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Overrepresentation of the *COL3A1* AA genotype in Polish skiers with anterior cruciate ligament injury

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ABSTRACT: Although various intrinsic and extrinsic risk factors for anterior cruciate ligament (ACL) rupture have been identified, the exact aetiology of the injury is not yet fully understood. Type III collagen is an important factor in the repair of connective tissue, and certain gene polymorphisms may impair the tensile strength. The aim of this study was to examine the association of the *COL3A1* rs1800255 polymorphism with ACL rupture in Polish male recreational skiers. A total of 321 male Polish recreational skiers were recruited for this study; 138 had surgically diagnosed primary ACL ruptures (ACL-injured group) and 183 were apparently healthy male skiers (control group – CON) who had no self-reported history of ligament or tendon injury. Both groups had a comparable level of exposure to ACL injury. Genomic DNA was extracted from the oral epithelial cells. All samples were genotyped on a real-time polymerase chain reaction instrument. The genotype distribution in the ACL-injured group was significantly different than in CON (respectively: AA=10.1 vs 2.2%, AG=22.5 vs 36.1, GG=67.4 vs 61.8%; p=0.0087). The AA vs AG+GG genotype of *COL3A1* (odds ratio (OR) = 5.05; 95% confidence interval (CI), 1.62-15.71, p = 0.003) was significantly overrepresented in the ACL-injured group compared with CON. The frequency of the A allele was higher in the ACL-injured group (21.4%) compared with CON (20.2%), but the difference was not statistically significant (p=0.72). This study revealed an association between the *COL3A1* rs1800255 polymorphism and ACL ruptures in Polish skiers.

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INTRODUCTION

Skiing as a recreational activity has increased exponentially in recent years [1]. Injuries in alpine skiing have been a serious concern since the very beginning of the sport. Assessed over many decades, incidence and injury prevention strategies for recreational skiers are well documented [2]. The most commonly injured body part was found to be the knee (35.6%), and rupture of the anterior cruciate ligament (ACL) was the most frequent specific diagnosis [3].

Multiple risk factors, both modifiable and non-modifiable, are known to exist within the noncontact ACL injury mechanism. Sports in which ACL injuries are common are those with a large demand for a random and often complex series of dynamic movements requiring an equally complex, centrally coordinated response [4]. In skiing, most ACL injuries result from internal rotation of the tibia with the knee flexed greater than 90° [5].

The ACL is one of four main knee ligaments. Skeletal ligaments are defined as dense bands of collagenous tissue that span a joint and are anchored to the bone at either end [6]. Ligaments are composed of cells called fibroblasts which are surrounded by a cellular matrix. These cells are responsible for matrix synthesis and represent a small percentage of the total ligament volume [7]. Ligaments and tendons are important in transmitting forces and facilitating joint articulation in the musculoskeletal system [8].

Collagen is the main component of ligaments. Type I collagen accounts for 85% of collagen, and the rest is made up of types III, VI, V, XI and XIV [9]. Collagen accounts for approximately 75% of the dry weight of ligaments, with the remainder composed of proteoglycans, elastin and other proteins and glycoproteins [6]. Type III collagen is a product of the *COL3A1* gene, which produces the

pro-α1 chains of type III collagen [10]. The *COL3A1* gene is located on chromosome 2q31 [11]. Collagen type III has an important role in adjusting the strength and flexibility of tissues where it is expressed. Furthermore, *COL3A1* is modulated in the wound response process. It is acutely unregulated in the early phases of wound healing and maintains high levels of expression for several weeks after injury. As healing progresses, collagen type III is replaced by collagen type I, leading to increased tissue strength [12].

