Is There a Genetic Predisposition to Anterior Cruciate Ligament Tear?

CME

A Systematic Review

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Background: Injuries to the anterior cruciate ligament (ACL) are among the most common knee ligament injuries and frequently warrant reconstruction. The etiopathogenesis of these injuries has focused mainly on mechanism of trauma, patient sex, and anatomic factors as predisposing causes. Several genetic factors that could predispose to an ACL tear have recently been reported.

Purpose: This systematic review summarizes the current evidence for a genetic predisposition to ACL tears. The principal research question was to identify genetic factors, based on the available literature, that could predispose an individual to an ACL tear.

Study Design: Systematic review.

Methods: The PubMed, EMBASE, Cochrane, and HuGE databases were searched; the search was run from the period of inception until June 21, 2015. A secondary search was performed by screening the references of full-text articles obtained and by manually searching selected journals. Articles were screened with prespecified inclusion criteria. The quality of studies included in the review was assessed for risk of bias by 2 reviewers using the Newcastle-Ottawa Scale.

Results: A total of 994 records were identified by the search, out of which 17 studies (16 case-control studies and 1 cross-sectional study) were included in the final review. Two studies observed a familial predisposition to an ACL tear. Fourteen studies looked at specific gene polymorphisms in 20 genes, from which different polymorphisms in 10 genes were positively associated with an ACL tear. In addition to these polymorphisms, 8 haplotypes were associated with ACL tear. One study looked at gene expression analysis.

Conclusion: Although specific gene polymorphisms and haplotypes have been identified, it is difficult to come to a conclusion on the basis of the existing literature. Several sources of bias have been identified in these studies, and the results cannot be extrapolated to the general population. More studies are needed in larger populations of different ethnicities. Gene-gene interactions and gene expression studies in the future may delineate the exact role of these gene polymorphisms in ACL tears.

Keywords: gene polymorphisms; single-nucleotide polymorphism (SNP); anterior cruciate ligament (ACL)

Injuries to the anterior cruciate ligament (ACL) are among the most common knee ligament injuries and frequently warrant reconstruction.[1,13] The etiopathogenesis of these injuries has focused mainly on mechanism of trauma, patient sex, and anatomic factors as predisposing causes.[27,28] Most ACL tears occur as a result of a noncontact valgus hyperextension mechanism, although direct trauma may also be causative.[29] Various intrinsic and extrinsic risk factors predispose an individual toward an ACL tear, although trauma to the knee is an essential prerequisite.[27,28] Extrinsic risk factors include type of playing surface, type of sport, level of activity, weather conditions, and type of footwear and protective gear used. Intrinsic risk factors include age, sex, anatomic risk factors (eg, knee joint geometry, notch width, Q angle, tibial slope, pelvic tilt, generalized/anterior knee joint laxity, body mass index, foot pronation, ACL size), neuromuscular and cognitive factors, hormonal factors, and genetic factors.[27,28]

In the past 2 decades, several researchers have investigated genetic factors that could predispose to an ACL tear. These studies have evolved from the simple familial predisposition studies to the more complex gene association studies.[3-5,8-11,14-20,22,24-26] Most research on genetic predisposition to ACL tears has focused on single-nucleotide polymorphisms (SNPs). SNPs are the most common type of genetic variations seen among individuals; each SNP represents a difference in a single nucleotide.[2] Collagen type 1 is

