Tendon and Ligament-Related Genes Associate with Elite Status in Rugby

Brazier, J.^{1, 8}, Antrobus, M.R.¹, Herbert, A.J.², Stebbings, G.K.¹, Day, S.H.³, Heffernan, S.M.⁴, Kilduff, L.P.⁴, Cullen, T.⁵, Raleigh, S.M.⁵, Erskine, R.M.^{6,7} & Williams, A.G.^{1,7}

¹Department of Sport and Exercise Sciences, Birmingham City University, Birmingham, UK, ³Faculty of Sciences, Birmingham, UK, ³Faculty of Science and Engineering, University, Manchester, UK, ⁴Applied Sport Technology Exercise and Medicine Research Centre (A-STEM), College of Engineering, Swansea University, Swansea, Wales, ⁵School of Health Sciences, Coventry, UK ⁶Research Institute for Sport & Exercise Sciences, Coventry, UK ⁶Research Institute for Sport, Exercise Sciences, Coventry, UK ⁶Research Institute for Sport & Exercise Sciences, Coventry, UK ⁶R London, UK.⁸ University of Hertfordshire, Department of Psychology and Sports Sciences, School of Life and Medical science, Hatfield, UK.

Introduction

Elite rugby has one of the highest reported injury incidences of any professional sport (Brooks and Kemp, 2008). Some of the most severe injuries are those affecting tendon and ligament (Brazier et al., 2019), and therefore potentially the most debilitating to a player and playing squad. Tendon and ligament injuries are multifactorial conditions. The aetiology of these injuries involve a number of intrinsic and extrinsic factors, with a growing body of evidence suggesting that some inter-individual variability in injury susceptibility may be due to genetic variation (September et al., 2006). Elite rugby athletes (RA) might benefit from superior ability to recover from or withstand performance limiting or career-ending soft tissue injury to achieve their elite status. Thus, it was hypothesised that RA would possess genotypes associated with reduced soft tissue injury compared to a non-athlete control population.

Method

Participants from the RugbyGene project were elite Caucasian male RA (n = 636; mean (standard deviation) height 1.85 (0.07) m, mass 101 (12) kg, age 28 (7) yr), including 535 rugby union athletes and 104 rugby league athletes. Non-athletes (NA) were 722 Caucasian men and women (58% female; height 1.69 (0.10) m, mass 72 (14) kg, age 41 (23) yr). PCR of genomic DNA was used to determine genotypes using TaqMan probes, then groups were compared using X² and odds ratio (OR) statistics, with alpha set at *P*<0.05.

Results

COLGALT1 rs8090 AA genotype was more frequent in RA (27%) than NA (23%) ($X^2 = 12.6$, P = 0.002; OR = 1.48, 95% confidence intervals (CI) = 1.1-2.0; Figure 1). The COL3A1 rs1800255 A-allele was more frequent in RA (26%) than NA (23%) due to more GA genotypes (39% v 33%, respectively; $X^2 = 9.0$, P = 0.011; OR = 1.1, 95% CI = 0.7-1.7). MIR608 rs4919510 CC genotype was more frequent in RA (63%) than NA (56%; X² = 16.4, P = 0.0003; OR = 1.7, 95% CI = 1.1-2.6; Figure 2). MMP3 rs591058 TT genotype was less frequent in RA (25%) than NA (31%; $X^2 = 10.8$, P = 0.005; OR = 1.33, 95% CI = 1.0-1.8), while MMP3 rs679620 TT genotype was less frequent in RA (24%) than NA (29%; OR = 1.3, 95% CI = 1.0-1.7). NID1 rs4660148 TT genotype was more frequent in RA (10%) than NA (6%; $X^2 = 14.5$, P = 0.001; OR = 1.6, 95% CI = 1.1-2.4; Figure 3), with VEGFA rs699947 AA genotype less frequent in RA (24%) than NA (29%; OR = 1.3, 95% CI = 1.0-1.8). There were no genotype differences between RA and NA for COL1A1 rs1800012, KDR rs1870377, MMP3 rs650108 or TIMP2 rs4789932 variants.

