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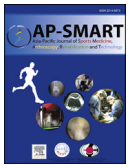

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Original article

Familial predisposition to anterior cruciate ligament injury

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Abstract

Although several risk factors for anterior cruciate ligament (ACL) injury have been evaluated in the literature, there are few reports on familial predisposition. This study investigated the familial predisposition to ACL injury. The study included 350 patients who underwent ACL reconstruction between January 2005 and September 2008. All patients were surveyed by telephone or a written questionnaire about family history (FH) of ACL injury, sports played by family members, and mechanisms of injury. We also compared age, sex, height, weight, body mass index, Tegner activity score, general joint laxity, and tibial slope between an FH group (with FH) and a control group (without FH). In addition, we compared the incidence of ACL graft rupture and contralateral ACL rupture 2 years after primary surgery. Complete information was obtained from 316 patients, 38 (12.0%) of whom had FH of ACL injury. Two families had three members with ACL injuries. Of the 40 family members with ACL injuries, 38 (95%) had noncontact injuries and 34 (85%) shared a similar mechanism of injury with the related patient. No significant differences were identified between the two groups, except that tibial slope was significantly greater in the FH group than in the control group. Although the incidence of repeat ACL injury was greater in the FH group (23.7%) than in the control group (16.4%), there was no significant difference. Our results indicated a high probability of familial predisposition to many of the identified risk factors for ACL injury. In addition, patients with FH of ACL injury might be at high risk for initial and repeat ACL injuries. Therefore, prevention programs should be implemented for patients with FH of ACL injury in order to decrease the risk of these injuries.
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Keywords: Anterior cruciate ligament; Familial predisposition; Risk factor

Introduction

Anterior cruciate ligament (ACL) injuries in athletes are common, with female athletes having a two to eight times higher incidence of ACL injuries compared with male athletes.[1,2] Most ACL injuries occurring in athletes are noncontact injuries that occur during sudden deceleration and changes in direction, such as cutting, pivoting, or landing after a jump.[3,4]

In most cases, surgical reconstruction of the ligament is recommended. Although many advances have been made in surgical and rehabilitative interventions for patients with ACL injuries, long-term outcome studies show that these patients are at high risk of developing osteoarthritis 10–15 years after ACL injury, regardless of treatment.[5–7] Therefore, prevention is important in reducing the effect of ACL injury. The cost of treatment, loss of participation in sports during peak season, long-term rehabilitation, and residual disability have prompted ACL injury-related research in terms of risk factors and prevention strategies.[8–10]

Several reports have examined the risk factors for noncontact ACL injury and injury mechanisms.[11–13] Risk factors are either extrinsic (those outside the body) or intrinsic

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(those within the body). Specific intrinsic factors that have been investigated include anthropometric, biomechanical, neuromuscular, anatomical, developmental, and hormonal and genetic factors; ligament integrity; activity level; and previous injury.

Decreased notch width, greater tibial slope, poor neuromuscular control, ligamentous laxity, high body mass index (BMI), sex, knee abduction (valgus), and knee laxity are all reportedly associated with an increased risk of ACL injury.[12–14] However, few articles have described familial predisposition to ACL injury. Anderson et al[15] did not observe any difference in the prevalence of ACL injuries between family members of injured patients and those of noninjured patients. By contrast, Harner et al[16] reported an increased prevalence of ACL injury among family members of injured patients than among those of control patients; 11 of 31 patients (35%) with ACL injury had a family history (FH) of ACL tear, whereas only one of 23 control patients (4%) had FH of ACL injury. Flynn et al[17] reported that patients with a history of ACL injury were twice as likely to have a first-degree relative with a history of ACL injury compared with a matched control group without a history of ACL injury. Similarly, Lambert[18] reported a higher prevalence of family members with a history of ACL rupture among ACL-injured patients. Thus, only a few studies have addressed familial predisposition to ACL rupture. However, to our knowledge, no study has specifically examined whether there are similarities in the ACL injury mechanisms, situation, and types of sports played between patients and their family members. Furthermore, it remains unknown whether there are differences in risk factors between patients with FH of ACL injury and those without. Thus, our objectives were to investigate whether there is a familial predisposition to ACL injury, examine the characteristics of injury mechanisms and situations in each family, and compare risk factors for ACL injury between patients with FH and those without FH.

