Institution: University of Northampton

Unit of Assessment: 3 – Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Research leads to genetic test that can help athletes and others avoid common sports injuries

1. Summary of the impact (indicative maximum 100 words)

Research led by Dr Stuart Raleigh at the University of Northampton's School of Health, in collaboration with Professor Malcolm Collins of the University of Cape Town, has identified genetic variants that predispose professional athletes and keen amateur sports persons to soft tissue musculoskeletal injuries. The genetic variants are particularly associated with damage to the Achilles tendon and rupture of the anterior cruciate ligament, one of the four main ligaments in the knee.

The findings have led to tests that can identify individuals with these genetic variants. The tests have been commercialised through four international patents. They are used, together with information on lifestyle and level of activity, to assess a person's risk of injury. Armed with this knowledge, individuals can change their lifestyle to prevent possible injury. Reducing injuries would reduce the cost of care.

2. Underpinning research (indicative maximum 500 words)

Genetic basis for common sports injuries: Damage to the Achilles tendon (in the heel) and the anterior cruciate ligament (ACL, in the knee) are two of the most common sports injuries. In 2005, research showed that physically active individuals who injured their Achilles tendons often shared genetic characteristics. Professor Malcolm Collins' research group at the University of Cape Town showed that mutation within specific genes (the tenascin C (TNC)[1] and Collagen 5A1 (COL5A1)[2] genes) was significantly associated with damage to the Achilles tendon (Achilles tendinopathy, ATP). These two genes carry the genetic information that is responsible for producing proteins that play a part in regulating and maintaining the structure of tendon tissue. The group also suggested that genes that carry the genetic instructions to code for proteins with other roles within the tendon, e.g. repair, might also influence the risk of musculoskeletal soft tissue injury.

In 2009 Dr Stuart Raleigh, then a Senior Lecturer in Human Biology at The University of Northampton, led work that demonstrated that mutations in three sections (three single nucleotide polymorphisms or SNPs– rs679620, rs591058 and 650108) within the MMP3 gene (a gene involved in regulating the extracellular matrix of tendons) were significantly associated with ATP in a South African study cohort[3].

Gene interaction; effects may be population-specific: Raleigh and co-workers also determined that mutation in one of the sections (rs679620) in the MMP3 gene interacted with the COL5A1 mutation identified by Collins. They established that South African individuals with both mutations were at even greater risk of ATP than individuals with one mutation[3]. However, the MMP3 variant was not found to be a risk factor for ATP in Australians, indicating that the risk may be population-specific.

The GDF-5 gene is involved with growth and repair within the tendon, and carries the genetic coding for growth differentiation factor 5 protein. Research in 2010 led by Raleigh and colleagues on a group of participants made up of both Australians and South Africans found that a variant SNP (rs143383) within the GDF-5 gene was a risk factor for ATP[4]. Since these initial findings, further work by South African colleagues has identified additional candidate gene SNPs that make people more susceptible to ATP[5] and it is likely that there may be more.

Implementing the research findings: Taken together, the information acquired by these studies has been used to select the SNPs in DNA samples to be analysed. Screening for these SNPs, combined with information on lifestyle, can be used to predict a person's risk of soft tissue injury.

The use of selected SNPs for determining risk of soft tissue injury was patented in 2011. The private healthcare company gknowmix (http://www.gknowmix.com/) now offers the tests.

The initial work on the MMP3 and GDF5 gene SNPs was conducted as a collaborative venture headed by Dr Stuart Raleigh (now Reader in Molecular Biology) in the University of Northampton School of Health and the group led by Professor Malcolm Collins at the University of Cape Town/South African MRC Unit for Exercise Science and Sports Medicine, South Africa (UCT/MRC). Collaboration to both identify additional risk-related genotypes (individuals with specific genetic makeup that puts them at risk in this respect), and to understand the population-specific nature of the risk these variants carry is on-going. This will improve targeting of individuals at risk.

3. References to the research (indicative maximum of six references)

1. Mokone GG, Gajjar M, September AV, Schwellnus MP, Greenberg J, Noakes TD,Collins M. The guanine-thymine dinucleotide repeat polymorphism within the tenascin-C gene is associated with achilles tendon injuries. Am J Sports Med.2005 Jul; 33(7):1016-21.

2. Mokone GG, Schwellnus MP, Noakes TD, Collins M. The COL5A1 gene and Achilles tendon pathology. Scand J Med Sci Sports. 2006 Feb; 16(1):19-26.

