This editorial refers to ‘Components of the transforming growth factor-β family and the pathogenesis of human Achilles tendon pathology—a genetic association study’, by Michael Posthumus et al., doi:10.1093/rheumatology/keq072, on page 2090.

In this issue of Rheumatology, Posthumus et al. [1] report the results of a genotype association study in patients with Achilles tendon pathology vs normal Achilles tendons. The main finding is that individuals who carry a particular single nuclear polymorphism (SNP; specifically, the TT genotype of the GDF5 rs143383 variant) have twice the risk of developing Achilles tendon pathology compared with non-carriers.

Tendon pathology is widespread in the general population, and occurs in both physically active and sedentary individuals. Many overuse sporting injuries are caused by tendinopathies, and the annual cost of these diseases in the workplace amounts to billions of dollars. The condition is frequently disabling, often requiring early retirement from a sport or change of occupation. From this point of view, tendinopathy remains under-researched in comparison with other rheumatological disorders. Hence, the importance of the paper by Posthumus et al. [1], a distinguished group of South African researchers who have established themselves as leaders in the genetics of tendinopathy.

Classic studies have pointed towards a genetic component to the risk of developing tendinopathy, but the mechanisms have been elusive. A study on twins published in this Journal several years ago revealed a heritability of 40% for tendinopathy at the lateral epicondylose [2]. A study of siblings also suggested a strong genetic component for rotator cuff tears: having a sibling with rotator cuff symptoms meant five times the risk of developing symptoms, which cannot be explained by environment alone [3]. Despite these suggestions of a genetic tendency to develop tendinopathies, determining the responsible gene variants has been challenging [4].

This paper by Posthumus et al. [1] represents the strongest genetic association study on tendinopathies to date. Although this study is a relatively small one (171 subjects and 235 controls), several aspects of its design provide internal validation and support its potential relevance for tendinopathy clinical research. The study included Achilles tendinopathy or Achilles rupture patients recruited from two geographically distinct populations (South Africa and Australia), each with its own control cohort. Both patient populations showed an elevated frequency of rs143383 compared with the controls. The replication of the finding in two distinct populations makes this less likely to be a spurious association. Furthermore, the effect size of carrying the TT genotype of GDF5 rs143383 was large, conferring twice the risk of developing Achilles tendinopathy, which makes it unlikely to be a false-positive finding.

Statistical association of an SNP with the occurrence of a particular disease or condition does not constitute conclusive proof of its mechanistic involvement. However, in the case of this particular SNP, mechanistic proof already exists in previously published studies. The TT genotype of GDF5 rs143383 correlates with reduced expression of GDF5 in human soft tissues [5]. Furthermore, tendons from GDF5 knock-out mice contain roughly 40% less collagen than wild type [6], and demonstrate significantly impaired healing of tendons. Conversely, GDF5 transfection improves tendon healing in rats [7]. However, clinical evidence of GDF5 efficacy in tendinopathy, as with other growth factors, is currently lacking.

To date, several treatments are available that may promote recovery from tendinopathy, most notably heavy load exercise as described by Scandinavian groups. Despite the excellent clinical and biological research base supporting the use of exercise for tendinopathies, many patients do not respond to treatment. Clearly, prevention would be the best medicine for tendinopathies. In that regard, identifying the most at-risk patients could alert clinicians to those most in need of preventive efforts.

However, a caveat is that early results from preventive clinical trials have been discouraging. In an excellent study by Fredburg et al. [8], 209 Danish Super League football players were randomly selected by the team to receive specific, eccentric training for the Achilles and patellar tendons or standard training without eccentric training [8]. Contrary to the expectations, eccentric training resulted in an overall higher incidence of patellar tendinopathy. The study by Posthumus et al. [1] leads one to wonder whether patients with lower GDF-5 expression levels resulting from the TT genotype of the GDF5 rs143383 variant are less able to mount an adaptive response to mechanical loading, such that additional superimposed training exercise is more likely to cause harm.

The injury prevention research scheme by Bahr and Krosshaug [9] is helpful in contextualizing the importance of the current study by Posthumus et al. [1] (Fig 1). With only a limited understanding of the aetiology of tendinopathies, the right preventive measures may be targeted at the wrong patients. Bahr and Krosshaug make the additional point that for overuse injuries, predisposing factors are a key element of the injury mechanism. As such, the current study provides a key piece of data and will...
probably inspire many follow-up studies. Although it may be too soon to incorporate GDF-5 SNP testing into routine clinical care, it clearly needs inclusion in our tendinopathy research paradigm.

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