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TABLE 1
Search Strategy

Database: Search Terms	Results
MEDLINE–PubMed (1950–June 21, 2015)	
("anterior cruciate ligament"[MeSH Terms] OR ("anterior"[All Fields] AND "cruciate"[All Fields] AND "ligament"[All Fields])) AND (("dna"[MeSH Terms] OR SNP[All Fields] OR "polymorphism"[All Fields] OR "polymorphism, single nucleotide"[MeSH Terms] OR "single nucleotide polymorphism"[All Fields] OR "polymorphism, genetic"[MeSH Terms] OR "genetic polymorphism"[All Fields] OR "genes"[MeSH Terms] OR "genes"[All Fields] OR "gene"[All Fields] OR variant[All Fields] OR "genotype"[MeSH Terms] OR "alleles"[MeSH Terms] OR "alleles"[All Fields] OR "allele"[All Fields] OR "genomics"[MeSH Terms] OR "genomics"[All Fields] OR "genetic"[All Fields] OR "exome"[MeSH Terms] OR "exome"[All Fields] OR "base sequence"[MeSH Terms] OR "sequence"[All Fields]) OR "Disease Susceptibility"[Mesh Terms] OR "susceptibility"[All Fields])	513
EMBASE (1946–June 21, 2015)	
1. anterior AND cruciate AND ("ligament" OR "ligament"/exp OR ligament)	17,628
2. anterior AND cruciate AND ("ligament"/exp OR ligament)	17,628
3. "genetics" OR "genetic predisposition" OR "allele" OR "polymorphism" OR "single nucleotide polymorphism" OR "genetic polymorphism" OR "dna" OR "susceptibility" OR "genotype" OR "genomics" OR "exome" OR "base sequence" OR "genes" OR "polymerase chain reaction"	3,323,558
4. (1) or (2) and (3)	429
Cochrane Library (inception to June 21, 2015)	
1. CRANIAL or ANTERIOR and CRUCIATE and LIGAMENT:ti,ab,kw (Word variations have been searched)	2700
2. "genetics" or "genetic predisposition" or "allele" or "polymorphism" or "single nucleotide polymorphism" or "genetic polymorphism" or "dna" or "susceptibility" or "genotype" or "genomics" or "exome" or "base sequence" or "genes" or "polymerase chain reaction":ti,ab,kw (Word variations have been searched)	24,504
3. (1) and (2)	27
HuGE database (inception to June 21, 2015)	
Anterior cruciate ligament	25

a major component of the ACL[6]; therefore, early studies looked at SNPs involving the *COL1* (collagen type 1) gene.[10,18] Subsequent studies have investigated other genes as well, including *COL12, COL5, COL3, COL6*, MMP (matrix metalloproteinase), and ECM (extracellular matrix) genes.[§]

In this systematic review, we look at the literature on genetic predisposition to ACL tears. Our principal research question aimed to identify those genetic factors that could predispose to ACL tears.

METHODS

We used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) checklist for all key aspects of this systematic review.[12] This review has been registered with the PROSPERO database; the protocol is available online (study registration CRD42015017193).

Search Methodology

The PubMed, EMBASE, Cochrane, and HuGE databases were searched from their inception until June 21, 2015 (Table 1). No language restrictions were applied. In addition to these databases, a secondary search was done by screening the references of full-text articles obtained. Also, the following journals were hand searched for relevant studies: *American Journal of Sports Medicine, British Journal of Sports Medicine, Journal of Bone and Joint Surgery (American), Bone and Joint Journal* (formerly *JBJS British*), *Clinical Orthopedics and Related Research, New England Journal of Medicine*, and *British Medical Journal*. The search results were imported into reference-manager software (EndNote v X2) to avoid duplication of records.

Inclusion and Exclusion Criteria

We included clinical studies of any design if the study's primary research question related to genetic factors predisposing to ACL tear. We limited our review to complete ACL tears only, and studies related to ACL avulsion fractures and incomplete ACL tears were excluded. We required at least 10 cases to be reported in the study for inclusion. Studies with <10 cases, narrative reviews, and conference abstracts were excluded.

Data Collection

The study results were screened and analyzed by 2 observers (R.J. and S.S.) independently. The study title was used to screen for potentially eligible studies, and the abstract of all selected studies was analyzed in detail to determine inclusion. When in doubt, inclusion or exclusion was ascertained after obtaining the full text. The full text was obtained for all studies that were included in the final

[§]References 4, 5, 8, 9, 11, 14-17, 19, 20, 22, 24, 25.

analysis. All conflicts were resolved by mutual agreement between the 2 observers, and when required, a third author (M.S.D.) made the final decision.

Data from the included studies were collected on prespecified data collection forms and included the journal name, year, country and language of publication, inclusion and exclusion criteria used by the authors, authors' definitions of cases and controls, type of genetic predisposition studied, methodology of genetic analysis, all outcome measures reported by the study authors, and sources of funding.

