Title: Hamstring injury prevention: A role for genetic information?

Authors: Craig Pickering[1,2], John Kiely[1]

1. Institute of Coaching and Performance, School of Sport and Wellbeing, University of Central Lancashire, Preston, UK
2. Exercise and Nutritional Genomics Research Centre, DNAFit Ltd, London, UK

Corresponding Author:

Craig Pickering

Institute of Coaching and Performance, School of Sport and Wellbeing, University of Central Lancashire, Fylde Road, Preston, PR1 2HE, UK.

Email: craig@dnafit.com.

Abstract

Hamstring Strain Injuries (HSI) are common within many sports, imposing a significant burden in terms of both financial cost, recovery time, and loss of performance. Recently, research has focused on better understanding the factors that increase an individual's risk of suffering a HSI, with both lower strength (particularly eccentric strength) and shorter hamstring muscle fascicles found to play a significant role. Such findings have led to an increased popularization of eccentric hamstring exercises, such as the Nordic Hamstring Exercise, the correct utilization of which has been shown to reduce HSI rates. However, despite the robust evidence of their efficacy, adherence to eccentric loading exercises is often poor, with concerns about soreness often cited. Here, we advance the hypothesis that the utilization of genetic information will, in the future, allow for the optimization of HSI prevention programmes, both in terms of training adaptations, and both muscle damage and soreness in the acute phase of post-training recovery. We also discuss whether this information could be utilised in sport in order to predict HSI injury. Such an hypothesis, if correct, could have important implications for the implementation of injury prevention programmes, particularly with regards to adherence, which evidence suggests is currently a major barrier to the utilization of eccentric hamstring exercises.

1. Introduction

During the 2016/17 football season, there were 614 significant injuries recorded amongst the players of the twenty English Premier League clubs. These injuries resulted in a loss of over 20,000 training days, with the associated costs imposed in terms solely of injured players wages, exceeding £131 million. Over the course of this season, the most frequently injured site was the hamstring muscle group, representing 27% of all injuries suffered [1]. The ubiquity of hamstring strain injury (HSI) is not unique to soccer, and HSI's typically represent the most prevalent form of non-contact injury within competitive athletics [2], American Football [3], rugby union [4], Australian Rules Football [5], cricket [6], and basketball [7]. Alongside the substantial financial implications, HSI also exert a large time-cost, with average recovery times ranging from 8 to 73 days depending on injury severity [8]. Furthermore, the unavailability of squad members due to injury diminishes team performance. As an illustration, in an eleven-season study of 24 European soccer clubs, lower injury prevalence was associated with a greater number of points gained per match, and a higher final league ranking [9]. Perhaps most insidiously, prior HSI serves to increase the risk of further HSI [10], other injuries [11], and future performance potential [12]. Consequently, avoiding, or at least reducing, HSI is a crucial consideration for many sports performance staff.

Although HSIs occur at varied locations within the muscle-tendon unit (MTU), the majority of injury mechanisms may be categorized within two broad classifications [13]. Firstly, and most commonly, HSIs occur during the late swing phase of high-speed running [14,15], as the rapid and forceful deceleration of the lower leg severely increases hamstring tension [15,16]. Such high-speed injuries tend to be located in the proximal portion of the

MTU [13] Conventionally, it is assumed that hamstring muscle fibres act eccentrically during this breaking action [16], as well as during the stance phase [17]. This perspective, however, has recently been challenged, with an argument suggesting that the hamstring muscle fibres act isometrically during the swing phase [18]. The other main provocative action occurs when the hamstring MTU is suddenly lengthened, for example during kicking, sliding, or sagittal splits activities [13].