Materials and methods

The study group comprised 350 consecutive patients (123 males, 227 females; average age, 21 years; range, 14–51 years) who underwent ACL reconstruction at our institution between January 2005 and September 2008. The various sports played by the patients included basketball ($n = 143$; 40.8%), handball ($n = 101$; 28.8%), soccer ($n = 31$; 9.0%), volleyball ($n = 27$; 7.7%), and other sports ($n = 48$; 13.7%). All patients provided a detailed medical history and underwent a thorough physical examination, which included a comprehensive examination of the knee and an assessment of generalised joint laxity. This study was conducted with the approval of the Kanazawa University Graduate School of Medicine Institutional Review Board, Kanazawa, Japan. Patient consent was obtained.

At first, all patients received a questionnaire about their FH of ACL injury 2 years after primary surgery. The patients were asked to complete and return the questionnaire using a postage-paid envelope that was provided to them. If the questionnaire was not returned, the participant was contacted by telephone and the questions were read over the phone. We included only first-degree relatives (parents, siblings, and children) in FH of ACL injury. Second- (aunts and uncles) and third-degree relatives (cousins) were excluded.

Patients having FH of ACL injury were questioned about the sports played by their family members and the mechanisms of injury, which were classified as contact or noncontact injuries. Contact injuries were defined as those that involved a direct physical force from an external source, such as a tackle during a football game. Noncontact injuries were defined as those arising from a manoeuvre without any external force, such as a side-stepping or pivoting manoeuvre. In addition, we compared the injury mechanisms between family members and classified them as same, almost same, and different mechanisms. (Examples: same mechanisms, landing and landing and turn and turn; almost same mechanisms, turn and pivoting; different mechanisms, landing and turn.).

The patients were then divided into two groups: an FH group, including patients with FH of ACL injury, and a control group, including those with no FH of ACL injury. Patients older than 35 years and those with incomplete data were excluded, which left 233 patients for review. The FH group comprised 38 patients and the control group comprised 195 patients. Age, sex, height, weight, BMI, Tegner activity score, generalised joint laxity, and posterior tibial slope were compared between the two groups. The incidence of ACL graft rupture and contralateral ACL rupture 2 years after primary surgery were also compared.

The Tegner activity scale was designed as a score of activity level for patients with ligament injuries.[19] Activity level is scored between 0 and 10, where 0 represents “on sick leave/disability” and 10 represents “participation in competitive sports such as soccer at a national or international elite level”.

Generalised joint laxity tests comprised seven items, including second finger to wrist and thumb to forearm opposition, elbow hyperextension $>15^\circ$, knee hyperextension $>10^\circ$, ankle hyperdorsiflexion $>30^\circ$ in knee extension, hyperexternal rotation of the hip $>90^\circ$ in standing position, anteflexion of the trunk, and shoulder hyperrotation. Positive shoulder hyperrotation was defined as that when the participants could grasp their back with their hands from both the cranial and caudal sides. Positive forward flexion of the trunk was defined as that when the participants could touch the floor with the bilateral palms of their hands while maintaining the lower leg in an extended position. Positive hyperexternal rotation of the hip was defined as that when the participants could maintain their toes at 180° of external rotation with the lower legs in an extended position.

Lateral knee radiographs were also evaluated to establish the posterior tibial slope for all patients, using the method described by Dejour and Bonnin.[20] A line perpendicular to the tibial axis and a line running along the tibial slope of the lateral condyle were used to obtain the angle of the tibial slope. To avoid interobserver error, all clinical tests and films were assessed by a single observer.