Risk-of-Bias Assessment

The quality of case-control studies included in the review was assessed by 2 reviewers (R.J. and S.S.) using the Newcastle-Ottawa Scale.[30] This scale depicts the risk of bias of each study as a "star" scoring system. It assesses studies on the basis of 3 domains: study selection (4 items; 1 star can be awarded for each item), comparability of cases (2 stars can be awarded), and exposure (2 items; 1 star can be awarded for each item). A maximum score of 8 is possible. Details on this scale are available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

Data Synthesis and Subgroup Analysis

Only qualitative analysis was performed, and the results were summarized in a tabular fashion. No subgroup analysis was performed. We reported whether various genetic risk factors had positive or negative associations with ACL tears. We described odds ratios (ORs), 95% CIs, and *P* values if reported by the study authors.

RESULTS

Literature Search

A flowchart of the studies included and excluded in this review is presented in Figure 1. A total of 994 records were identified by our search, out of which 17 studies were included in the final review after removing duplicates, screening abstracts, and obtaining full texts. Sixteen selected studies were case-control studies, whereas 1 was a cross-sectional study. Two case-control studies looked at familial predisposition to ACL tears.[5,8] Both reported statistically significant association of family history of ACL tear in patients with ACL tears. Fourteen studies investigated various gene polymorphisms. The only cross-sectional study in this review compared gene expression among male and female patients with ACL tears.[9] The results of these studies are summarized in Table 2.

Risk-of-Bias Assessment

Several sources of bias were identified in the included studies. In many studies, confounding factors such as sex, age, and body mass index were significantly different between the case and control groups. Only 1 study (Harner et al[8]) compared the anatomic risk factors between cases and controls. Nonresponse bias was addressed by only 2 of the 16 case-control studies (Flynn et al[5] and Harner et al[8]). Furthermore, the participant database was common for many studies; therefore, biases unique to the participant database were shared across such studies. The 2 studies by Ficek et al,[3,4] 3 studies by Słodkowska et al[24,25] and Stępień-Słodkowska et al,[28] 3 studies by Posthumus et al[17,19,20] (*COL5A1, COL12A1*, and MMP), and the studies by Mannion et al[15] and Rahim et al[22] (5 groups) were from the same South African research team. The risk of bias of the included studies is presented in Table 3.

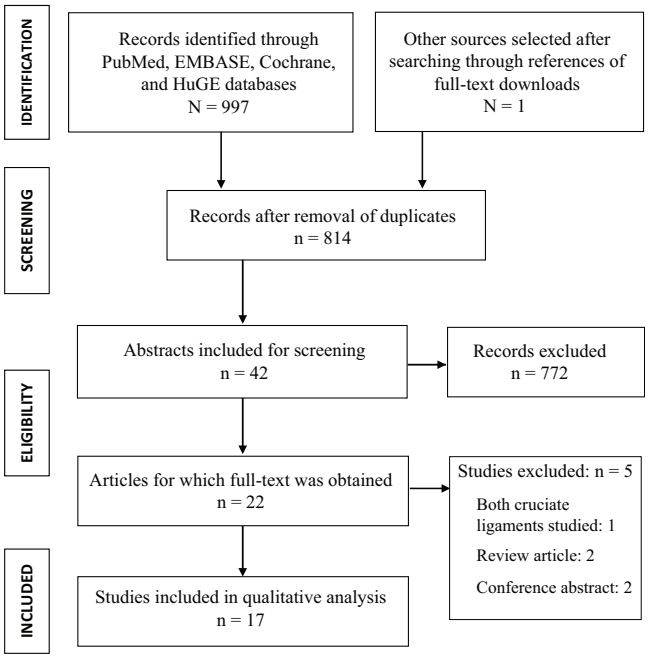

Figure 1. PRISMA flow diagram of the search strategy.