Given both the high frequency and associated costs of HSI, it is unsurprising that, in both academic and practical contexts much effort has been dedicated to answering two currently contentious, unresolved, and critical questions:

i) Can we identify players most at risk of HSI? [19]

ii) How can we best design physical training interventions to most productively enhance hamstring resilience? [20]

In relation to screening for HSI risk, although some anatomical and historical features – such as age, [19], low levels of eccentric strength [19], muscle fascicle length [21] and previous injury history [22] – have been associated with likelihood of HSI occurrence, developing tests with true predictive value has proven problematic [23]. Similarly, given the assumed role of eccentric contractions in HSI aetiology, over a decade of empirical evidence supports the notion that the capacity to tolerate high forces during an increase in muscle length is an important aspect of HSI prevention [20]. Such findings have led to the popularization of exercises such as the Nordic hamstring exercise (NHE) [24] and Yo-Yo hamstring curl [25]. Utilization of these eccentric loading exercises have been shown to be effective in reducing the prevalence of HSI in athletic populations [24-28], through the likely mechanisms of increasing eccentric strength and hamstring muscle fascicle length [20,21].

Given these findings, eccentric hamstring exercises such as the NHE are given increasing priority in elite sports programmes as an injury reduction tool [28], and as a potential means to enhance sprint performance [29]. However, implementation of, and compliance with, these exercises is often problematic [30], with concerns regarding increased muscle soreness, and a perceived lack of effectiveness, often cited by staff and players alike [28].

2. The hypothesis

There is, however, an additional source of insight that may help both illuminate the answers to these questions, and, furthermore, may provide practitioners with meaningful guidance relating to the personalization of injury prevention interventions. Previously, we have argued that the utilization of genetic information, alongside other more conventional measures, may aid in both explaining and predicting individualised training responses [31]. Here, we explore the currently untested hypothesis that genetic information may be used to inform hamstring injury prevention programmes, increasing outcomes and leading to a reduction in future HSI. Additionally, we consider whether genetic information has the potential to be used to identify those athletes most at risk of developing a HSI; such information could be utilised to make early interventions, modifying key risk factors, and preventing the athlete from subsequent HSI.

3. Evaluation of the hypothesis

3.1 A genetic influence on the response to mechanical loading

Adaptive responses to imposed exercise interventions vary extensively between individuals [32-34]. This inter-individual diversity has been attributed to within-subject

random variation and measurement error [35] along with true between-subject neuro-biological variability [34]. These true between-subject differences can be broadly characterized as genetically, environmentally, and epigenetically driven [31], with heritable factors estimated to explain approximately 50% of the between-subject variance in strength [36].

This phenomenon is most well explored in relation to concentric muscle contractions, the contraction mode most commonly used in general resistance training activities. Here, a number of SNPs have been associated with modifying the training response. These include *ACTN3* [37,38], *IGF1* [39], and *ACE* [40,41]. However, there are also considerable inter-individual variations in response to both isometric and eccentric training. Firstly, heritable factors have been shown to account for between 14-83% of the variance in isometric strength [42], with a value typically towards the higher end of this range often reported [43,44]. As with concentric contractions, numerous SNPs have been associated with this phenotype, with *ACE* leading the way; in this case, the D allele appears to be associated with enhanced improvements following isometric loading [45].

3.1.1 Genetic insights into the response to eccentric loading.

However, perhaps of greatest interest in terms of HSI prevention are eccentric training protocols. As discussed in the introduction, exercises designed to increase eccentric hamstring strength are popularly used within sport to reduce the prevalence of HSI [25]. Such interventions have been shown to be effective [24-26], with the proposed mechanism that they increase both the strength of the hamstring muscles [46], and also the muscle fascicle length [47,48]. As with other training modalities [32-34] the magnitude of improvement following eccentric training is likely to exhibit inter-individual variability [49], with