Statistical analysis

Statistical means and standard deviations (SDs) for all measured variables were calculated. Statistical analysis was conducted via Logistic regression with SPSS for Windows software version 19.0 (SPSS Inc., Chicago, IL, USA). Fisher's exact test was used to determine sex differences. In addition, we performed statistical comparison of rate of ACL graft rupture or contralateral ACL injuries between the patients with and without FH using a Chi-square test. A p value <0.05 was considered statistically significant.

Results

The FH group comprised 38 patients (10 males, 28 females) and the control group (without a FH of ACL injury) comprised 195 patients (63 males, 132 females). Complete information was obtained from 316 of the 350 patients (90.3%). Thirty-eight patients (12.0%) had FH of ACL injury. The family relationships were sisters ($n = 24$; 5 brothers, 19 sisters) and parents ($n = 16$; 6 fathers, 10 mothers). Two families had three members with ACL injuries.

The 38 patients with FH of ACL injury played the following sports: basketball ($n = 18$), handball ($n = 8$), volleyball ($n = 4$), soccer ($n = 3$) and other sports ($n = 5$). The sports played by the 40 family members with ACL injury included basketball ($n = 17$), volleyball ($n = 11$), handball ($n = 5$) and other sports ($n = 7$). Twenty-six of the 40 family members (65.0%) sustained ACL injuries while playing the same sport as the related patient. Of the 40 family members, 38 (95%) had noncontact ACL injuries. Twenty-three (57.5%) injured their ACL by the same mechanism as the related patient, 11 (27.5%) by almost the same mechanism and 6 (15%) by a different mechanism.

The physical profiles of the two study groups are demonstrated in Table 1. No significant differences in age, height, weight, BMI, and Tegner activity score were observed between the two groups. In addition, there were no significant sex differences between the two groups (Table 2).

The mean generalised joint laxity score was 2.7 ± 1.6 points for the FH group and 2.3 ± 1.6 points for the control group; however, the difference was not significant ($p = 0.33$). The mean value of the tibial slope was significantly higher in the FH group (12.4 ± 1.9°) than in the control group (9.7 ± 2.3°; $p < 0.05$; Table 1).

In the FH group, rupture of the ACL graft occurred in three patients (7.9%), whereas contralateral ACL injury occurred in six patients (15.8%). In the control group, rupture of the ACL graft occurred in nine patients (4.6%), whereas contralateral ACL injury occurred in 23 patients (11.8%). Both these events occurred over a period of 2 years in both groups. Although the incidence of repeat ACL injury was greater in the FH group (23.7%) than in the control group (16.4%), there was no significant difference (Table 3).

Table 1
Physical profile of study participants.

	FH group		Control group		OR (95% CI)	p
	Mean	SD	Mean	SD		
Age (y)	17.9	3.8	19	4.6	0.94 (0.84, 1.04)	0.17
Height (cm)	166.2	8.1	164.8	8.3	1.11 (0.87, 1.41)	0.51
Weight (kg)	62.5	13.2	61.5	13.5	0.92 (0.68, 1.26)	0.77
BMI (kg/m^2)	22.4	3.2	22.4	3.4	1.19 (0.51, 2.78)	0.95
Tegner activity score (0–10)	7.1	0.7	7	0.8	1.14 (0.65, 2.00)	0.44
Generalized joint laxity (0–7)	2.7	1.6	2.3	1.6	1.05 (0.81, 1.35)	0.33
Tibial slope (°)	12.4	1.9	9.7	2.3	1.73 (1.42, 2.11)	<0.05

BMI = body mass index; CI = confidence interval; FH = family history; OR = odds ratio; SD = standard deviation.

Table 2
Sex differences between the family history and control groups.