Conclusion

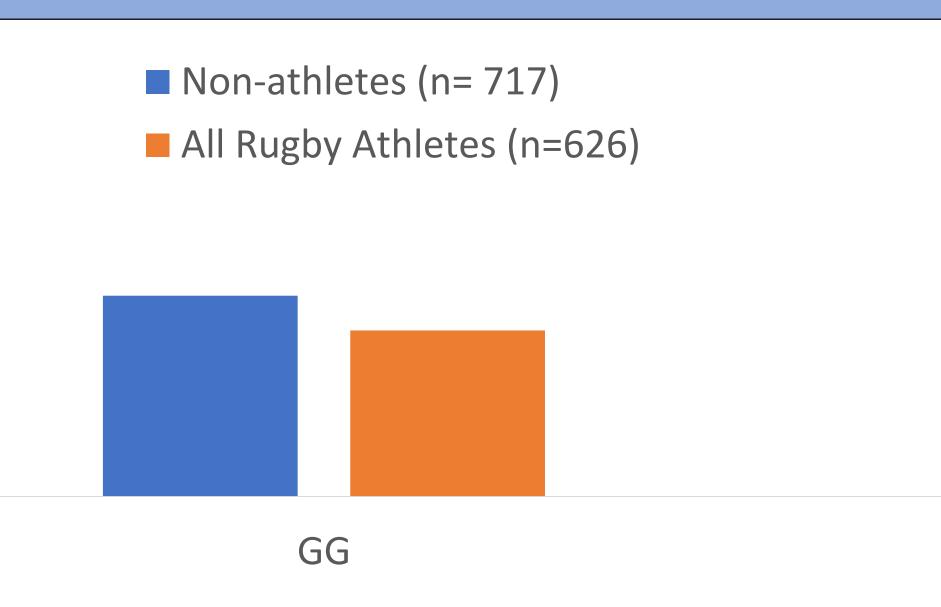
We provide evidence for elite RA possessing a possible protective genetic profile regarding tendon and ligament injury risk. Notably, there was approximately 1.7 times the odds of RA possessing the CC genotype of *MIR608* rs4919510 than NA and 1.6 times the odds of RA possessing the TT genotype of *NID1* rs4660148 than NA. Additionally, more frequent COLGALT1 AA, NID1 TT, MIR608 CC and COL3A1 GA genotypes in RA, as well as less frequent MMP3 rs591058 TT, MMP3 rs679620 and VEGFA rs699947 genotypes in RA suggest a lower genetic risk of injury could enhance career success in rugby. Future research should focus on establishing how gene variants affect the collagen and extracellular matrix structures, as this may help develop more individualised injury prevention and management plans.