differences in genotype partially explaining this variation [50]. The genetic influence on eccentric loading has been most well-studied with regards to the inflammatory and muscle damage response to an acute eccentric-loading session [51], reviewed in depth in section *3.1.3*, but these differences in damage response may contribute to inter-individual variation in chronic eccentric exercise adaptations. One such gene that may exert a relatively sizeable influence is *ACTN3*, where a common SNP results in a premature stop codon (X allele). Individuals with the XX genotype cannot produce the α-actinin-3 protein, which is expressed in type-II muscle fibres [52]. As a result, these individuals typically present with smaller percentages of type-II fibres [53], Individuals with the R allele of *ACTN3* also tend to exhibit less muscle damage and inflammation following an eccentric exercise bout [54], suggesting that they may be able to tolerate a greater training frequency. X allele carriers of *ACTN3* also tend to have greater increases in cortisol post-eccentric loading [54], and have lower levels of testosterone [55], which again may limit their adaptive potential. Finally, muscle fibre type in general, and the magnitude of hypertrophy following training, are partially genetically determined [56,57]. Given that eccentric training appears to preferentially drive hypertrophy in type-II, and in particular type-IIx, muscle fibres [58], the potential for SNPs that influence muscle fibre type, such as *ACTN3* [53] and *ACE* [59] to also impact the hypertrophy response to eccentric loading is highly feasible.

3.1.2 Genetics and muscle fascicle length

Alongside improvements in muscle strength, a further beneficial eccentric training adaptation is an increase in muscle fascicle length [47,60]. Again, inter-individual variation in this adaptation is likely to exist, with such variation partially genetically mediated. *TTN*, the gene encoding for the structural protein titin, may modify changes in muscle fascicle length. Here, a C>T transition at rs10497520 has been reported to impact muscle fascicle

length in males [61], with CC homozygotes having longer vastus lateralis fascicles than CT heterozygotes. Whether this finding would be replicated in the hamstring muscle group, and whether it will impact changes in muscle fascicle length, remains to be elucidated.

3.1.3 Genetics and post-exercise recovery

Muscle damage: Alongside modifying the adaptive response to eccentric training, genetic variation may also impact recovery from such training. This was recently covered in an exceptional review by Baumert and colleagues [51], to which interested readers are directed to. Here, genetic variation was determined to impact both the initial post-exercise damage phase and the subsequent inflammatory stage. In the initial damage phase, again *ACTN3* has been shown to play a role, with XX genotypes expected to exhibit greater muscle damage following exposure to eccentric loads [54,62], although this finding remains equivocal [63]. Here, the purported explanation is that the lack of α-actinin-3 in XX genotypes leads to weaker z-lines in type-II fibres, increasingly their susceptibility to damage from eccentric contractions [64-67]. Other SNPs that appear to affect muscle damage during eccentric contractions include two in *MLCK* (rs2700352 and rs28497577) [67], and one in *CK-MM* (rs1803285), although this SNP has thus far yielded confounding results [68-70].

Inflammation: Genetic variation can also predispose individuals to increased inflammation following eccentric exercise [51]. Many of these SNPs are from the interleukin family, with a polymorphism in *IL6* (rs1800795) perhaps the most prominent. Here, the C allele is associated with a greater increase in creatine kinase (CK) activity following maximal eccentric contractions [71]. Genes encoding for other pro-inflammatory cytokines, such as tumor necrosis factor (TNF), also modify the post-training inflammatory response following exercise [71,72], and appear likely to influence recovery following eccentric.

Taken together, it is clear that genetic variation influences multiple dimensions of eccentric exercise recovery. This can be in terms of muscular damage, for example though the mediation of *ACTN3* [54], or modulation of the inflammatory response, exemplified by *IL-6* [71].

Muscle soreness: A feature of un-habituated eccentric exercise is that it typically results in muscle soreness [73]. This is one of the cited reasons why elite athletes, despite the demonstrated value of eccentric hamstring exercise, have historically been slow to engage in such training [28]. Accordingly, information relating to the likelihood of suffering from post-eccentric loading discomfort could be useful. If the magnitude of soreness following eccentric loading can be predicted – even partially - then training interventions can be adjusted to promote engagement and adherence accordingly. In the case of acute muscle damage, for example, this could inform the individual calibration of training volumes and/or intensities. Here, knowledge of *ACTN3* genotype may be helpful, with XX homozygotes expected to experience greater levels of soreness. Of further relevance, a second SNP in *TTN*, rs11693372, may impact post-eccentric muscle soreness, with the CC genotype protective against subjective soreness [50].