3. Raleigh SM, van der Merwe L, Ribbans WJ, Smith RK, Schwellnus MP, Collins M. Variants within the MMP3 gene are associated with Achilles tendinopathy: possible interaction with the COL5A1 gene. Br J Sports Med. 2009 Jul; 43(7):514-20.

4. Posthumus M, Collins M, Cook J, Handley CJ, Ribbans WJ, Smith RK, Schwellnus MP, Raleigh SM. Components of the transforming growth factor-beta family and the pathogenesis of human Achilles tendon pathology – a genetic association study. Rheumatology (Oxford). 2010 Nov; 49(11):2090-7.

5. Abrahams Y, Laguette MJ, Prince S, Collins M. Polymorphisms within the COL5A1 3'-UTR that alters mRNA structure and the MIR608 gene are associated with Achilles tendinopathy. Ann Hum Genet. 2013 May; 77(3):204-14.

4. Details of the impact (indicative maximum 750 words)

Musculoskeletal soft tissue injuries such as damage to the Achilles tendon and rupture of the anterior cruciate ligament, one of the four main ligaments in the knee, are prevalent in both recreational and elite athletes. The Achilles tendon is the tendon in the lower leg athletes most commonly injure and is the most common to rupture spontaneously[1]. Injury to this tendon alone is estimated to affect around 10% of the general population and 50% of elite male distance runners[2]. Affected individuals can suffer long-term disability and, in some cases, require surgery[3]. A recent US study found that rupture of the Achilles tendon has increased over recent years, and 68% of cases were associated with sports activity.[4] Likewise data from the US suggests that between 100,000 and 250,000 surgical reconstructions occur annually due to ACL rupture[5]. With the growing popularity of sport increases in these injuries are more likely, with a corresponding increase in burden on healthcare services.

Identifying people at risk will mean that, by taking preventative measures such as changing training programmes or sporting behaviours, they are likely to reduce the incidence of injury with a commensurate reduction in pain, disability and long-term physical inactivity. Injury to these tendons and ligaments means formerly active people cannot exercise, which increases their likelihood of gaining weight making them more at risk of cardiovascular disease and other diseases related to over-weight such as late onset diabetes, with a further economic impact on health services.

The economic benefit of this genetic screening test, in terms of reduced healthcare costs, has not yet been fully estimated. However preventing such injuries is anticipated to make a substantial cost saving, in terms of reducing the need for treating patients. For example, it has been estimated that in the US the annual cost of reconstructive surgeries due to ACL rupture exceeds one billion

dollars[5]. One current UK estimate for self-funding patients is £6,101 to treat a ruptured Achilles tendon and £6,260 for ACL repair, plus approximately £500 in each case for diagnostics and a further £1,000 for braces and physiotherapy[6].
The research findings that genetic mutations appear to increase the risk of these injuries were disseminated from 2005 to 2013 through publications in the scientific literature (section 3, refs 1-5). As the research developed there were presentations at international conferences aimed at informing practitioners such as clinicians and sports professionals of the implication of the results of the research. At a conference (the Clinical Sports Medicine Conference Cape Town, South Africa, October 2010), which explored the interaction between biomedical scientists and sports injury clinicians, Dr Raleigh gave two presentations on his work[7]. The research was also presented to those involved in sport at an elite level, for example via the annual meeting of the International Olympic Committee, in Monaco, April 2011[8].

This collective effort by Dr Raleigh and Professor Collins[9] resulted in the successful filing in 2011 of four international patents[10] for a genetic screening test. The patents were filed by the South African Medical Research Council in collaboration with the University of Northampton and Cape Town University. The Sport Injury Genescreen™ is now being used, in combination with patients' lifestyle data, to predict their risk of certain musculoskeletal soft tissue injuries. In South Africa, the private healthcare company gknowmix (http://www.gknowmix.com/) has been granted the licence for using the patented gene screen invention to assess individuals' risk of sustaining a musculoskeletal injury, such as an Achilles tendinopathy or cruciate ligament rupture. Gknowmix commercialised this test because its development and impact fitted with their mission *'To engage clinicians and medical scientists in the development and implementation of innovative Pathology Supported Genetic Tests™',* and their vision *'To provide a global genetic testing service delivery system and database tool for seamless conversion of research and innovation'.*

An important part of the concept for gknowmix is the integration of the tests themselves and the expert report written and approved by the scientist involved in the development of the tests. This ensures that the patient and requesting clinician are aware of all the implications of the results of the tests and lifestyle analysis, and the interventions required to reduce risk. As such Prof Collins is now approving test reports for clinicians in South Africa and Dr Raleigh will be in the UK. The availability of the tests was marketed by gknowmix online in March 2013 at a cost of £140, with the first requests being received in August. As of summer 2013, twenty South Africans have benefited from DNA analysis and assessment of their risk of musculoskeletal injury. Athletes from Slovenia are currently undergoing screening[9].

