

Research article

## Epigenetic Status of The Human *MMP11* Gene Promoter is Altered in Patellar Tendinopathy

Rebecca Rickaby<sup>1,2</sup>, Louis Y El Khoury<sup>3</sup>, Tom Samiric<sup>4</sup> and Stuart M Raleigh<sup>5</sup>✉

<sup>1</sup> Faculty of Health and Society, University of Northampton, UK; <sup>2</sup> Faculty of Science, School of Pharmacy, University of Nottingham, UK; <sup>3</sup> Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester, MN, USA; <sup>4</sup> School of Life Sciences, La Trobe University, Melbourne, Victoria, Australia; <sup>5</sup> Centre for Sport, Exercise and Life Sciences, Coventry University, UK

### Abstract

Patellar tendinopathy (PT) is a debilitating condition that often affects those who are physically active. Gene variation is known to contribute to human tendinopathy but the role of DNA methylation, as an epigenetic factor, has only recently been discovered. Using a case-control approach, we sought to determine whether differences existed between the methylation status of the *MMP11* gene promoter in patellar tendinopathy compared to healthy tendon. We used PCR and pyrosequencing to interrogate the methylation profiles of 4 CpG sites (areas of the genome rich in C/G nucleotides) upstream of the *MMP11* gene in DNA from males with PT (n = 10) and those with healthy tendon (n = 10). We also conducted a correlation analysis to establish whether age influenced methylation in the PT patients and controls. We found a significant (p = 0.045) difference in the methylation status of a single CpG site 65 base pairs (bp) upstream of the *MMP11* promoter between the PT group and controls. There were no other differences in the extent of *MMP11* promoter methylation between the two groups. Interestingly, we also found that in controls the degree of methylation at a second CpG site, 55 bp upstream of the first exon, tentatively correlated (r = 0.77, p = 0.009) with age. However, the correlation did not reach significance when a potential outlier was removed. This is the first study to show an epigenetic alteration to a member of the *MMP* gene family in human patellar tendinopathy. The data add to our understanding of how epigenetics should be considered when developing appropriate risk models.

**Key words:** Tendon, genetics, epigenetics, sports injury, tendinopathy .

### Introduction

Patellar tendinopathy (PT), is an exercise-associated injury that results in significant disability and can compromise the career of an athlete (Peers and Lysens, 2005). The prevalence of PT is high in sports, such as volleyball (44.6% ± 6.6%) and basketball (31.9% ± 6.8%) (Lian et al., 2005) and it accounts for up to 15% of the soft tissue injuries reported in military cohorts (Rutland et al., 2010). Recently, a study by Bode et al. (2017) found prevalence rates as high as 13.4% in young elite level soccer players (Bode et al., 2017). Furthermore, in addition to the type of sports participation, the duration of training, female gender and hamstring flexibility have all been shown to affect the risk of PT (Morton et al., 2017). There is also some evidence to suggest that both back pain and a family history of tendon problems might be related to the risk of PT (Morton et al.,

2017).

From a histological perspective, the development of PT is associated with neovascularisation, an increase in collagen type III fibers and an accumulation of glycosaminoglycans (Rosso et al., 2015). Such changes may, in part, be due to the altered expression of matrix metalloproteinase (MMP) enzymes that have been shown to have an important role in regulating tendon extracellular matrix (ECM) homeostasis (Del Buono et al., 2013). Interestingly, genetic variation within genes (like the *MMPs*), that code for enzymes that regulate ECM homeostasis, are known to impact on Achilles tendinopathy risk (Raleigh and Collins, 2012; Collins and Raleigh, 2009). However, genetic association studies conducted to identify risk variants have sometimes yielded conflicting data. For example, Raleigh et al. (2009) demonstrated that the G allele of the rs679620 variant within the *MMP3* gene increased the risk of Achilles tendinopathy in a South African study, whereas the same variant in a British cohort did not increase risk (El Khoury et al., 2016). Likewise, the *COL5A1* rs12722 T variant has been shown to increase risk of Achilles tendinopathy in both South African and Australian cohorts (September et al., 2009) but in British Caucasians this variant does not modify risk (Brown et al., 2017).