Genetic Predisposition to ACL Tear

Case-Control Studies

Familial Predisposition Studies. Harner et al[8] observed that individuals with a family history of an ACL tear were twice as likely to suffer an ACL tear than the general population, suggesting a possible congenital origin. Flynn et al[5] observed that participants with an ACL tear were twice as likely to have a relative (first, second, or third degree) with an ACL tear compared with participants without an ACL tear (adjusted OR = 2.00). When the analysis was limited to first-degree relatives only, participants with an ACL tear were more than twice as likely to have a relative with an ACL tear (adjusted OR = 2.24), indicating a definite familial predisposition.[5]

Genetic Association Case-Control Studies

COL1A1. Posthumus et al[18] observed that the rare TT genotype (Sp1 binding site polymorphism/rs1800012) was

TABLE 2
Summary of Studies Included (in Chronological Order)[a]

Author (Year)	Target Gene	Target Population	Participants (Cases), n	OR (95% CI)	*P*	Comments/Significant Findings
Harner et al[8] (1994)	None	US	54 (31)	—	<.01	Familial predisposition study
Flynn et al[5] (2005)	None	Canada	342 (171)	2 (1.19-3.33)	—	Familial predisposition study
Posthumus et al[18] (2009)	*COL1A1*	South Africa	247 (117)	0.08 (<0.01-1.46)	.031	Underrepresentation of TT genotype in injured group
Posthumus et al[20] (2009)	*COL5A1*	South Africa	345 (129)	6.6 (1.5-29.7)	.006	Underrepresentation of CC genotype of BstUI RFLP of *COL5A1* in females only
Posthumus et al[19] (2010)	*COL12A1*	South Africa	345 (129)	2.4 (1-5.5)	.048; .73	Overrepresentation of AA genotype of rs970547 (AluI RFLP) in injured females only; no association of rs240736 (BsrI RFLP).
Malila et al[14] (2011)	MMP genes	Thailand	186 (86)	2.25 (1.18-4.25)	.38; .02	No significant association; however, 5A+ (5A/5A, 5A/6A) genotype and 5A allele frequencies were significantly higher in ACL tear patients participating in contact sports than in noncontact sports
Posthumus et al[17] (2012)	MMP genes	South Africa	345 (129)	0.39 (0.15-0.89)	.03	AG and GG genotypes of *MMP12* were significantly underrepresented. *MMP1, MMP3, MMP10* not associated with ACL tear
Stępień-Słodkowska et al[28] (2013)	*COL1A1*	Poland	366 (183)	—	.045	+1245G/T polymorphisms in rs1800012 SNP in *COL1A1*
Ficek et al[3] (2013)	*COL1A1*	Poland	234 (91)	—	.08; .048	No significant association of polymorphisms; overrepresentation of G-T haplotypes (–1997G+1245T).
O'Connell et al[16] (2014)	*COL3A1, COL6A1*	South Africa and Poland	711 (333)	—		Overrepresentation of AA genotype of rs1800255 of *COL3A1* in the Polish ACL subgroup
Mannion et al[15] (2014)	Proteoglycans genes	South Africa	561 (227)	0.72 (0.55-0.96) 9.231 (1.16-73.01) 0.33 (0.14-0.78)	.024 .015 .013	For G allele of *ACAN* rs1516797 For *DCN* rs516115 GG genotype For *DCN* rs516115 AA genotype
Rahim et al[22] (2014)	Angiogenesis-associated signaling pathway genes	South Africa	554 (227)	1.9 (1.17-3.17) 1.70 (1.16-2.50) 2.16 (1.11-4.2)	.01 .007 .023	For *VEGFA* (rs699947 CC) For *VEGFA* (rs1570360 GA) For *KDR* (rs2071559 GA)
Ficek et al[4] (2014)	*COL12A1*	Poland	234 (91)	0.82 (0.50-1.34)	.4	No association between ACL tears and rs970547 polymorphism (A9285G)
Słodkowska et al[24] (2015)	*COL5A1*	Poland	321 (138)	0.82 (0.59-1.14) 0.97 (0.68-1.38)	.467 .393	For BstU1 RFLP C/T For DpnII RFLP C/T No association between ACL tears and *COL5A1* polymorphisms
Słodkowska et al[25] (2015)	*COL3A1*	Poland	321 (138)	5.05 (1.62-15.78)	.003	Positive association of rs1800255 SNP with ACL tear
Khoury et al[11] (2015)	ECM genes (*ELN* and *FBN2*)	South Africa	360 (141)	1.76 (1-3.1)	.047	Frequency of the G allele of *FBN2* gene significantly different; *ELN* rs207137 variant not associated with ACL tear
Johnson et al[9] (2015)	Gene expression study	US	14 (14)	—		Gene expression of *ACAN* and *FMOD* upregulated in female vs male subjects, *WISP2* downregulated

