been shown to be associated with cruciate ligament ruptures and shoulder dislocations.

Objective: To determine whether the functional Sp1 binding site polymorphism within intron 1 of the *COL1A1* gene is associated specifically with ACL ruptures in an independent population.

Methods: 117 Caucasian participants with surgically diagnosed ACL ruptures, and 130 Caucasian physically active controls without any history of previous ligament or tendon injuries were recruited for this case-control genetic association study. All participants were genotyped for the *COL1A1* Sp1 binding site polymorphism (G/T; rs1800012).

Results: The rare TT genotype was significantly ($p = 0.031$, OR = 0.08, 95% CI <0.01 to 1.46) under-represented in the ACL group (0 out of 117, 0%), compared with the controls (6 out of 130, 4.6%).

Conclusion: The TT genotype of the *COL1A1* Sp1 binding site polymorphism was significantly under-represented in South African participants with ACL ruptures. We propose that this sequence variant be the first specific genetic element to be included in multifactorial models developed to understand the aetiology and risk factors for ACL rupture.

Injury to the anterior cruciate ligament (ACL) has been described as one of the most severe injuries sustained in a sporting population.¹ Participants in sports that involve sudden deceleration or change in direction are particularly at risk of rupturing the ACL.² Although the incidence of this injury is low in the general population (<1 per 10 000 athlete-hours),^{2,3} regular participation in organised sports may place an individual at up to 10 times greater risk of ACL rupture.⁴

Although several intrinsic and extrinsic risk factors for ACL ruptures have been identified,⁵ the exact aetiology of this injury is not yet fully understood. Two studies have suggested that genetic elements should also be considered as possible intrinsic risk factors for ACL rupture.^{6,7} In the first of these studies, it was shown that individuals who had a blood relative with a history of ACL rupture were at twice the risk of rupturing their ACL.⁶ Although no specific genes were identified in this study, it nevertheless suggested that there is, at least in part, a genetic component

to ACL ruptures. In the second, more recent study, a genetic case-control association study, cruciate ligament ruptures and shoulder dislocations were shown to be associated with a functional Sp1 binding site polymorphism (single-nucleotide polymorphism (SNP) rs1800012; IVS1 +1023 G→T) within the first intron of the *COL1A1* gene.⁷ In addition, an increased risk of tendon injuries, which are structurally similar to ligaments, have also been shown to be associated with specific genetic risk factors.⁸⁻¹¹

Both ligaments and tendons are collagenous bands of fibrils consisting of various collagen types, proteoglycans and glycoproteins.¹² Type I collagen is the major protein component of ligaments and constitutes 70–80% of its dry weight.¹³ The type I collagen molecule is a heterotrimer consisting of two $\alpha 1(I)$ and one $\alpha 2(I)$ chains, which are encoded for by the *COL1A1* and *COL1A2* genes respectively.¹⁴

In addition to the reported association of the *COL1A1* Sp1 binding site polymorphism and cruciate ligament ruptures,⁷ mutations within the *COL1A1* gene have been shown to cause monogenetic connective tissue disorders such as osteogenesis imperfecta and Ehlers-Danlos syndrome.¹⁴ The functional Sp1 binding site polymorphism has also been shown to be associated with other multifactorial disorders such as osteoporotic fractures,¹⁵ bone mineral density,^{15,16} osteoarthritis,¹⁷ myocardial infarction,¹⁸ lumbar disc disease¹⁹ and stress urinary incontinence.²⁰ It was proposed that the G→T substitution within the intronic Sp1 binding site increases the affinity for the transcription factor Sp1, resulting in increased *COL1A1* gene expression.¹⁶ As type I collagen is the most important structural component of ligaments, the association of the *COL1A1* gene with ACL ruptures, the most severe injury sustained by athletes, therefore warrants further investigation.

In the single study in which the association of the *COL1A1* Sp1 binding site polymorphism and acute soft tissue injuries, including cruciate ligament ruptures and shoulder dislocations, was reported, all cruciate ligament ruptures (not limited to ACL) were investigated.⁷ Further, the control group consisted only of female subjects, whereas the injury group consisted of both female and male subjects. Repeating this association in an independent population focusing on a specific clinical phenotype, such as ACL ruptures, with gender-matched controls should provide further evidence to support the initial association. The aim of this study was therefore to determine whether the functional Sp1 binding site polymorphism

within intron 1 of the *COL1A1* gene is associated specifically with ACL ruptures in an independent population with gender-matched controls.