We recently suggested that epigenetic modifications, such as DNA methylation, might explain discrepant association signals sometimes obtained in studies on human patellar tendinopathy (El Khoury et al., 2018). Indeed, we demonstrated that methylation changes to a CpG site upstream of the *ADAMTS4* promoter were associated with patellar tendinopathy (El Khoury et al., 2018). However, to date, and as far as we are aware, no other research has been published to address the impact of DNA methylation on the risk of human tendinopathy.

The *MMP11* enzyme catalytically degrades several components of the extracellular matrix (ECM) including aggrecan, fibronectin and laminin (Araki and Mimura, 2017). Although the detailed role that *MMP11* plays in ECM homeostasis is poorly understood, the expression of *MMP11* in Achilles tendinopathy is substantially affected. For example, it has been shown that *MMP11* RNA levels are both five and six-fold higher in painful and ruptured Achilles tendon respectively, compared to control tissue (Jones et al., 2006). Furthermore, *MMP11* expression decreases nearly twofold in human Achilles tenocytes that have been subjected to mechanical strain (Jones et al., 2013). Although these observations may infer a role for

MMP11 in tendinopathy, the mechanisms underlying the observations are unknown.

The *MMP11* gene was originally mapped to chromosome 22 (Anglard et al., 1995). Multiple transcripts are encoded within the region 24,110,413-24,126,503 (GRch37-hp19 at: <https://grch37.ensembl.org/index.html>) and expression is known to be altered by DNA methylation (Navarro et al., 2012). Specifically, hypomethylation is associated with transcriptional upregulation of *MMP11* (Navarro et al., 2012). With this in mind, we hypothesized that the methylation status of the *MMP11* promoter might differ in DNA isolated from patellar tendinopathy compared to normal tendon. If this were the case, such differences in methylation might explain why *MMP11* expression is substantially altered in tendinopathy and lead the way to novel strategies that could reduce the incidence of these injuries.

## Methods

Patellar tendon tissue was obtained from 10 males with healthy patellar tendons (CON) and 10 males with patellar tendinopathy (PT). The CON samples were from patients undergoing ACL reconstruction surgeries using a patellar tendon graft and had no history of tendinopathy. Controls also had magnetic resonance imaging (MRI) to confirm their injury. The PT samples were from patients undergoing surgical debridement for recalcitrant overuse patellar tendinopathy (Parkinson et al., 2010). The PT specimens all had ultrasound scans (US) or MRI confirmation of the diagnosis by a medical doctor. PT samples were taken from the proximal tendon. Normal (CON) tendons were also taken from the proximal end, at the margins of the graft. Participants were Caucasian, aged from 19 to 41 years and they were all otherwise healthy. All participants provided written informed consent and approval for this study was obtained from the University of Northampton's School of Health Research Ethics Committee.

We originally extracted, and bisulfite treated, the DNA from these samples as described in our previous study (El Khoury et al., 2018). Hence for this study we re-interrogated the same DNA samples using a pyrosequencing assay specific for the *MMP11* gene (Hs\_CHCHD10\_01\_PM) promoter that was selected from the Pre-Designed PyroMark® CpG Assays (Qiagen, Hilden, Germany). Using this assay, we measured the methylation statuses of 4 separate CpG sites that were -38 (CpG 1), -55 (CpG 2), -58 (CpG 3) and -65 (CpG 4) bp respectively from the first exon of the *MMP11* gene (transcript 003, GRch37, hg19).

The bisulfite treated DNA samples were amplified on a Techne TC-512 thermocycler (Bibby Scientific Ltd, Staffordshire, UK), using the PCR primer sets of the PyroMark® CpG Assay. This amplified the specific region of interest (141 bp amplicon product) within the *MMP11* gene promoter at 31 bp from the first exon. PCR amplification was confirmed by running the products on a 1x agarose gel alongside a GeneRuler™ 100 bp ladder (MBI Fermentas, UK).