[a]A dash (—) indicates the information was not available in the article. ACL, anterior cruciate ligament; ECM, extracellular matrix; MMP, matrix metalloproteinase; OR, odds ratio.

significantly underrepresented in the ACL group compared with the controls (OR = 0.08 [95% CI, <0.01-1.46]; *P* = .031). Their study sample included 117 Caucasian participants with surgically diagnosed ACL tear and 130 physically active, healthy controls with no previous history of ligament or tendon disorders. None of the ACL tear cases had the TT genotype, whereas 6 of the 130 controls had the TT genotype, which led the authors to suggest that the presence of the TT genotype may be protective against ACL tear.[18]

Stępień-Słodkowska et al[28] observed that the risk of ACL tear was lowered by 1.43 times in carriers of a minor allele G as compared with carriers of the allele T (polymorphism studied: +1245G/T). The study sample was limited to male skiers of Polish descent (138 recreational skiers with ACL tears and 183 healthy skiers with no personal/family histories of tendon/ligament injuries).[28]

Ficek et al[3] noted that higher frequency of the *COL1A1* G-T (–1997G/T and +1245G/T polymorphisms) haplotype expression was significantly associated with decreased risk of ACL tear (haplotype score, –1.98; *P* = .048). Although the TT genotype was underrepresented in the ACL tear study group, this result was not statistically significant (*P* = .084) in contrast to the results obtained by Posthumus et al.[18] The study population of Ficek et al[3] included 234 professional male soccer players (91 males with surgically diagnosed ACL tears against a matched control group of 143 healthy males with no history of ligament/tendon injury) to examine the association of –1997G/T and +1245G/T polymorphisms in the *COL1A1* gene, individually and as haplotypes, with ACL tears.[3]

COL12A1. Posthumus et al[19] noted that the AA genotype of the AluI RFLP (rs970547) was significantly overrepresented in female cases (*P* = .048). They genotyped 129 patients with ACL tear (38 females) and 216 healthy controls with no history of ligament injuries (83 females) for the AluI and BsrI restriction fragment length

TABLE 3
Risk of Bias Assessed by the Newcastle-Ottawa Scale[30,a]

Study	Newcastle-Ottawa Scale Score[a]			
	Selection	Comparability of Cases	Exposure	Total
Ficek et al[3] (*COL1A1*)	★★★	★★	★	6
Ficek et al[4] (*COL12A1*)	★★★	★★	★	6
Flynn et al[5]	★★★★	★★	★★	8
Harner et al[8]	★★★★	★★	★★	8
Malila et al[14]	★★★★	★	★	6
Mannion et al[15]	★★★★		★	5
O'Connell et al[16]	★★★★		★	5
Posthumus et al[18] (*COL1A1*)	★★★	★	★	5
Posthumus et al[20] (*COL5A1*)	★★★★	★	★	6
Posthumus et al[19] (*COL12A1*)	★★★★	★	★	6
Posthumus et al[17] (MMP genes)	★★★★	★	★	6
Rahim et al[22]	★★★★		★	5
Stępień-Słodkowska et al[28]	★★★	★★	★	6

[a]Study selection: 4 items, 1 star can be awarded for each item; comparability of cases: 2 stars can be awarded; exposure: 2 items; 1 star can be awarded for each item. A maximum score of 8 is possible. MMP, matrix metalloproteinase.

polymorphisms (SNPs rs970547 and rs240736, respectively). They concluded that females with AA genotype of the AluI RFLP (rs970547) were at an increased risk for an ACL tear. However, no significant difference was noted among the males or when the study population was analyzed as a whole. No significant difference was noted in the genotype or allele distributions of the BsrI RFLP (rs240736) between the study and control groups.[19]

Ficek et al[4] observed no statistically significant association of rs970547 polymorphism (A9285G) and ACL tears. The study population was the same as that used for genotyping *COL1A1* SNP by the same research group.[3]