METHODS

This study was approved by the Research Ethics Committee of the Faculty of Health Sciences within the University of Cape Town, South Africa (reference number 164/2006). Before participation in this study, all the participants gave informed written consent. In addition, each participant completed questionnaire forms for personal details, injury details and medical history.

Participants

In total, 117 Caucasian participants with surgically diagnosed ACL ruptures were recruited by convenience sampling for this study from the Sports Science Orthopaedic and Sports Medicine Clinics in Cape Town, South Africa. In total, 11 (9.4%) of the participants had a history of bilateral ACL rupture. In addition, 130 apparently healthy, unrelated, physically active, gender-matched Caucasian participants without any self-reported history of ligament or tendon injury were recruited as the control group. Participants for whom there was detailed information available on the mechanism of ACL rupture were subdivided into subgroups consisting of those where the injury was sustained through direct contact ($n = 15$), indirect contact ($n = 18$) or non-contact ($n = 50$), using the American Orthopedic Society for Sports Medicine classification system.² In 34 (29%) of the participants who had ruptured their ACL, no clear mechanism of injury could be identified and these were not included in any of the subgroups. In total, 29% (31 of 106) of all participants with ACL ruptures did not sustain any associated injuries. The most common associated injury was injury to the meniscus (52 of 106; 49%) and injury to the MCL (21 of 106; 20%).

DNA extraction and *COL1A1* genotyping

Approximately 4.5 ml of venous blood was obtained from each participant by venepuncture of a forearm vein and collected into an EDTA vacuum container tube. Blood samples were stored at 4°C until total DNA extraction. DNA was extracted using the procedure described by Lahiri and Nurnberg²¹ and modified by Mokone *et al.*⁸

DNA samples were genotyped for the Sp1 binding site polymorphism (SNP rs1800012; IVS1+1023G→T) within intron 1 of the *COL1A1* gene using a nested PCR assay as previously described.²² The secondary PCR products were digested with the restriction endonuclease *MscI* for 3 hrs at 37°C. The resultant fragments, together with a 100 bp molecular weight marker (Promega Corporation, Madison, Wisconsin, USA) and a nucleic acid gel stain (SYBR Gold; Invitrogen Molecular Probes, Oregon, USA) were separated in 6% non-denaturing polyacrylamide gels. The gels were photographed under UV light using a photo-documentation system (Uvitec Ltd, Cambridge, UK) and the sizes of the DNA fragments determined. The G allele produces a 260 bp fragment while the T allele produces fragments of 242 bp and 18 bp.

Statistical analysis

ANOVA was used to determine any significant difference between the characteristics of the controls and ACL groups, and between the three ACL subgroups (direct contact, indirect contact and non-contact). A least squares difference (LSD)

post-hoc test was used to identify specific differences when the overall F value was found to be significant. A χ^2 analysis or the Fisher exact test was used to analyse any differences in the genotype and allele frequencies, and in family injury history between the groups. When appropriate, adjusted p values are indicated. Significance was accepted when $p < 0.05$. Hardy-Weinberg equilibrium was established using the programme Genepop Web V.3.4 (<http://genepop.curtin.edu.au/>).

RESULTS

Participant characteristics

The participants within the controls and ACL groups, and within the three ACL subgroups, were similarly matched for height (table 1). The mean age of the control group at recruitment was significantly older than the mean age of the ACL group overall and of the three subgroups when they first ruptured their ACLs ($p < 0.001$); the ACL participants were recruited on average 5.1 (8.7) years after their initial ACL rupture. Although there were no significant differences in weight between the control and ACL groups after adjusting for age, only the indirect contact subgroup was significantly heavier at the time of injury than the control group at the time of recruitment. The body mass index (BMI) was significantly higher in the ACL group ($p = 0.030$), even after adjusting for age ($p = 0.018$). The ACL participants were on average 1.3 (4.4) kg heavier, with a correspondingly higher average BMI (0.4 (1.5) kg/cm²), at recruitment compared with their weight at the time they ruptured their ACL. The controls and ACL groups were similarly matched for gender. There were significantly fewer South African-born participants in the control group ($p < 0.012$) than in the ACL group, but similar results were obtained when only South African-born participants were analysed (data not shown).