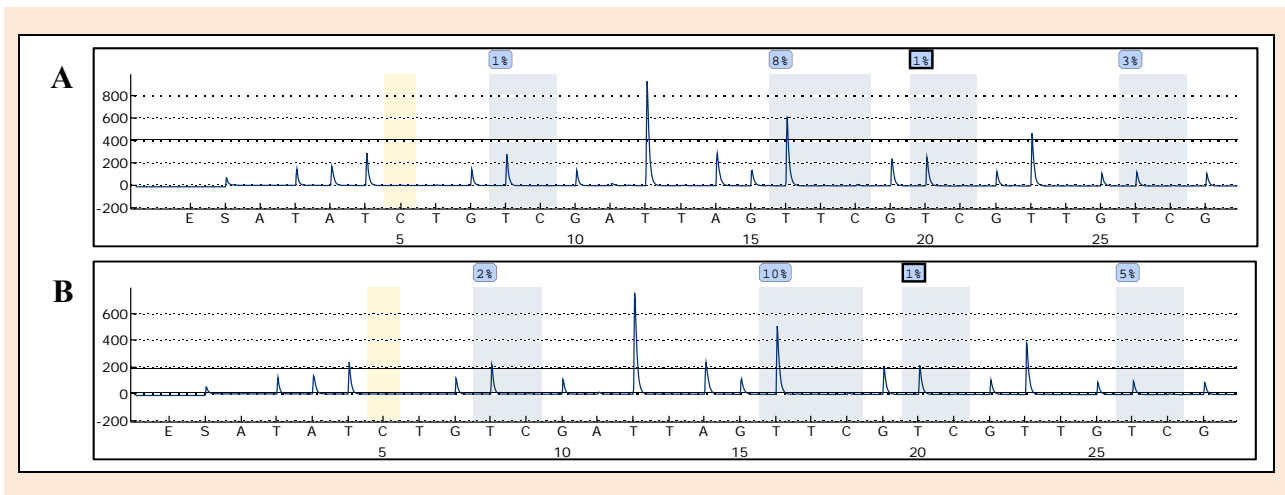
Following gel electrophoresis, the biotinylated PCR products were immobilized to Streptavidin-coated Sepharose high-performance beads (GE Healthcare, Buckinghamshire, UK). The PyroMark® Q24 vacuum (Qiagen, Hilden, Germany) was used to capture the immobilized PCR products, before releasing them into a 24 well PyroMark® Q24 plate containing 1x sequencing primer diluted in 25 µl PyroMark® Annealing Buffer. In order for the sequencing primer to anneal to samples, the PyroMark® Q24 plate was placed on a hot-plate at 80 °C for 2 min, followed by 10 min incubation at room temperature. The samples were then loaded into the PyroMark® Q24 for pyrosequencing. Each run included hypo and hyper methylated DNA control samples.

We used PyroMark® Q24 (Version 2.0.6) software to analyse the percent methylation of each CpG site in both PT and CON groups. An independent samples t-test was used to establish whether significant differences ( $p < 0.05$ ) existed between each CpG site in PT and CON groups, based on a normal distribution of our data. We also determined the effect of age on methylation status by conducting a Pearson's correlation analysis for each CpG site in the PT, CON and combined groups. All data analyses were performed using SPSS Version 20 (IBM Corp. Armonk, NY).