COL5A1. Posthumus et al[20] reported that the CC genotype of the BstUI RFLP is significantly underrepresented in female patients with ACL tear (CC genotype was overrepresented in the control group within the female population; OR = 6.6 [95% CI, 1.5-29.7]; $P = .006$). The participants were genotyped for BstUI and DpnII RFLPs. The study population is the same as that used to genotype *COL12A1* polymorphisms.[19] However, when both sexes were analyzed together, there were no significant differences in genotype/allele frequencies.[20]

Słodkowska et al[24] noted no significant differences in genotype distribution of BstUI RFLP C/T and DpnII RFLP C/T polymorphisms between the ACL tear and control groups. In the haplotype analysis, it was noted that the T-T (BstUI RFLP T, DpnII RFLP T) haplotype was the most common (55.6%), whereas the haplotype T-C was not present in any of the subjects. An underrepresentation tendency of the C-T haplotype was noted in the ACL case group under recessive mode of inheritance, but the results were not statistically significant.[24]

COL3A1 *and* COL6A1. O'Connell et al[16] genotyped 333 ACL tear patients and 378 healthy controls (of both South African and Polish descent) for *COL3A1* rs1800255 (G/A), *COL5A1* rs12722 (T/C), *COL6A1* rs35796750 (T/C), and *COL12A1* rs970547 (A/G). They noted no significant associations between *COL6A1* rs35796750 and *COL3A1* rs1800255 genotypes and risk of ACL tear in the South African cohort; however, the *COL3A1* AA genotype was significantly ($P = .036$) overrepresented in the Polish ACL injury group compared with the control group.[16]

The chief finding of this study was the significant interaction between the *COL5A1* rs12722 T/C and *COL12A1* rs970547 A/G variants and risk of ACL tear. Although there were genotype distribution differences between the South African and Polish cohorts, the T+A-inferred pseudo-haplotype constructed from *COL5A1* and *COL 12A1* was significantly overrepresented in the female ACL group when compared with the female control group within the South African cohort (T+A ACL: 50.5%, T+A control: 38.1%; $P = .022$), Polish cohort (T+A ACL: 56.3%, T+A control: 36.3%; $P = .029$) and combined cohorts (T+A ACL: 51.8%, T+A control: 37.5%; $P = .004$).[16]

Słodkowska et al[25] reported that the AA versus AG+GG genotype of *COL3A1* rs1800255 polymorphism was significantly overrepresented in the ACL-injured group compared with the control group (AA: 10.1% vs 2.2%, AG: 22.5% vs 36.1, GG: 67.4% vs 61.8%; $P = .0087$). The frequency of the A allele was higher in the ACL-injured group compared with controls, but the difference was not statistically significant ($P = .72$). The study population used was the same as that used for the *COL1A1* and *COL5A1* study by the same research team.[24,28]

MMP Genes. Posthumus et al[17] genotyped 345 Caucasians (129 subjects with ACL tears and 216 asymptomatic control subjects) for the *MMP10* C/T rs486055, *MMP1* 1G/2G rs1799750, *MMP3* G/A rs679620, and *MMP12* A/G rs2276109 variants. They noted that in patients with an ACL tear, AG and GG genotypes of *MMP12* were significantly underrepresented as compared with controls. The haplotype frequencies of the variants within the gene were also significantly different for injured and control groups.

Malila et al[14] evaluated 86 patients with ACL tears and 100 healthy controls without any history of ligament/tendon injuries for relationship between the –1612 5A/6A polymorphism of the *MMP3* gene and ACL tear predisposition. They observed that 5A+ (5A/5A, 5A/6A) genotype and 5A allele frequencies were significantly higher in subjects participating in contact sports when compared with those participating in noncontact sports.