Family history

The family history of any ligament injury, which includes ligament injury to any blood relative as reported by the participant at the time of recruitment, was significantly higher in the ACL group (39.6%; $n = 106$) compared with the control group (13.5%; $n = 126$) ($p < 0.001$). Within the ACL group there was a similar incidence in the family history of any ligament injury in the direct contact ($n = 14$; 35.7%), indirect contact ($n = 18$; 38.9%) and non-contact ($n = 50$; 40.0%) subgroups ($p = 0.981$).

COL1A1 genotype frequencies

There were no significant differences in the distribution of the genotype (GG vs GT + TT, $p = 0.890$) or allele ($p = 0.745$) frequencies of the *COL1A1* Sp1 binding site polymorphism between the ACL and controls, or in the genotype (GG vs GT + TT, $p = 0.548$) or allele ($p = 0.935$) frequencies between the controls and non-contact subgroups (table 2). Although the sample size of the direct contact and indirect contact subgroups were small, these subgroups seemed to have similar genotype distributions to the non-contact subgroup. None of the ACL participants were homozygous for the minor T allele. The rare TT genotype was significantly under-represented in the ACL group compared with the control group ($p = 0.031$, odds ratio (OR) 0.08, 95% CI < 0.01 to 1.46).

The *COL1A1* genotype distribution of the controls ($p = 0.219$) and ACL ($p = 0.075$) groups were in Hardy-Weinberg equilibrium. More women had a TT genotype (4 of 6; 66.7%) compared with the GT (18 of 70; 25.7%) and

Table 1 General characteristics of the control and ACL rupture group and its subgroups

	Controls	ACL	p Value†	ACL subgroups, based on mechanism of injury			p Value‡
				Direct	Indirect	Non-contact	
Age, years*	37.7 (10.0) (n = 125)§¶	29.0 (11.2) (n = 114)	<0.001	26.3 (12.3) (15)§	32.8 (12.3) (n = 18)	28.0 (10.9) (n = 50)¶	<0.001
Height, cm*	177.4 (9.6) (n = 126)	176.7 (9.8) (n = 104)	0.578	175.4 (8.2) (14)	180.9 (8.9) (n = 17)	177.0 (9.5) (n = 49)	0.418
Weight, kg*	76.2 (13.1) (n = 130)**	79.4 (17.3) (n = 104)	0.094††	81.4 (12.5) (14)	87.9 (15.9) (n = 17)**	79.9 (17.9) (n = 49)	0.008††
BMI, kg/cm ² *	24.1 (3.3) (n = 126)	25.1 (3.7) (n = 100)	0.018††	26.2 (2.7) (14)	25.9 (2.8) (n = 16)	25.3 (4.4) (n = 47)	0.014††
Males, %	74.6 (n = 130)	69.0 (n = 116)	0.325	93.3 (n = 15)	88.9 (n = 18)	66.0 (n = 50)	ND
South African, %	71.1 (n = 128)	85.1 (n = 107)	0.012	92.9 (n = 14)	83.3 (n = 18)	84.0 (n = 50)	ND

ACL, anterior cruciate ligament; ND, not determined due to small sample sizes.

*Age, weight and BMI are self-reported values at the time of the first ACL rupture for the ACL group and the three subgroups and at recruitment for the control group. For the ACL group the age, weight and BMI at recruitment were 5.1 (8.7) years (n = 114), 1.3 (4.4) kg (n = 103) and 0.4 (1.5) kg/cm² greater than at the time of the first ACL rupture.

†Controls vs ACL.

‡Controls vs direct contact vs indirect contact vs non-contact.

Pairwise, post hoc significant differences: §controls vs direct contact (p<0.001); ¶controls vs non-contact (p<0.001); **controls vs indirect contact (p = 0.010).

††Adjusted for age.

Data are mean (SD) (n) for most values except gender and country of birth, which are frequency (n).

GG (47 of 125; 27.3%) genotypes, but there were no *COL1A1* genotype effects on any of the other physical characteristics of the participants when adjusted for gender (table 3).