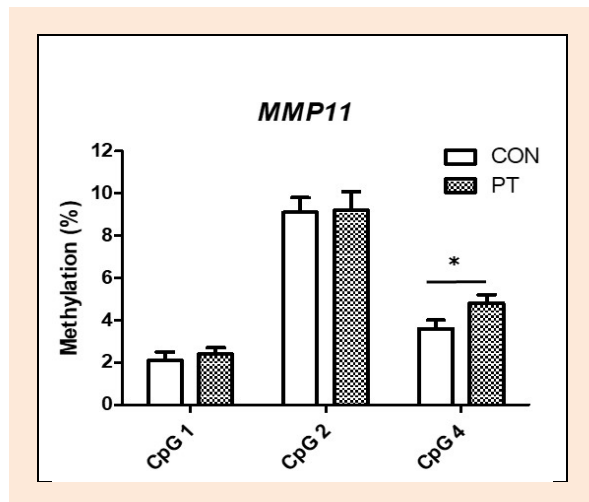
## Results

The recruited CON and PT groups were similarly matched for age ( $p = 0.449$ ). Typical pyrograms showing the percentage DNA methylation at the 4 CpG sites within the *MMP11* gene promoter (panels A and B) are shown in Figure 1. We found a significant difference ( $p = 0.045$ ) in DNA methylation between the CON and PT group at the CpG 4 site that sits 65 bp upstream of the *MMP11* first exon (Figure 2). At this CpG site, the mean percentage methylation in the PT samples was  $4.8 \pm 0.4$  (95% CI 3.98 to 5.66) compared to the CON value of  $3.6 \pm 0.4$ , (95% CI 2.88 to 4.33). The effect size (Cohens  $d$ ) for this difference was 0.966. We were unable to quantify the methylation status at CpG site 3 in both the CON and PT groups as the data did not meet an acceptable quality control standard. The reason for this, at present, is unknown. Finally, we found no additional differences in methylation status, for each CpG site measured, between the CON and PT groups.

In addition, for the CON group, we found a tentative correlation ( $r = 0.77$ ;  $p = 0.009$ ) between participant age and degree of methylation at the CpG 2 site (Figure 3A). However, the correlation failed to reach significance ( $p > 0.05$ ) when a potential outlier was removed. By comparison there was no correlation ( $r = 0.11$ ;  $p = 0.764$ ) between participant age and degree of methylation at the CpG 2 site in the PT group (Figure 3B). Furthermore, there were no other correlations between age and degree of methylation at any of the other CpG sites measured in both the CON and PT groups. Indeed, when the analyses were pooled to contain both groups, there were no additional correlations. The mean age of the CON and PT groups was  $25.1 \pm 6.4$  and  $23.2 \pm 4.4$  years respectively.



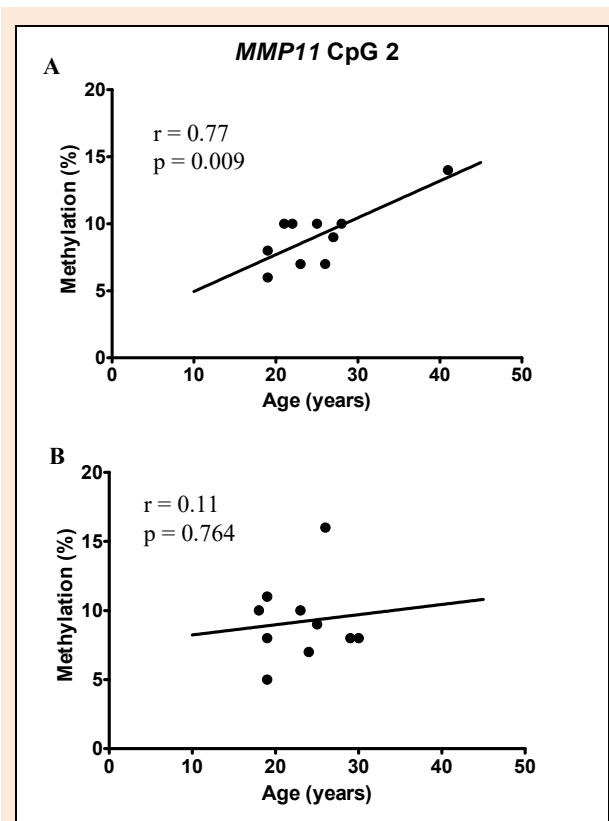
**Figure 1 (Panel A-B).** Typical Pyrograms showing methylation status at CpG sites within the *MMP11* gene promoter from control and PT samples. The CpG sites are shown shaded in blue/grey with the percentage (%) methylation above each site. Yellow shaded areas are bisulfite controls. **Panel A**) Percentage methylation at four CpG sites within the *MMP11* gene promoter from a CON sample. **Panel B**) Percentage methylation at four CpG sites within the *MMP11* gene promoter from a PT sample. Sites from left to right are: -38 (CpG 1), -55 (CpG 2), -58 (CpG 3) and -65 (CpG 4) bp respectively from the first exon of the *MMP11* gene.