Proteoglycans Genes. Mannion et al[15] genotyped 227 ACL tear patients and 234 healthy controls for 10 polymorphisms in 5 genes, encoding for 5 proteoglycans. The proteoglycan molecules whose genes were tested were aggrecan (*ACAN*), biglycan (*BGN*), decorin (*DCN*), fibromodulin (*FMOD*), and lumican (*LUM*). Haplotypes were also constructed for specific regions. The authors observed that the G allele of *ACAN* rs1516797 was significantly underrepresented in the controls compared with the ACL group ($P = .024$). For *DCN* rs516115, the GG genotype was significantly overrepresented in female controls ($P = .015$) as compared with the ACL group, and the AA genotype was significantly underrepresented in controls ($P = .013$) as compared with the female noncontact ACL injury subgroup. Haplotype analyses implicated regions overlapping *ACAN* (rs2351491 C>T-rs1042631 T>C-rs1516797 T>G), *BGN* (rs1126499 C>T-rs1042103 G>A), and *LUM-DCN* (rs2268578 T>C-rs13312816 A>T-rs516115 A>G) in ACL tear predisposition. On the basis of both the independent associations and the haplotype analysis, the authors postulated that regions within *ACAN, BGN*, and *DCN* and a region spanning *LUM-DCN* are positively associated with ACL tear susceptibility.

Angiogenesis-Associated Signaling Pathway Genes. Rahim et al[22] genotyped 227 asymptomatic controls and 227 participants with ACL tears for 7 polymorphisms within 4 genes; they looked at vascular endothelial growth factor A isoform (*VEGFA*), kinase insert-domain receptor (*KDR*), nerve growth factor (*NGF*), and hypoxia inducible factor 1α (*HIF1A*). The authors observed that the *VEGFA* rs699947 CC was significantly overrepresented in participants with ACL tears owing to a noncontact mode of injury only ($P = .01$). The *VEGFA* rs1570360 GA genotype was significantly overrepresented in the control group ($P = .007$). Also, the *KDR* rs2071559 GA genotype was significantly overrepresented in the female controls ($P = .023$). Genomic regions spanning the *VEGFA* and *KDR* genes were implicated in haplotype analysis. These observations suggest that regions within *VEGFA* and *KDR* genes may be implicated in the etiopathogenesis of ACL tears.

Other ECM Genes. Khoury et al[11] genotyped 141 ACL cases and 219 controls for the *ELN* rs2071307 and *FBN2* rs331079 variants. The *ELN* rs207137 variant was not associated with ACL tear. However, the frequency of the G allele was significantly different between the ACL group (OR = 1.76 [95% CI, 1.00-3.10]; $P = .047$) and the controls. DNA sequence variation within the *FBN2* gene is associated with ACL tears.

Observational Studies

Gene Expression Analysis. Johnson et al[9] conducted a study to compare gene expression and structural features in torn ACL tissue obtained intraoperatively from young female and male athletes during surgical ACL reconstruction. Biopsy samples of ACL stumps were collected from 7 female and male athletes each and divided into 2 portions: 1 for histologic examination and 1 for gene expression analysis. Specimens for gene analysis were frozen and ground, and RNA was extracted and purified. Microarray analysis was performed on RNA isolated from participants who had a noncontact mode of injury (4 female and 3 male participants). Genes with expression levels differing significantly between these female and male players were assembled into functionally associated networks. The authors further validated 3 genes of interest—namely, *ACAN* (aggrecan), *FMOD* (fibromodulin), and *WISP2* (WNT1 inducible signaling pathway protein 2)—by reverse transcription quantitative polymerase chain reaction analysis in all 14 cases, which confirmed significant differences in gene expression: *ACAN* and *FMOD* were upregulated in female versus male subjects, and *WISP2* was downregulated. No morphologic difference was noted on histologic examination of the ACL tissue samples.[9]

This might mean that the ACL in females may be structurally weaker as compared with their male counterparts because of the differences in expression of genes of the extracellular matrix proteins.

DISCUSSION

It has been established that ACL tears occur because of a multifactorial situation, and the exact origin and mechanism of this injury remain unclear.[27] In the past decade, several researchers have proposed associations of various gene polymorphisms with ACL tears and other soft tissue injuries, such as Achilles tendinopathy and shoulder dislocations.[3-5,8-11,14-26] Research has evolved from simple familial predisposition studies to genetic association studies and is now headed in the direction of gene expression and gene-gene interaction studies.[3-5,8-11,14-20,22,24-26]