	Family history group	Control group	p
Male:female	10:28	63:132	0.57

Discussion

Several risk factors for ACL injury, including anatomical risk factors such as generalised joint laxity, intercondylar notch width and tibial slope, biomechanical factors, neuromuscular factors, and hormonal factors, have been evaluated in the literature.[11–14] However, few articles have described a familial predisposition to ACL injury. Anderson et al[15] found no greater prevalence of ACL injuries among family members or ethnic groups, whereas Lambert,[18] Harner et al,[16] and more recently, Flynn et al[17] concluded that there was a familial predisposition. A recent 4-year cohort study found that white European–American athletes were 6.6 times more likely to suffer an ACL injury than were other ethnic groups, which was indicative of the genetic component of the risk for ACL injury.[21] Posthumus et al[22] reported that the *COL5A1* gene is associated with an increased risk of ACL rupture in female athletes.

In the current study, 38 patients (12.0%) had a family history of ACL injury. In addition, 26 of the 40 injured family members (65.0%) suffered the injury while playing the same sport as the related patient. Furthermore, 38 of the 40 family

Table 3
Incidence of anterior cruciate ligament graft rupture and contralateral anterior cruciate ligament rupture in the family history and control groups.

	FH group	Control group	p
No. of patients with ACL graft rupture/ total (%)	3/38 (7.9)	9/195 (4.6)	0.40
No. of patients with contralateral ACL rupture/total (%)	6/38 (15.8)	23/195 (11.8)	0.49
No. of patients with repeat ACL injury/total (%)	9/38 (23.7)	32/195 (16.4)	0.28

ACL = anterior cruciate ligament; FH = family history.

members (95%) had a noncontact ACL injury, and 34 (85%) had injured their ACL by the same/almost the same mechanism as did the related patient. Hewett et al[12] reported that prescreened mature female twins who subsequently experienced ACL injuries demonstrated multiple potential risk factors, including increased knee abduction angles, decreased knee flexion angles, increased generalised joint laxity, decreased hamstring:quadriceps ratio, and decreased femoral intercondylar notch width. On the basis of our findings, we speculated that there may be a familial predisposition to ACL tears in addition to familial inheritance of anatomical, neuromuscular, and biomechanical risk factors for ACL injury.

Increased risk of ACL injury in athletes is multifactorial. Uhorchak et al[23] studied noncontact ACL injuries and the associated risk factors over a period of 4 years in 859 US military recruits. A predictive model was developed on the basis of 24 noncontact ACL injuries that included the following factors: narrowed femoral notch width, increased BMI, generalised joint laxity, and increased KT-2000 scores. These factors accounted for 28% variance in the occurrence of noncontact ACL injuries in all patients, whereas it predicted 75% of the noncontact ACL injuries to occur in females. Women with BMI $\geq$1 SD above average had a 3.5-times higher relative risk for noncontact ACL injury compared with women with lower BMI. However, men with high BMI did not demonstrate this finding. In the current study, we compared some risk factors between the FH and control groups. There were no significant differences in age, sex, height, weight, BMI, Tegner activity score, and generalised joint laxity. However, tibial slope was significantly greater in the FH group than in the control group. Tibial slope is an identifiable risk factor for ACL injuries. Brandon et al[24] and Todd et al[25] concluded that there was a relationship between increased tibial slope and ACL injuries. Recently, Koga et al[26] reported new mechanisms for noncontact ACL injuries. According to them, when valgus loading is applied, the medial collateral ligament becomes taut and lateral compression occurs. This compressive load, together with the anterior force vector caused by quadriceps contraction, results in a displacement of the femur relative to the tibia; the lateral femoral condyle shifts posteriorly and the tibia translates anteriorly and rotates internally, resulting in ACL rupture. They reported that the internal rotation is caused by the joint surface geometry, including greater posterolateral tibial plateau slopes. In our study, patients with FH of ACL injury had greater tibial slopes. These findings suggested that patients with FH of ACL injury constitute a high-risk group for ACL tears.