**Figure 2.** Comparison of the mean DNA methylation between the CON and PT groups within the promoter region of the *MMP11* gene. Sites are: -38 (CpG 1), -55 (CpG 2) and -65 (CpG 4) bp respectively from the first exon of the *MMP11* gene. Bars represent mean (%)  $\pm$  standard error of the mean (SEM). CON, white bars and PT, shaded bars. \*,  $p = 0.045$ .

## Discussion

We have shown a statistically significant difference ( $p = 0.045$ ) in DNA methylation at a CpG site (CpG 4) in the *MMP11* gene promoter in patellar tendinopathy, compared to controls. This CpG site lies 65 bp upstream of the *MMP11* gene and showed higher methylation in the PT group. At present we do not know why this change takes place but methylation changes to the *MMP11* gene are known to alter *MMP11* RNA expression levels (Navarro et al., 2012). For example, hypomethylation causes an increase in *MMP11* (Navarro et al., 2012). Indeed, it is possible that hypomethylation of the *MMP11* gene promoter may, in part, explain the elevated levels of *MMP11* mRNA expression previously observed in both ruptured and painful Achilles tendon (Jones et al., 2006) compared to normal tendon.



**Figure 3. A)** Correlation between age and degree of DNA methylation at CpG 2 in the CON group ( $r = 0.77$ ,  $p = 0.009$ ). **B)** Lack of correlation between age and degree of DNA methylation at CpG site 2 in the PT group ( $r = 0.11$ ,  $p = 0.764$ ). CpG 2 is 55 bp upstream of the *MMP11* TSS.

Interestingly, we found a hypermethylation (not hypomethylation) event within the *MMP11* promoter in PT samples compared to controls. Hypermethylation is typically associated with reduced gene expression (Roach et al., 2005). Therefore it might be expected that *MMP11* substrates accumulate within PT, as the amount of *MMP11* enzyme available for catalysis would become limited. Indeed,

proteoglycan accumulation has been observed in PT. Specifically, Parkinson and colleagues found increased levels of proteoglycans such as aggrecan in the tendon samples from patients that were used in this study (Parkinson et al., 2011). Normally aggrecan can protect tendon from damage as it binds to water molecules, aiding hydration and reducing the effect of over compression (Riley, 2004; Cook and Purdam, 2012). However over-hydration can lead to swelling in tendinopathy (Parkinson et al., 2011) and it is possible that hypermethylation of the *MMP11* promoter might exacerbate this process.

It is interesting that we found a tentative correlation between age and degree of methylation at CpG site 2 that sits 55 bp upstream of the *MMP11* first exon. This correlation was apparent in the CON group but not in DNA from those with PT. However, this result must be considered preliminary as when we removed a potential outlier from the data set the correlation disappeared. Although we cannot yet comment on the significance of this finding, it is possible that an increase in methylation in the promoter of the *MMP11* gene might be necessary to allow for ECM adaptations as a person ages. Therefore, the lack of correlation between age and CpG methylation observed by us in the PT group may indicate an abnormal promoter methylation pattern that precedes tendinopathy. However, this will need to be verified by additional research.