This may also be useful in-season, with those players predicted to experience increased soreness being guided to undertake eccentric loading exercises further away from a competition or match-play. The same is true for the inflammatory response, which modulates recovery time, and influences soreness [74]. In this case, personalized nutrition guidelines could be formulated based on genotype. Here, individuals with a genetic predisposition to an increased inflammatory response may increase intake of flavonoids, omega-3 fatty acids, and

other nutrients associated with a reduction in inflammatory biomarkers following eccentric exercise [75-77]. To our knowledge, such genotype-based nutritional interventions have yet to be tested in sports people, but a number of SNPs – including *ACTN3, CM-MM, IL6,* and *TNF* – have been utilised as part of a Total Genotype Score (TGS) to explain individual variations in the level of muscle damage [76,77] following endurance activity.

3.2 Can we use genetic information to predict HSI?

The influence of genetics on injury predisposition has been most well studied in relation to tendon and ligament injury, with SNPs in two genes, *COL1A1* and *COL5A1*, associated with an increased injury vulnerability [80-82]. There is, however, very little research examining the interaction of specific genotypes on skeletal muscle injury, and even less specifically looking at HSI.

Regarding muscle injuries in general, Pruna and colleagues [83] examined the influence of 10 such SNPs on the type and degree of injury, in 73 professional elite male soccer players, playing for FC Barcelona, over three seasons. A total of 203 non-contact muscle injuries were recorded. Two SNPs, one each in *IGF2* and *CCL2*, were associated with muscle injury severity. *IGF2* acts to influence tissue repair [84], whereas *CCL2* is implicated in inflammation [85]. Consequently, variation in these genes may modify chronic load tolerance. Interestingly, when stratifying for ethnicity, an association between a SNP in *ELN* and injury severity emerged in Hispanics [86], illustrating that, although in a low sample size (n=19), ethnicity is a potential modifier in the relationship between genetics and injury. *ELN* encodes for elastin, which is believed to modify tissue elasticity [87]. When these elite soccer players were followed for an additional two seasons, with further candidate SNP analysis,

additional tentative associations relating to injury prevalence in two SNPs in *HGF*, and one in *SOX15*, were established [88]. Regarding injury severity, the previously reported associations between *IGF2* and *CCL2* [83] were confirmed, and further associations uncovered for an additional four SNPS, one in *COL5A1* and three in *HGF*. *HGF* aids in the activation of muscle satellite cells [88], and thus is likely implicated in skeletal muscle repair, as is *SOX15* [88].

Similar to the work by Pruna and colleagues [83,86,88], Massidda et al. [89] examined the impact of a single SNP in *ACTN3* on the frequency and severity of muscle injuries in 257 Italian male professional soccer players. *ACTN3* encodes for α-actinin-3, a protein that is an important component of the z-disc [52]. Individuals with the XX genotype cannot produce α-actinin-3, and so are believed to be predisposed to greater muscle damage following eccentric loading [54], potentially increasing injury risk. Furthermore, within this cohort, players with the XX genotype were significantly more likely to suffer an injury compared to R allele carriers (Odd Ratio = 2.66). These injuries were also significantly more likely to be of greater severity (OR = 2.13). In a smaller cohort of Italian footballers (n=173), a SNP in *MCT1* (rs1049434) was also significantly associated with muscle injury incidence [90]. As *MCT1* is a lactate transporter, the proposed mechanism is that this SNP partially mediated muscle fatigue, a known injury risk-factor [91].

To our knowledge, only one paper has examined the interaction between genotype and hamstring injury. Larruskain et al. [92] recruited 107 elite male soccer players, recording hamstring injury prevalence from the start of the 2010-11 season until the end of 2014-15 season (5 seasons in total). The players were genotyped for 37 SNPs previously associated with musculoskeletal injuries and/or exercise-induced muscle damage. Five SNPs were

significantly associated with the risk of HSI in a multivariable model; *MMP3* (rs679620), *TNC* (rs2104772), *IL6* (rs1800795), *NOS3* (rs1799983), and *HIF1A* (rs1159465). Age (>24y) and previous hamstring injury were also risk factors for hamstring injury. However, whilst this model proved useful in explaining the prevalence of historical hamstring injury, in the predictive stage of the study, it was found to be no better than chance at predicting future injury. As such, whilst we might be able to retrospectively explain hamstring injuries through understanding genetic variation, it appears we cannot use this information to predict future injury, presumably due to the complex multifactorial nature of sporting injury [93].