Although SNPs in *COL1A1, COL12A1, COL5A1, COL 3A1, MMP3, MMP12*, and various ECM genes have been shown to be associated with ACL tear, 13 of the 14 genetic association studies are from the South African or Polish population only and thus are not representative of the world population.[3,4,11,15-20,22,24-26] Furthermore, within the 2 populations studied, there appears to be sharing of the database for the different polymorphisms tested.[3,4,11,15-20,22,24-26] A major drawback of the Polish studies by Słodkowska et al,[24,25] Stępień-Słodkowska et al,[28] and Ficek et al[3,4] is that they were conducted exclusively in males and the population database appears to be the same, given that the case and control group numbers remained the same across all the studies. This indicates that subjects tested in these studies may actually have >1 polymorphism associated with ACL tear. The possible interaction between these polymorphisms and the molecular mechanism through which these gene polymorphisms render ACL tissue structurally weaker has not yet been elucidated.

It is now established that ACL tears are more common in females than in males, and various risk factors have

been identified that place females at an increased risk.[27,28] Polymorphisms in *COL5A1* and *COL12A1* were shown by Posthumus et al[19,20] to be associated with ACL tear in females only. The same polymorphisms, when tested by Słodkowska et al[24] and Ficek et al[4] in exclusive male cohorts, did not show positive association, which further strengthens the possibility that these polymorphisms may predispose only females to ACL tears. Johnson et al[9] noted differences in expression of 3 genes (*ACAN, FMOD*, and *WISP2*), which render female ACL tissues structurally weaker than male ACL tissue. These observations lend an extra dimension to the reasons that females are more predisposed to an ACL tear when compared with males.

Although much data have been generated over the past few years regarding different polymorphisms, there is a paucity of literature regarding the molecular mechanisms/gene expression and gene-gene interaction studies. In the future, more studies will be needed in these specified areas to clearly understand the relation of these polymorphisms with ACL tear and other musculoskeletal injuries.

The idea of genetic tests for screening athletes predisposed to sports-related injuries is certainly an appealing one. Such tests could help to identify at-risk athletes and enable implementation of preventive measures. Goodlin et al[7] conducted a pilot study in which 14 triathletes were genetically screened for 6 sports-related injuries, including ACL tear. Subjects were screened for SNPs in *COL1A1, COL5A1, COL12A1*, and *MMP12* genes. The authors noted that the SNPs associated with ACL tear have high allelic ORs (2.4-50). One triathlete had a genetic score that indicated protection against ACL tears, while several athletes were found to be at risk. Through hour-long personal consultations, these athletes were educated about how their individual genetic makeup may affect their personal risk profile. The authors noted that participants were largely favorable of the program and found it informative and that most acted on their genetic results. Customized warm-up protocols that target proper landing and cutting form, core strength, and hamstring strength may reduce the risk of sustaining ACL tear in these genetically predisposed athletes.[7]

Ours is the first systematic review concerning genetic predisposition to ACL tear. The systematic review was conducted according to the PRISMA guidelines, which are considered the standard reference for conducting systematic reviews and meta-analyses.[11] We conducted a thorough and comprehensive search for eligible studies from the PubMed, EMBASE, Cochrane, and HuGE databases. The study protocol was registered in the PROSPERO database before the commencement of the systematic review, and search strategy, inclusion criteria, and final results of the assessment have been presented so that readers can make their own determinations of the results and our conclusions.

We acknowledge the limitations of this review. The evidence level presented in this study is low (level 3a), as most included studies are case-control studies. However, this limitation is inevitable, as this is a diagnostic test; the only observational study that can be designed is a case-control study, and experimental studies are not applicable. The level of evidence therefore cannot be more than 3a for this kind of topic. There exists a potential for bias in the review process, as the 2 review authors who assessed the methodological quality (R.J. and S.S.) were not blinded for authors, journal, or institution. However, the review authors did not have any financial interest in positive or negative results. There is also a possibility of publication bias in this systematic review. However, a comprehensive search of the published literature for potentially relevant studies was conducted, based on a systematic strategy to avoid bias.

CONCLUSION

Although a genetic predisposition to ACL tear may exist, the level of evidence is still low for various reasons. The studies conducted so far have not looked at various confounding factors; hence, the risk of bias is high in all these studies. Also, the results of these studies cannot be extrapolated to the general population, as the cases studied are not representative of the general population. Larger, multicentric studies with different ethnic populations are needed to further elucidate the genetic element in ACL tears.

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