

ACL injuries — problem solved?

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To the novice reader, it must seem like sports medicine journals provide inordinate attention to the middle and anterior third of the tibia plateau and the ligament attaching there: the anterior cruciate ligament. This issue of the *BJSM* is no exception, with as many as five papers on the ACL; but why all the fuss? Aren't there excellent programmes to prevent ACL injuries?

It is true that last year three large-scale studies reported that serious knee injuries can be prevented. In the *BMJ*, Pasanen and colleagues¹ showed that their neuromuscular training programme is effective in preventing non-contact leg injuries in elite female floorball players and Soligard and colleagues² showed that a structured warm-up programme — The 11+ — can prevent lower extremity injuries in young female football players. In addition, Gilchrist *et al*³ showed that a similar programme, also focusing on neuromuscular control, reduced the risk of ACL injuries in collegiate female soccer players. So, isn't the problem solved?

Not according to Quatman and Hewett,⁴ who in their linked paper discuss the controversy regarding the main mechanism of injury (MOI) for non-contact ACL injuries in team sports such as basketball, handball and football. The two opposing theories are “the sagittal plane” vs “the valgus plane” hypotheses. Proponents of the first theory argue that ACL injuries result from loading in the sagittal plane only, primarily as a result of anterior shear forces caused by forceful quadriceps contraction when landing or cutting. In contrast, Quatman and Hewett⁴ argue that knee abduction is associated with ACL injury, and that the MOI involves multiplanar loading, which also includes a valgus collapse. Providing further evidence for their view, the same group also reviewed video evidence from 10 female and seven male ACL-injured players. They show that female athletes landed with greater knee abduction during ACL injury than did male athletes or female controls, and that lateral trunk motion also seemed to be a factor. This paper, now available Online First and

coming out in print next month (June *BJSM*)⁵ confirms and extends the findings of initial video analyses by Krosshaug *et al*,^{6,7} thus providing additional support for the “valgus plane” hypothesis.

An innovation of their study was that they compared videos of athletes who sustained injury with those of athletes doing similar landing and cutting tasks not leading to injury. As pointed out by Meeuwisse in a recent editorial,⁸ it is equally important to ask: “Why did an injury NOT occur?” as “Why did an injury occur?” He argues that athletes constantly place their bodies under extreme load, yet rarely suffer an injury, and that we need to measure and understand this “mechanism of no injury” (MONI) to begin to understand which component of the apparent MOI is actually responsible for an injury. Identifying this critical factor or factors will permit accurate characterisation of the MOI. However, one challenge for future researchers will be how to select appropriate control situations for video analyses.

Why is the mechanism of injury important? Well, for two main reasons. First, prevention programmes that specifically target the high-risk landing mechanics are much more likely to be effective. For example, all of the recent large-scale intervention trials^{1–3,9} were clearly focused on exercises to avoid a valgus collapse when landing and cutting. If we knew even more about the MOI, these programmes could perhaps be refined to focus even more on the critical factors, making them less time-consuming and more acceptable to athletes and coaches. Second, if we are able to identify athletes with a propensity for inappropriate landing mechanics, as suggested by Hewett *et al* in a previous study¹⁰, perhaps we could target these programmes to the true population at risk.

Another major challenge for ACL researchers is that a number of intrinsic risk factors are likely also involved in the aetiology of injury. In a case-control study, Posthumus *et al*¹¹ show that the TT genotype of the COL1A1 Sp1 binding site polymorphism was significantly under-represented in South Africans with ACL ruptures. They suggest that this sequence variant be the first specific

genetic element to be included in multifactorial models developed to understand the aetiology of ACL injuries.

Two other studies^{12,13} in this issue also illustrate why we will continue to see many ACL-related research papers in this and other sports medicine journals. Meuffels and colleagues¹² report on a study where they compared 25 patients who had been treated conservatively for 10 years after being diagnosed with an ACL rupture with a matched group who underwent a bone–patella–tendon–bone ACL reconstruction 10 years previously. As the study groups were small, statistical comparisons should be interpreted with caution. However, both groups had a high rate of meniscal lesions and, although the patients who were treated operatively had a significantly better stability of the knee at examination, there was a tendency to have more radiological osteoarthritis in the reconstructed group (48% versus 28%). In another case-control study, Butler and colleagues¹³ show that individuals who have undergone an ACL reconstruction exhibit an increased peak knee abduction moment during walking compared with healthy controls, suggesting that this gait pattern may contribute to the earlier onset of knee osteoarthritis in this population. It is precisely this, the dramatic increase in the risk of future osteoarthritis,¹⁴ which remains a burden to the patient, a challenge for the clinician and a key incentive for those involved in injury prevention.