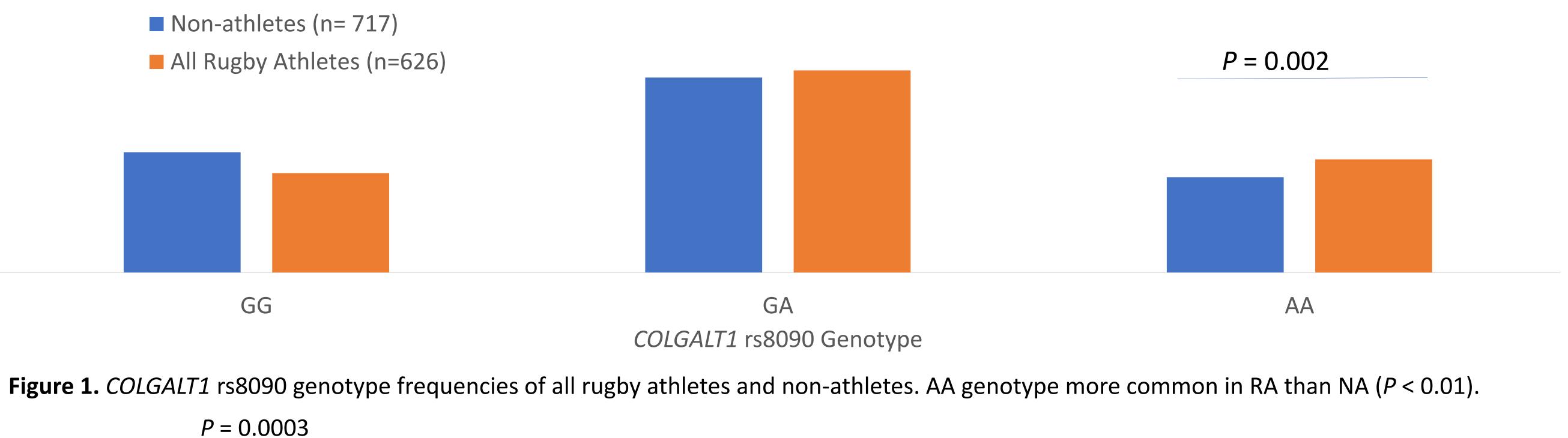


60 <u></u>50 **G** 30 e 20

60 <u></u> ^a 30 **b** 20









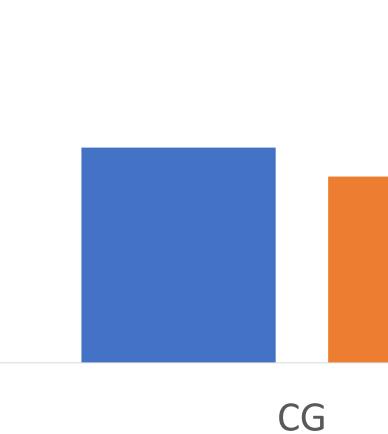
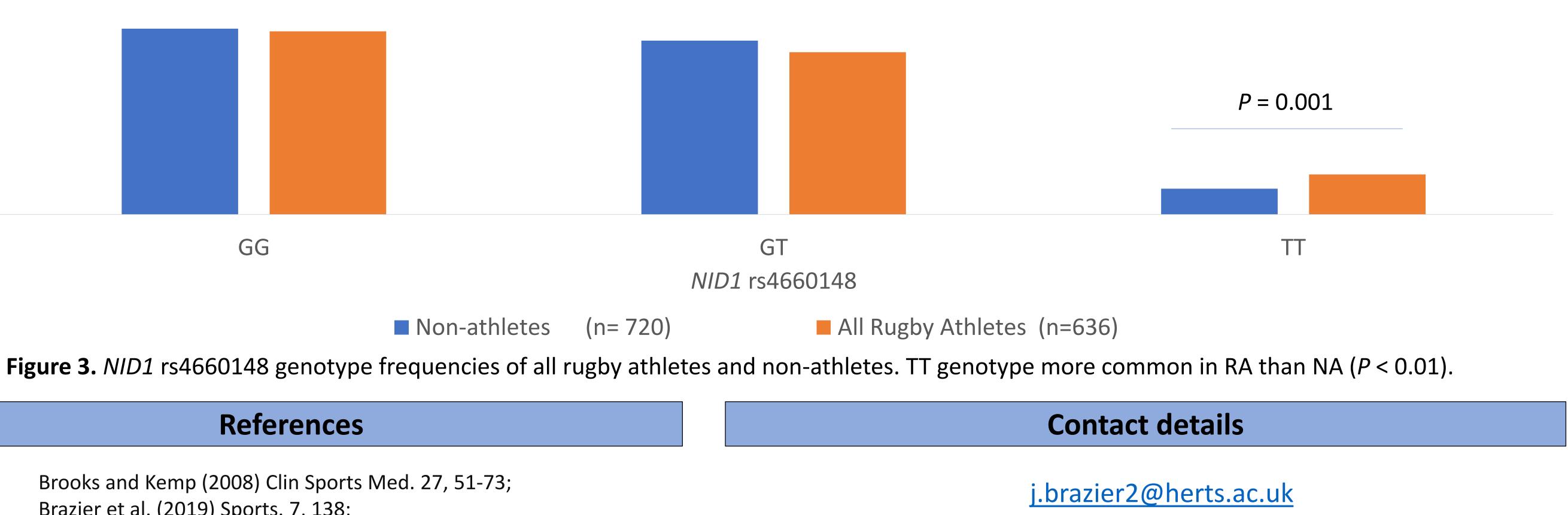
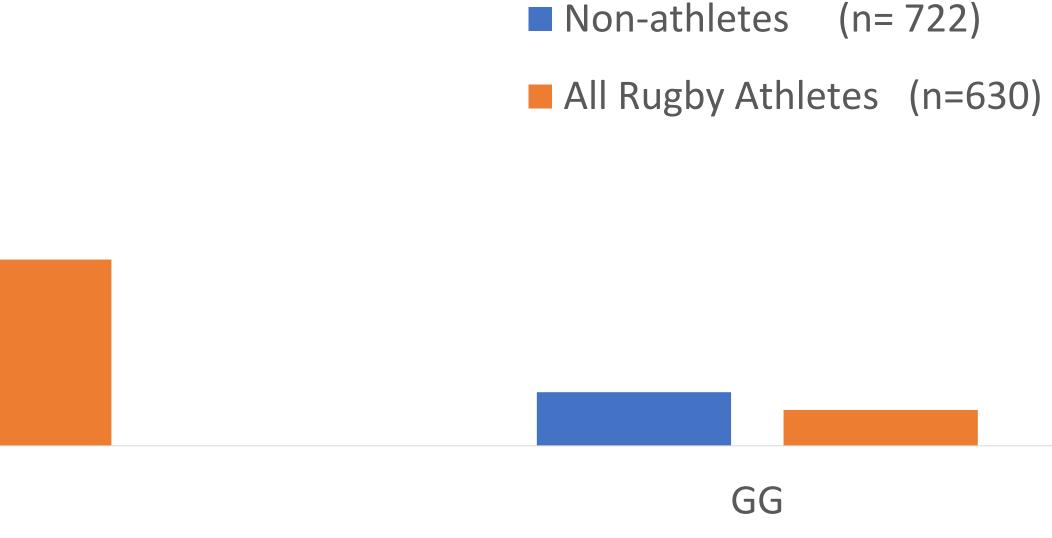


Figure 2. MIR608 rs4919510 genotype frequencies of all rugby athletes and non-athletes. CC genotype more common in RA than NA (P < 0.01).



Brazier et al. (2019) Sports. 7, 138; September et al. (2006) Int J Sports Med. 7, 201-215





MIR608 rs4919510 Genotype