Association of *MMP3* but not *TIMP2* gene variants with elite rugby player status and rugby code

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Introduction

Achilles tendon pathology and anterior cruciate ligament rupture are multifactorial conditions for which genetic risk factors have been identified[1,2,3]. Single nucleotide polymorphisms (SNPs) within the *MMP3* (rs591058, rs679620, rs650108) and *TIMP2* (rs4789932) genes have previously been associated with tendon and ligament pathologies[4,5,6,7]. Although not entirely clear, prior literature indicates the risk alleles for Achilles tendon pathology as T (rs591058), G (rs679620) and A (rs650108) for *MMP3*. However, prior evidence regarding *TIMP2* is equivocal[4]. *MMP3* is considered an essential regulator of matrix degradation and remodelling within diseased and normal musculoskeletal soft tissues[8]. *TIMP2* maintains homeostasis in the extracellular matrix in part by inhibiting MMP function. Given the high incidence and severity of tendon and ligament injuries in elite rugby athletes, we hypothesised that the aforementioned SNPs would be associated with career success.

Method

Participants were from the RugbyGene project, comprising elite Caucasian male rugby athletes (n = 528; mean (standard deviation) height 1.85 (0.07) m, mass 101 (14) kg, age 29 (7) yr), including 420 rugby union (RU) athletes that for some analyses were divided into forwards and backs and 108 rugby league (RL) athletes. Non-athletes were 592 Caucasian men and women (57% male, height 1.72 (0.10) m, mass 74 (14) kg, age 31 (7) yr). PCR of genomic DNA was used to determine genotypes using TaqMan probes, then groups were compared using χ^2 and odds ratio (OR) statistics.

Results

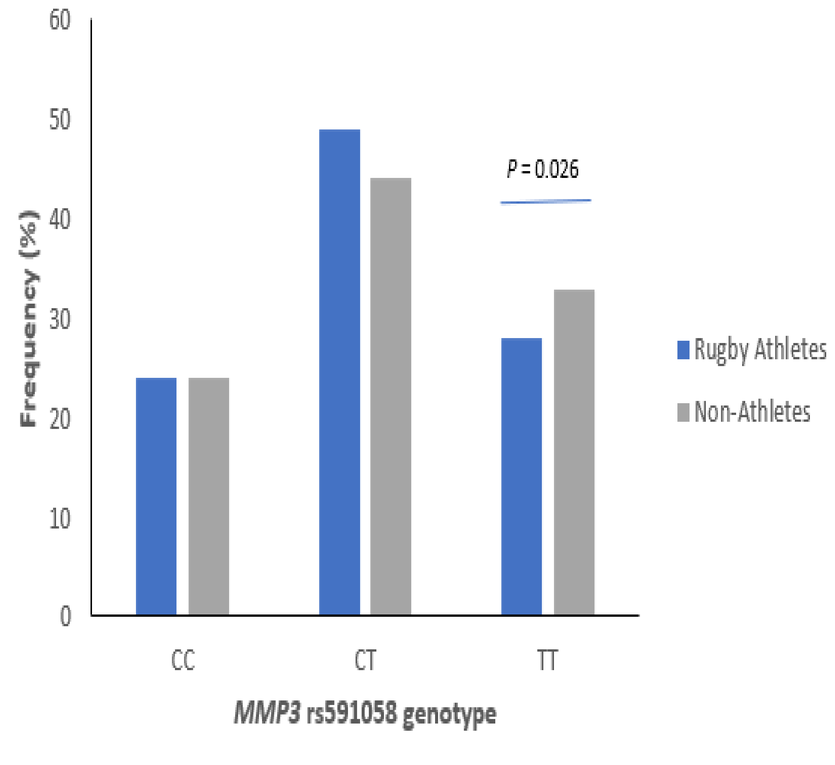

Figure 1. *MMP3* rs591058 genotype frequencies of all rugby athletes and non-athletes