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Genetic association studies for complex traits: relevance for the sports medicine practitioner

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In this issue of *BJSM*, September *et al*¹ report DNA variants within the *COL5A1* gene among patients with Achilles tendinopathy (the cases) and among controls with no tendinopathy, matched for age and country of origin. Their findings suggest that a common DNA variation in the *COL5A1* gene may be a risk factor for Achilles tendinopathy. Replication of their results among larger cohorts will be necessary to validate this finding.

It can be a challenge for the busy sports medicine practitioner to distil the clinical relevance of association studies such as this one. Although genetic testing for mendelian (single-gene) disorders is widely available in many countries, genetic testing for single-nucleotide polymorphisms (SNPs) is generally unavailable outside research laboratories. With certain notable exceptions (eg, the link between apoE variants, cardiovascular and neurological disease),^{2,4} statistical associations between common SNPs and complex diseases have not been borne out by further study. Numerous pitfalls occur in both the design and interpretation of these studies, which has resulted in a poor track record for independent replication. Thus, a brief summary of these pitfalls may be useful to the *BJSM*'s readership.

By way of background, there are just over 14 million SNPs known to exist in the human genome.⁵ Most of these exist in two possible forms, reflecting variation in the sequence that arose as a new mutation many generations ago. At some loci, any of three or even all four DNA

bases (adenine, guanine, cytosine and thymine; A,G, C and T) may occur at measurable frequency in a population. Once a variant's frequency reaches 1% of all alleles in the population, such a variant is no longer considered a "mutation," but rather a "polymorphism." Recent advances in the rapidity and cost-effectiveness of DNA sequencing technologies have enabled the assessment of such variants as risk factors for a broad range of medical conditions. Association studies have been used for many years to search for genes that predispose to aetiologically complex diseases such as obesity, type 2 diabetes, heart disease and adult-onset dementia. Case-control studies that examine SNPs at "candidate" genes are often used, in which a gene is selected as a candidate based on the plausibility of its involvement in a molecular pathway relevant to the disease under study.

One often-overlooked pitfall of such an approach is that of the a priori equivalence of the two SNP variants. For most SNPs, no obvious functional effect will be discernible from visual inspection of the DNA sequence. If the SNP occurs in a protein-coding sequence and terminates the protein prematurely, one can have reasonable confidence that it has a true functional effect. Unfortunately, our ability to use theoretical algorithms to predict the biological effect of a particular SNP is relatively poor, apart from this rare situation. Most SNPs occur outside of coding areas, and most (even coding SNPs) will not change the amount or activity of any gene product. From a prior hypothesis standpoint, then, either SNP allele is equally likely to confer disease risk, but on a biological basis only one variant allele can confer increased risk,

and if the risk factor were any other type of risk factor (smoking, viral exposure, etc.), this variant would have to be defined as "exposed" before the study were carried out.

Consider the example of a C or T polymorphism at a specific locus. A human subject can then have SNP genotypes CC, CT or TT. With no obvious reason to prefer the C or T allele as the "at-risk" allele, a statistical association with the C or with the T allele remains equally plausible. This is somewhat akin to a situation in which "exposure to virus" is equally believable as a risk factor for heart disease as "lack of exposure to virus." Epidemiological studies concluding that "lack of exposure to virus" conferred

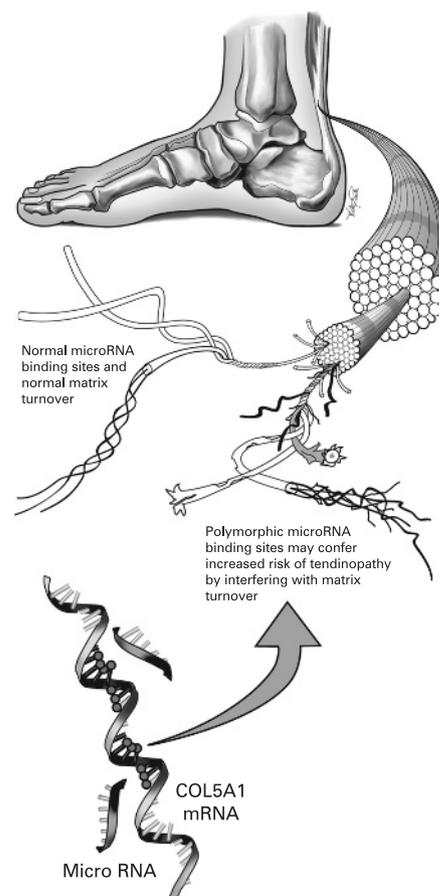


Figure 1 Postulated effect of *COL5A1* SNP on susceptibility to Achilles tendinopathy, according to September *et al.*¹

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