A similar Pathology-Supported Genetic Testing (PSGT) algorithm for breast cancer screening also marketed by gknowmix has recently been estimated In a South African study to save 600m Rand in chemotherapy costs[9]. Although it is difficult to make a direct comparison, this does demonstrate the power of PSGT to save healthcare costs and patient distress.

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Thompson J, Baravarian B. Acute and chronic Achilles tendon ruptures in athletes. ClinPodiatr Med Surg. 2011 Jan;28(1):117-35. doi: 10.1016/j.cpm.2010.10.002.

2. September AV, Posthumus M, Collins M. Application of genomics in the prevention, treatment and management of Achilles tendinopathy and anterior cruciate ligament ruptures. Recent Patents on DNA & Gene Sequences 2012; 6: 216-223.[Cites section 3 Ref 1 Mokone 2005: p 219, Ref 2 Mokone 2006: pp 217, 218, Ref 3 Raleigh 2009: p 221, Ref 4 Posthumus 2010: p220

3. Den Hartog BD. Insertional Achilles tendinosis: pathogenesis and treatment. Foot Ankle Clin. 2009 Dec;14(4):639-50.

4. Raikin SM, Garras DN, Krapchev PV. Achilles tendon injuries in a US population. Foot & Ankle

International 2013; 34(4): 475-480.

5. Hewett TE, Lynch TR, Myer GD, Ford KR, Gwin RC, Heidt RS Jr. Multiple risk factors related to familial predisposition to anterior cruciate ligament injury: fraternal twin sisters with anterior cruciate ligament ruptures. Br J Sports Med.2010;44(12):848-55.

6. Current patient prices supplied by Professor W Ribbans, The County Clinic, 57 Billing Road, Northampton, UK (wjribbans@uk-consultants.co.uk).
7. Presentations at 4th Clinical Sports Medicine Conference, Cape Town, South Africa, October 2010 by Dr Raleigh entitled Sequence variation within the Matrix Metalloproteinase genes and the predisposition to musculoskeletal soft tissue injury and pathology (invited talk) and Possible epigenomic factors that might predispose to musculoskeletal soft tissue injury and pathology.

8. Posthumus M, Collins M, Van der Merwe L, O'Cuinneagain D, Van der Merwe W, Ribbans WJ, Schwellnus M, Raleigh SM (2010). Matrix Metalloproteinase genes on Chromosome 11q22 and the risk of anterior cruciate ligament (ACL) rupture. Presented at the 2011 meeting of the International Olympic Committee, Monaco, April 2011.

9. For confirmation of the research collaboration and its implementation:

Chief Specialist Scientist South African Medical Research Council/Head of UCT/MRC Research Unit for Exercise Science and Sports Medicine, University of Cape Town, SA.
Senior Research Officer, UCT/MRC Research Unit for Exercise Science and Sports Medicine, University of Cape Town, SA.
Executive Director, gknowmix

10. Details of patents:

Collins M, Raleigh SM, Ribbans WJ, Schwellnus MP, Smith RKW. Genetic Risk Factors for Tendon and Ligament Injuries. South Africa. ZAxPCTIB09/05489, 2011.

Collins M, Raleigh SM, Ribbans WJ, Schwellnus MP, Smith RKW. Genetic Risk Factors for Tendon and Ligament Injuries. United States. 13/127,668, 2011.

Collins M, Raleigh SM, Ribbans WJ, Schwellnus MP, Smith RKW. Genetic Risk Factors for Tendon and Ligament Injuries. Europe. 09824482.5, 2011.

Collins M, Raleigh SM, Ribbans WJ, Schwellnus MP, Smith RKW. Genetic Risk Factors for Tendon and Ligament Injuries. Australia. 2009312451, 2011.