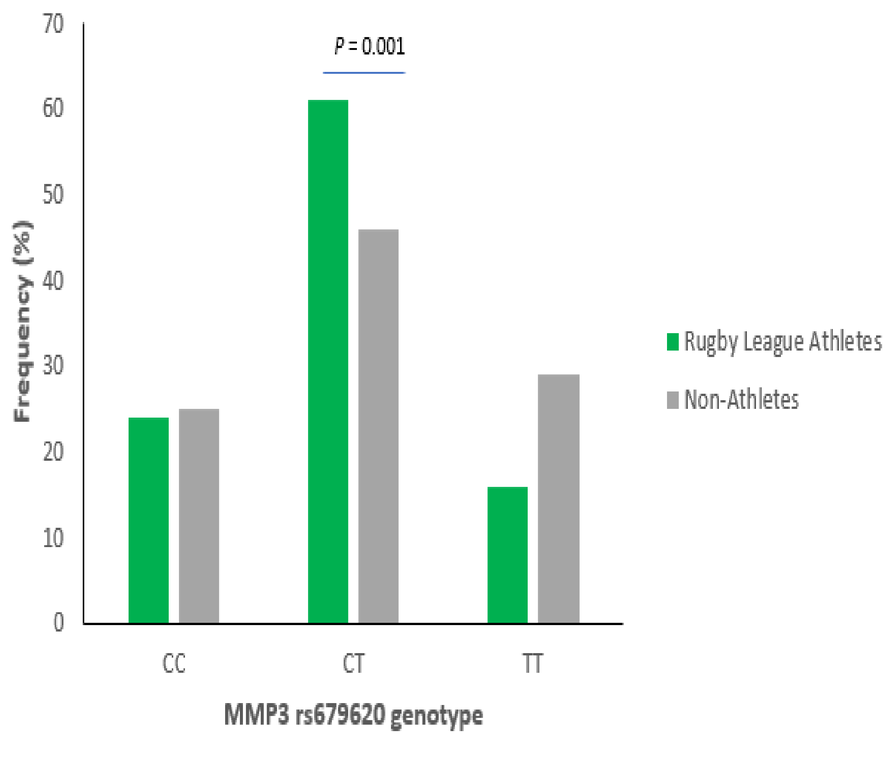

Figure 2. *MMP3* rs679620 genotype frequencies of rugby league athletes and non-athletes

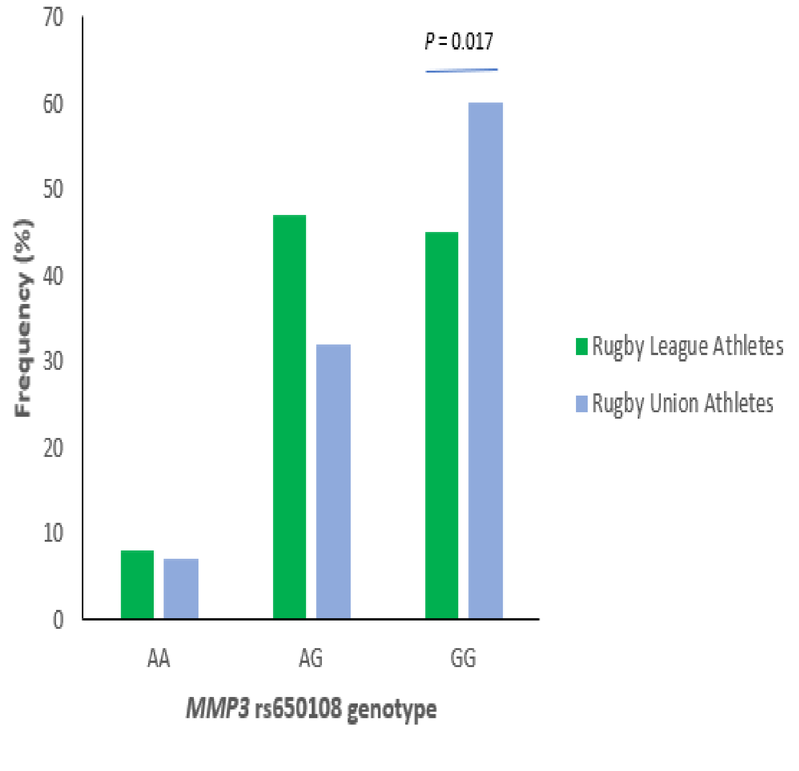

Figure 3. *MMP3* rs650108 genotype frequencies of rugby league athletes and rugby union athletes

As hypothesized, the *MMP3* rs591058 risk genotype (TT) was less frequent in rugby athletes (28%) compared to non-athletes (33%) (Figure 1) (χ^2 = 7.265, *P* = 0.026; OR = 1.18, 95% confidence intervals (CI) = 0.86-1.63). No differences were found for *MMP3* rs679620, rs650108 or *TIMP2* rs4789932 between rugby athletes and non-athletes. When RL athletes were compared to non-athletes, the risk genotype (TT) of *MMP3* rs591058 was underrepresented in RL athletes (19%) compared to non-athletes (33%). The *MMP3* rs679620 'protective' allele (C) was more frequent in RL athletes (55%) compared to non-athletes (48%) (OR = 1.3, 95% CI = 0.98-1.74) (Figure 2). However, for *MMP3* rs650108 the 'risk' allele (A) was overrepresented in RL athletes (32%) compared to non-athletes (26%). There were no genotype differences for any gene variant between RU athletes and non-athletes. The 'risk' allele (T) of the *MMP3* rs679629 polymorphism and the 'protective' allele (G) of the *MMP3* rs650108 polymorphism were less common in RL (45%, 68%, respectively) than RU athletes (54%, 76%, respectively)(Figure 3).

Conclusion

We provide evidence for elite rugby athletes possessing a protective genetic profile regarding tendon and ligament injury risk. Notably, a less frequent rs591058 TT genotype in athletes suggests a lower risk of injury could therefore enhance career success in rugby. Furthermore, RL players appear to have differing genetic characteristics compared to their RU counterparts, which might reflect some differences in physiological demands between codes.

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