Although the sequences of the 3.2 billion bases of human DNA exhibit over 99.9% identity, the sequence variations (polymorphisms) in human DNA contribute to the visible and measurable biological variation observed in individuals. Mutations within the genes that encode collagens cause severe musculoskeletal tissue disorders [10]. Therefore genetic factors have been suggested as intrinsic risk factors for acute or chronic ACL injuries [13]. Initial studies by Collins et al. investigating the influence of genetic factors on the occurrence of ACL ruptures demonstrated a significant familial predisposition [14]. Moreover, genetic case-control association studies have identified sequence variants within the *COL1A1*, *COL5A1* and COL12A1 genes that predispose individuals to ACL ruptures [15].

Abnormalities in the *COL3A1* gene and consequently in type III collagen in the arterial walls cause familial intracranial aneurysms (IAs) [16]. It was found that allele A of the single nucleotide polymorphism (SNP) rs1800255 (Ala531Thr, A531T, 2209G>A) conferred a 1.71-fold increased risk for IAs in Chinese of Han nationality. Case-control association studies have shown that pelvic organ prolapse (POP) may be associated with *COL3A1* polymorphisms. The distribution of the *COL3A1* rs1800255 genotypes was significantly different among affected women and controls [17]. Genotype AA was significantly associated with risk of POP.

The aim of this study was to examine the association of the *COL3A1* rs1800255 polymorphism in the *COL3A1* gene with ACL ruptures in Polish male recreational skiers in a case-control study. We hypothesized that *COL3A1* rs1800255 polymorphism is associated with the incidence of ACL rupture and predisposes athletes to a greater risk of ACL rupture. Hence the genotype and allele (A and G) frequencies for the *COL3A1* rs1800255 polymorphism will show a statistically significant difference between the ACL rupture group and the control group.

MATERIALS AND METHODS

Participants. A total of 138 male recreational skiers (27±2 years) with surgically diagnosed primary ACL ruptures, all of whom qualified for ligament reconstruction, were recruited for this study. The control group was composed of 183 apparently healthy male skiers (26±3 years) with a comparable level of exposure to ACL injury, none of whom had any self-reported history of ligament or tendon injury.

Ethics Committee

The Pomeranian Medical University Ethics Committee approved the study, and written informed consent was obtained from each participant. The study complied with the guidelines set out in the ethics policy of Szczecin University [18].

Determination of COL3A1 genotypes

Genomic DNA was extracted from the oral epithelial cells using GenElute Mammalian Genomic DNA Miniprep Kit (Sigma, Germany) according to the manufacturer's protocol. Allelic discrimination of the *COL3A1* rs1800255 polymorphic site was performed using TaqMan Pre-Designed SNP Genotyping Assays (Applied Biosystems, USA), including primers and fluorescently labelled (FAM and VIC) MGB probes for the detection of alleles. All samples were genotyped on a real-time polymerase chain reaction (PCR) instrument (Step One, Applied Biosystems, USA). Thermal cycler conditions were as follows: an initial step at 95°C for 5 min, followed by 45 cycles of denaturation at 94°C for 15 s and annealing/extension at 60°C for 1 min.

Statistical analysis

Differences in the genotypes and allele (G and A) frequencies were analysed using the χ^2 or Fisher exact test. The genotypes of cases and controls were compared in three ways. First, a general test of association in a 2-by-3 phenotype-by-genotype table was performed. Then two different modes of inheritance of the minor allele were assumed: dominant, in which homozygotes and heterozygotes for the minor allele were pooled and compared to homozygotes for the major allele; and recessive, in which homozygotes for the minor allele were compared with pooled homozygotes and heterozygotes for the major alleles. In addition, the programming language and environment R (http://www.r-project.org) was used for Hardy-Weinberg and linkage disequilibrium (LD) testing. P values <0.05 were considered statistically significant.

RESULTS

Genotype distributions met Hardy-Weinberg proportions in the control group ($p=0.166$) and in the cases ($p=0.0002$). The distributions of the *COL3A1* rs1800255 genotypes and alleles are given in Table 1. The genotype distribution in the cases was different from that in controls ($p=0.0087$). Overrepresentation of the AA genotype in the ACL rupture group was statistically significant ($p=0.003$, Fisher's exact test, recessive mode: AA vs AG+GG). The frequency of the A allele was higher in the cases (21.4%) compared with controls (20.2%), but the difference was not statistically significant ($p=0.72$). The allelic OR for ACL injury was 1.07 in A allele carries, when compared to G allele carries.