DISCUSSION

The main finding of this study was that the rare TT genotype of the functional *COL1A1* Sp1 binding site polymorphism was significantly under-represented among participants with ACL ruptures, indicating a possible protective role of this genotype for this injury. The second finding of this study was that participants with an ACL rupture were more than four times as likely to report that a blood relative had a history of any ligament injury compared with the control participants. The third finding was that the mechanism of most of the ACL ruptures in our population was the result of a non-contact event and that the genotype distribution in this subgroup was similar to that of the indirect and direct injury subgroups.

Our finding of an under-representation of the TT genotype in the ACL participants is in agreement with that previously reported in a Swedish population.⁷ Furthermore, the genotype distribution of the control participants in this study were similar to another study of South African participants,²² to the Swedish study⁷ and to other larger cohorts.^{16 17} Of specific clinical importance is that the TT genotype was absent from all 117 participants with ACL ruptures in our study, whereas only 1 of 233 participants (0.4%) with a cruciate ligament rupture in

the Swedish study had the TT genotype.⁷ Furthermore, similar observations have been documented for two other acute soft-tissue injuries.^{7 22} In the same study from Sweden,⁷ only 1 of 126 participants (0.8%) with a shoulder dislocation had the TT genotype, and the TT genotype was also absent in 43 participants with an Achilles tendon rupture.²² Combined analysis of these studies strongly suggests that the TT genotype of the Sp1 binding site polymorphism within *COL1A1* has a protective role in both cruciate ligament and Achilles tendon ruptures, as the TT genotype was identified in only 4.1% of the combined control subjects.²³

The second finding from our study, that participants with an ACL rupture were more than four times as likely to have a blood relative with a ligament injury, also supports a genetic risk for ligament injury. Despite the fact that we were not able to control for exposure to non-genetic factors in family members of our participants with ACL ruptures, our results are similar to that reported by Flynn *et al*,⁶ who found that siblings of patients who had had an ACL tear had twice the risk of also tearing their ACL.

The third finding of this study was that most ACL ruptures (57.7%) occurred during a non-contact event compared with direct contact (19.2%) or indirect contact (23.0%) events. Non-contact ACL ruptures occur from the athlete's own movements, not as a result of contact with another athlete or objects.² It may thus be hypothesised that intrinsic risk factors, in

Table 2 Relative genotype and allele frequencies of the *COL1A1* Sp1 binding site polymorphism within the control and ACL rupture group and its subgroups

	Controls (n = 130)	ACL (n = 117)	ACL subgroups, based on mechanism of injury		
			Direct (n = 15)	Indirect (n = 18)	Non-contact (n = 50)
GG genotype, %	70.0 (n = 91)	68.4 (n = 80)	80.0 (n = 12)	66.7 (n = 12)	72.0 (n = 36)
GT genotype, %	25.4 (n = 33)	31.6 (n = 37)	20.0 (n = 3)	33.3 (n = 6)	28.0 (n = 14)
TT genotype, %*	4.6 (n = 6)	0.0 (n = 0)	0.0 (n = 0)	0.0 (n = 0)	0.0 (n = 0)
G allele, %	82.7 (n = 215)	84.2 (n = 197)	90.0 (n = 27)	83.3 (n = 30)	86.0 (n = 86)
T allele, %	17.3 (n = 45)	15.8 (n = 37)	10.0 (n = 3)	16.7 (n = 6)	14.0 (n = 14)

ACL, anterior cruciate ligament.

*Owing to the absence of participants with a TT genotype in the ACL group and three subgroups, the GT and TT participants were combined and compared with the GG participants.

Controls vs ACL genotypes, p = 0.890.

Controls vs ACL, TT genotype vs GG + GT genotypes, p = 0.031, OR = 0.08, 95% CI <0.01 to 1.46.

Controls vs non-contact genotypes, p = 0.935.

Controls vs ACL alleles, p = 0.745.

Controls vs non-contact alleles, p = 0.548.

Data are % (n).