In this study, we looked at the methylation statuses of several CpG sites upstream of the *MMP11* gene in DNA from males with PT and compared them to controls. We found a significant difference (hypermethylation) in the methylation profile between these two groups for the CpG site 4 that is -65 bp away from the start of the gene. Although most studies relating to DNA methylation in musculoskeletal disorders report more extensive methylation changes over numerous CpG rich regions (Reynard, 2017), there is compelling evidence that methylation changes at single CpG sites can also have profound effects. For example, we have previously shown that methylation change at a single CpG site within the *ADAMTS4* gene promoter also associates with PT (El Khoury et al., 2018). Furthermore, Nile and colleagues (2008) have shown that single CpG site methylation changes alter interleukin-6 expression, which impacts on the pathogenesis of rheumatoid arthritis (Nile et al., 2008). Methylation of single CpG sites upstream of the *SLC23A* and *NCOR2* genes are also known to influence the severity of spinal muscular atrophy (Zheleznyakova et al., 2015).

Although we have shown that the degree of methylation, at a single CpG site -65 bp away from the start of the *MMP11* gene differs in patellar tendinopathy compared to healthy tendons our study does have limitations. Firstly, as we only had access to a limited amount of sample for each patient we were unable to measure the mRNA expression levels of *MMP11*. However, previous studies have shown that *MMP11* promoter methylation does influence its expression (Navarro et al., 2012; Veerla et al., 2008). Secondly, we only investigated a small section of the promoter for *MMP11* transcript 003 and additional work should focus on other regions. Thirdly, the clinical samples available for this study were from a small group of male Caucasians and the same results might not be obtained in female or

non-Caucasian groups. Indeed, we would recommend repeating this study in different population cohorts to establish whether similar DNA methylation events are observed across populations. Finally, although there were no differences between age in our PT and control groups, we were unable to control for both weight and height as these data were not available to us at the time of sampling.

## Conclusion

We provide the first preliminary data that suggests DNA methylation of a member of the *MMP* family of genes differs in patellar tendinopathy compared to healthy tendon. Our data add to our earlier work on the epigenetics of human tendinopathy and suggest that risk assessment, on the basis of genetics alone, is incomplete without a knowledge of epigenetic factors.

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✉ **Dr Stuart Raleigh**

School of Life Sciences, Centre for Sport, Exercise and Life Sciences, Coventry University, Coventry, CV1 5FB, UK

### Key points

- An understanding of the epigenetics of tendinopathy leads the way to possible future preventative strategies, as epigenetic factors can be modified by the environment. Hence, we speculate that specific changes to training, diet and possibly training surface and climate, informed by epigenetics, could reduce incidence of these injuries.
- DNA methylation changes, including those reported here in the *MMP11* gene promoter, may partially explain the different patterns of genetic risk factors that are sometimes observed between different population cohorts.
- DNA methylation patterns coupled with genomic factors and other epigenetic markers, such as miRNA expression profiles, will improve current risk models for tendinopathy.

### AUTHOR BIOGRAPHY



**Rebecca RICKABY**

**Employment**

A Teaching Associate, University of Nottingham's School of Pharmacy, UK

**Degree**

PhD

**Research interest**

DNA methylation and genetic variation and how they contribute to a number of diseases.



**Louis Y El KHOURY**

**Employment**

A Senior Research Fellow in Epigenomics at the Mayo Clinic, USA

**Degree**

PhD

**Research interest**

The genetic and epigenetic basis of common human diseases.



**Tom SAMIRIC**

**Employment**

Senior Lecturer at the School of Life Sciences, La Trobe University, Melbourne, Australia

**Degree**

PhD

**Research interest**

Extracellular matrix changes during overuse tendinopathy.



**Stuart M RALEIGH**

**Employment**

Senior Lecturer in Biosciences at Coventry Univ.'s School of Life Sciences, UK

**Degree**

PhD

**Research interest**

Genetic and epigenetic mechanisms related to musculoskeletal pathologies. Novel biomarkers for dementia and the link between exercise and cognition.

**E-mail:** ac8510@coventry.ac.uk