DISCUSSION

Our results were consistent with the hypothesis that the *COL3A1* rs1800255 polymorphism is associated with ACL injury. The novel main finding of this study is the observed significant overrepresentation of the AA genotype in the ACL rupture group among Polish skiers. The allelic OR for ACL injury was 1.07 in A allele. We did not find a significant difference between allele frequencies, but we found a signifi-

TABLE I. Genotype and allele frequencies of Ala531Thr (Sp1, rs1800255) *COL3A1*.

Group	Genotype count			p†	pD [OR(95%CI)]	pR [OR(95%CI)]	Allele frequency		p†	Allelic OR (95%CI)
	GG	AG	AA				G	A		
Cases	93 (67.4)	31 (22.5)	14 (10.1)	0.0087*	0.347 [0.78 (0.49-1.24)]	0.003* [5.05 (1.62-15.78)]	78.6	21.4	0.720	1.07 (0.72-1.60)
Controls	113 (61.8)	66 (36.1)	4 (2.2)	1.000	1.000	1.000	79.8	20.2	1.000	1.000

Note: * statistically significant differences, † χ^2 p value, pD and pR are two-sided Fisher's exact test probabilities with dominant (AA+AG vs GG) and recessive (AA vs AG+GG) modes of inheritance of the minor allele (A), respectively.

cant difference in the tested genotype in male skiers with surgically confirmed primary ACL ruptures compared to injury-free recreational skiers. The genotypes in the ACL group were not in Hardy-Weinberg equilibrium (HWE). Although genotyping errors can cause deviations from HWE, this also occurs when a marker is associated with an examined phenotype. The data may show apparent departure from HWE, even if the marker is in HWE in the population [19]. We investigated male skiers with surgically confirmed primary ACL rupture who were qualified for an ACL reconstruction procedure. The control group consisted of subjects who were all men of the same ethnicity, similar in age, participating in the same sport, their knee joints being exposed to comparable forces and movements, thereby controlling the many internal and external risk factors in this study.

ACL ruptures are common and well-known injuries, dreaded among athletes of all abilities and disciplines. The ACL is frequently injured during both competitive and recreational activity [20]. If the diagnosis is missed at first presentation, it is difficult to attribute ongoing instability and recurrent injury to an ACL tear. Often patients improve shortly before repeatedly reinjuring their knee. As a consequence, the knee may lock, necessitating an arthroscopic meniscectomy. Making matters worse, this then hastens the progression of joint arthrosis and the decline of joint function [21]. Osteoarthritis prevalence following ACL injury is as high as 80%, and most young patients suffer from early-onset osteoarthritis with associated knee pain and reduced quality of life between 30 and 50 years of age [22]. ACL rupture is costly, with conservative estimates of surgery and rehabilitation at $17,000-$25,000 per injury [23].

A familial predisposition to ACL rupture, well documented in a few studies, would suggest that there is a genetic component to this knee injury and possibly to other musculoskeletal soft tissue injuries [24, 25]. Studies have also suggested that there is, at least in part, a genetic component to Achilles tendon and rotator cuff injuries [26]. Pre screened mature female twins who subsequently experienced ACL injury demonstrated multiple potential risk factors including increased knee abduction angles, decreased knee flexion angles, and increased general joint laxity [24]. Therefore genetic makeup should be considered as an intrinsic risk factor for ACL rupture. Stępien-Slodkowska et al. examined 138 male recreational skiers with surgically diagnosed primary ACL ruptures and a control group (183 apparently healthy male skiers with a comparable level of exposure to ACL injury) [26]. DNA samples were genotyped for the COL1A1 +1245 G/T polymorphisms. There was a significant difference in the genotype distribution between skiers and the control group, but there was no significant difference in allele distribution.