Table 3 Genotype effects of the Sp1 binding site polymorphism within the *COL1A1* gene on the characteristics of the combined control and ACL participants

	GG	GT	TT	p Value*
Age, years†	33.2 (11.3) (n = 165)	33.8 (11.7) (n = 68)	39.3 (10.2) (n = 6)	0.425
Height, cm†	176.9 (9.9) (n = 158)	177.9 (9.1) (n = 66)	172.8 (9.4) (n = 6)	0.750
Weight, kg†	77.7 (15.8) (n = 162)	78.9 (13.1) (n = 66)	62.7 (8.5) (n = 6)	0.334
BMI, kg/cm ² †	24.6 (3.8) (n = 155)	24.9 (2.7) (n = 65)	20.9 (1.3) (n = 6)	0.152

*Except for age, p values are co-varied for gender.

†All values are self-reported values at the time of the first ACL rupture for the ACL-injured participants and at recruitment for the control participants.

Data are mean (SD) (n).

particular genetic elements, may have a greater contributing role in non-contact ACL ruptures. Even though the direct and indirect contact subgroups did involve the application of an external force, it might be of clinical relevance that the TT genotypes were also absent in these subgroups.

It is important to note that there are strengths and limitations to our study design. Our injury population consisted of a homogenous group of participants with confirmed diagnosis of ACL ruptures at surgery. Furthermore, our injured population and controls included both genders and were suitably matched. One of the limitations of our study was that the exposure to extrinsic risk factors could not be well documented in all the control participants. Although care was taken to recruit physically active individuals, participation in high-risk sports such as sports involving cutting, pivoting and landing was not known for all the control participants. Sample sizes in our subgroups (according to injury mechanism) were small, and therefore separate analysis of genotype frequencies need to be interpreted with caution.

The main findings of our study support the hypothesis that genetic factors are associated with the risk of ACL ruptures. However, it is important to emphasise that ACL ruptures are multifactorial disorders and is therefore caused by a complex interaction of a number of different intrinsic and extrinsic risk factors.⁵ In any multifactorial model²⁴ that is developed to understand the aetiology and risk factors of ACL ruptures, we propose, based on our findings, that a genetic component is included. Our results provide evidence that the Sp1 binding site

polymorphism within the *COL1A1* gene may be the first genetic component to be included in an ACL rupture risk model. It is noteworthy that this *COL1A1* polymorphism has also been associated with other multifactorial disorders, such as bone mineral density,^{15 16} osteoporotic fractures,^{15 16} osteoarthritis,¹⁷ lumbar disc disease,¹⁹ myocardial infarction,¹⁸ and stress urinary incontinence.²⁰

Previous investigations have proposed that the increased Sp1 transcription factor binding, which occurs when a G nucleotide is substituted for a T at the Sp1-binding site, leads to increased expression of the $\alpha 1(I)$ chain.¹⁶ However, the consequence of this increased expression is not yet fully understood, but the increased expression of the $\alpha 1(I)$ chain has been shown to reduce the quality and strength of bone.¹⁶ However, no previous work has investigated the effect of this polymorphism on other type I collagen-containing connective tissues such as ligaments. However it is interesting that the TT genotype of the Sp1 binding site polymorphism is not always associated with increased risk of pathology and has also been shown to be associated with reduced risk of radiographic osteoarthritis of the hip characterised.¹⁷ To our knowledge, no studies have investigated changes in *COL1A1* RNA or type I collagen protein levels in ruptured ACL material, but differential expression of the type I collagen genes has been shown to be associated with the degree of healing after an ACL rupture.²⁵

In conclusion, this study found that the rare TT genotype of the functional Sp1 binding site polymorphism within intron 1 of *COL1A1* was significantly under-represented in participants who have ruptured their ACL, compared with gender-matched controls in an independent population. It is therefore proposed that this polymorphism be the first specific genetic element to be included in multifactorial models developed to understand the aetiology and risk factors for ACL rupture. However, this study does need to be repeated in non-Caucasian populations.

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Competing interests: None.

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What is already known on this topic

- ▶ ACL ruptures are multifactorial disorders that are associated with several intrinsic and extrinsic risk factors.
- ▶ Recently, a single study has suggested that the functional Sp1 binding site polymorphism within the *COL1A1* gene is associated with cruciate ligament ruptures and shoulder dislocations.

What this study adds

- ▶ The TT genotype of the *COL1A1* Sp1 binding site polymorphism is under-represented in participants with ACL ruptures in an independent population.
- ▶ We propose that this specific genetic variant be included in multifactorial models developed to understand the aetiology and risk factors for ACL rupture.

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