Repeat ACL injury occurred in 9 of 38 patients (23.7%) in the FH group and 32 of 195 patients (16.4%) in the control group. The incidence of repeat ACL injury was greater in the FH group than in the control group. Salmon et al[27] reported that 72 of the 612 patients with ACL tears (12%) who underwent ACL reconstruction suffered a repeat ACL injury over the 5-year follow-up period. In a recent systematic review, the risk of ACL tear in the contralateral knee (11.8%) was reportedly twice that of ACL graft rupture in the ipsilateral knee (5.8%) after more than 5 years of follow-up.[28] In the current study, repeat ACL injury occurred in 23.7% of the FH group patients over the 2-year follow-up period. Despite short-term follow-up, the reported rate in our study was higher than that reported in the previous studies. Therefore, we speculated that patients with FH of ACL injury constitute a high-risk group, not only for ACL tears but also for repeat ACL injuries.

Recently, it was reported that neuromuscular and proprioceptive training programs can decrease the incidence of noncontact ACL injuries.[8,29,30] However, they may be difficult to implement within an entire team or the community at large. In addition, the method of determining high-risk populations that can benefit the most from neuromuscular training remains unknown. When high-risk athletes are identified, they may be targeted for appropriate interventions to reduce ACL injury risk. Hewett et al[12] reported that screening tests for a family history of ACL injury can be used to identify athletes at high risk and the target timing of intervention for injury prevention. Noncontact ACL injuries in athletes probably have a multifactorial aetiology. The identification of athletes at increased risk may be a salient first step prior to designing and implementing specific pre- and in-season training programs aimed at modifying the identified risk factors and decreasing ACL injury rates. According to the findings of the current study, it is highly probable that many of the identified risk factors for ACL injury are passed through families. Therefore, prevention programs are very important for patients with a family history of ACL injury because they may play a significant role in decreasing the risk of this injury.

Our study has some limitations that need to be addressed. First, we did not evaluate FH of ACL injuries in patients without ACL tears. Harner et al[16] reported that only 1 of 23 control group patients (4%) had FH of ACL injury. In our study, 12.0% of patients with ACL injury had FH of this injury. Our results suggested that there is a familial predisposition to ACL injury. However, further investigation is required to evaluate the control group matched by age, sex, and primary sport played by patients. A second limitation is the potential for recall bias. The patients may not have been aware of relatives who truly had ACL tears. Similarly, another limitation was the difficulty of ensuring that all ipsilateral and contralateral injuries were identified. There was also a lack of data on BMI, Tegner activity score, generalised joint laxity, and posterior tibial slope in family members. Therefore, we could not address the specific risk factors passed through families. In addition, we did not investigate the neuromuscular factors such as muscle strength, the ratio of hamstring and quadriceps strength, and dynamic knee alignment in this retrospective study. To better define familial predisposition to ACL injury, a future investigation must incorporate a combination of several risk factors, including anthropometric, anatomical, neuromuscular, and biomechanical factors.

The causes of both initial and repeat ACL injury are clearly multifactorial, and it is difficult to determine the predictors that can be modified to prevent these injuries. Our results suggested that individuals with FH of ACL injury constitute a high-risk group, not only for ACL tears but also for repeat

ACL injuries. Therefore, screening tests for FH of ACL injury can be used to identify athletes at high risk, followed by the implementation of prevention programs to decrease ACL injury rates.

In conclusion, the results of the current study indicated that 12.0% of patients with ACL injuries had FH of this injury. Among the family members with ACL injuries, 95% had a noncontact injury, and 85% had injured their ACL by the same/almost the same mechanism as did the related patient. These findings suggest a high probability of familial predisposition to many of the identified risk factors for ACL injury. In addition, patients with FH of ACL injury had significantly greater tibial slopes, and repeat ACL injury occurred in 23.7% patients with FH of ACL injury. From our results, we speculated that individuals with FH of ACL injury constitute a high-risk group not only for ACL tears but also for repeat ACL injuries. Therefore, prevention programs should be implemented for patients with FH of ACL injury in order to decrease the risk of these injuries.

Conflicts of interest

All authors declare no conflicts of interest.

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