Intercondylar notch width, notch morphology, and gender have all been implicated as factors that may predispose an individual to ACL rupture [20]. Many of the common intrinsic risk factors implicated in these injuries are determined by genetic factors such as somatotype, neuromuscular characteristics, biomechanical features, anatomical features and flexibility or laxity, though other non-genetic factors such as previous injury may also play a role [13].

The homogeneity of the investigated groups seems to be a strength of this study. However, this fact may be considered as a limitation, because we examined only male skiers, while studies suggest that women are at greater risk of tearing their ACL than men participating in similar athletic activities. There is currently no conclusive explanation for this disparity; however, as ACL injuries in women have been linked to oestrogen fluctuations during the menstrual cycle, one hypothesis is that oestrogen has a direct detrimental effect on the mechanical properties of knee ligaments [27]. Hewett argues that ACL injury occurs with a four- to six-fold greater incidence in female athletes compared to males playing the same 'landing and cutting' sports [23]. Sexual dimorphism in modifiable neuromuscular factors linked to ACL injury is well documented, with the "female" movement pattern interpreted as riskier. Females land in a more extended posture, are more quadriceps reliant, and demonstrate altered muscle activation and co-activation in addition to greater out-of-plane knee motions and loads than males [28].

The *COL3A1* gene belongs to the highly homologous family of fibrillar collagens, which have several aspects in common, one of which is a triple-helical domain characterized by repeating Gly-X-Y triplets encoded by 43 exons (in *COL3A1*, exon 4 and 5 are fused in a single exon 4) that invariably begin with a glycine codon and have a similar pattern of size [29]. The *COL3A1* gene encodes type III collagen, a fibrillar, mono-trimeric, extracellular matrix protein that is present in extensible connective tissues such as skin, lung, and the vascular system, frequently together with type I collagen [12].

Mutations in the *COL3A1* gene are associated with paediatric and adult gastro-oesophageal reflux disease, hiatus hernia in adult males and Ehlers-Danlos syndrome type IV – an autosomal dominant con-

nective tissue disorder [30]. The cause of the disease is a defect in procollagen III synthesis, which results in a structural modification in this protein. Affected individuals have a high risk of vascular, intestinal and uterine rupture [31]. The expression of *COL3A1* is closely related to chronic liver diseases. One study investigated whether SNPs of *COL3A1* confer genetic susceptibility to patients with hepatitis B virus-infected liver diseases, including chronic hepatitis B, liver cirrhosis, and hepatocellular carcinoma [32]. A familial tendency has been demonstrated in the aetiology of pelvic organ prolapse (POP) [33]. Type III collagen is an important factor in the repair of connective tissue, and gene polymorphisms may impair the tensile strength. These polymorphisms in the alpha I chain of the type III collagen protein-encoding gene (*COL3A1*) put women at risk for POP. A homozygous single-nucleotide substitution in the coding region of type III collagen rs1800255 was identified in 27 (13%) POP patients and 3 (3%) controls. Other studies have shown that the frequency of the G allele was significantly higher in patients with pelvic organ prolapse than in controls (0.8 vs 0.6, p = 0.002) [34]. In women with the G allele the OR for pelvic organ prolapse was 3.2 (95% CI 1.4-7.3). The collected data suggest that the *COL3A1* rs1800255 polymorphism could be a candidate for genotyping in sport practice to predict tendon susceptibility to injuries and apply dedicated preventive interventions [35].

CONCLUSIONS

This study revealed an association between the *COL3A1* rs1800255 polymorphism and ACL ruptures in a population of Polish skiers. Nearly 5-fold higher likelihood of ACL injury was found in skiers with the AA genotype than in skiers with the AG+GG genotype. 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. Knowledge of the role of individual genes in the processes occurring in the human body can and should be applied to sport rehabilitation and injury prevention, and, accordingly, the role of genetics in sport research increases with every passing year [36].

Conflict of interests: the authors declared no conflict of interests regarding the publication of this manuscript.

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