In summary, a breadth of SNPs show tentative associations with muscle injury. However, few of these have been tested and/or associated with hamstring specific muscle injury in elite sportspeople. These SNPs come from genes influencing a variety of potential injury mechanisms, including muscle architecture (*ACTN3*) [89], muscle fatigue (*MCT1*) [90], inflammation (*IL6*) [92], and tissue repair and remodeling (*HGF* and *IFG1*) [83,88]. Whilst these examples illustrate the complexly entangled influence of genetic factors on injury risk, as of yet utilization of this information remains unable to predict future HSI [92].

4. Conclusion – Potential implications for practice

Whilst certain genetic variants may increase the predisposition to HIS [83,92], as of yet it does not appear possible to utilise such genetic information to predict HSI occurrence [92]. This lack of predictability reflects the complex, multifactorial nature of sporting injuries [23, 93], as well as the fact that very few studies have been conducted on the topic. At present, it therefore appears difficult to make specific recommendations based on an athlete's genetic predisposition to HSI, because genetic predispositions appears to explain very little of

the between-athlete variance in HSI prevalence. That said, whilst injuries cannot be accurately predicted – such that all “at-risk” athletes get injured, and no “low-risk” athletes do – genetic information could be used alongside other, more traditional methods such as acute:chronic workload [94] and eccentric strength testing [95] to develop a clearer picture of individual risk, perhaps guiding the customization of hamstring robustness-enabling interventions.

However, athlete genotype potentially modifies training adaptations to eccentric loading [50], as well as altering the acute inflammatory [71] and muscle-damage [78,79] response to such exercises. Accordingly, there remains the possibility that genetic information, although inadequate as a predictive tools for HSI, could instead enable a more informed application of preventative exercises. In this scenario, genetic information could be used to best inform loading schemes [96,97] and recovery strategies. This could be especially important during the competitive season, when avoiding excessive post-exercise soreness prior to key competitions and matches is crucial. In this case, genetic information could be used alongside more conventional measures in order to optimally position the eccentric loading bout within the training week for that athlete. Similarly, utilizing genetic information may aid in the process of introducing this training modality to eccentric-naïve individuals, with coaches using information relating to post-exercise soreness to modify the load and intensity accordingly.

Such an hypothesis remains largely untested and highly speculative, especially with regards to the hamstring muscles themselves, representing an avenue for future research. This is of increased importance given the lack of intervention-based studies in the field of sports genetics, and represents an ideal opportunity to move from observational research to that

which directly impacts practice [98] particularly as both athletes and coaches appear amenable to the utilization of genetic information [99]. In moving this field forward, future research should therefore aim to elucidate:

1. The extent to which specific gene variants modify HSI risk.
2. Whether knowledge of this information can be predictive in terms of HSI probability.
3. Whether modification of training variables based on genotype leads to better outcomes following eccentric hamstring exercises in terms of injury resilience and athletic performance.

Given the prevalence of HSI within elite sport, such insights have the potential to inform and enhance hamstring performance and robustness training process. Whilst not necessarily predictive of HSI injury in and of themselves, genetic variants do provide insights into the likely predispositions certain athletes may have to such to injury, and subsequently provide an additional layer of relevant information that can be combined with more conventional assessments to guide to customization of hamstring-specific exercise prescription and monitoring strategies. Despite the recent surge in HSI research, it remains clear that prevention remains an unresolved problem [100]. Solving such a complex, multi-factorial phenomenon will likely demand the integration of insights and information from multiple domains. In pursuing this objective, we propose that an appreciation of the underlying genetic mechanisms influencing HSI risk and training responsiveness provides a useful – albeit partial – insight that could positively contribute to more perceptive management of hamstring health.

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