



## Article

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

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## **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  $\alpha$ -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  $\alpha$ -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 through 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  $\alpha$ -actinin-3, a protein that is an important component of the z-disc [52]. Individuals with the XX genotype cannot produce  $\alpha$ -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 HSI [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 tool 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.

## **References**

1. Coates C. English Premier League Injury Analysis: 2016/17 Season (internet). 2017. <https://www.physioroom.com/info/english-premier-league-injury-analysis-201617-season>. Accessed 19 Feb 2018.
2. Edouard P, Branco P, Alonso JM. Muscle injury is the principal injury type and hamstring muscle injury is the first injury diagnosis during top-level international athletics championships between 2007 and 2015. *Br J Sports Med*. 2016;50(10):619-30.
3. Elliott MC, Zarins B, Powell JW, Kenyon CD. Hamstring muscle strains in professional football players: a 10-year review. *Am J Sports Med*. 2011;39(4):843-50.
4. Brooks JH, Fuller CW, Kemp SP, Reddin DB. Incidence, risk, and prevention of hamstring muscle injuries in professional rugby union. *Am J Sports Med* 2006;34(8):1297-306.
5. Orchard J, Seward H. Epidemiology of injuries in the Australian Football League, seasons 1997–2000. *Br J Sports Med*. 2002;36(1):39-44.
6. Orchard J, James T, Alcott E, Carter S, Farhart P. Injuries in Australian cricket at first class level 1995/1996 to 2000/2001. *Br J Sports Med*. 2002;36(4):270-4.
7. Meeuwisse WH, Sellmer R, Hagel BE. Rates and risks of injury during intercollegiate basketball. *Am J Sports Med*. 2003;31(3):379-85.
8. Ekstrand J, Healy JC, Waldén M, Lee JC, English B, Hägglund M. Hamstring muscle injuries in professional football: the correlation of MRI findings with return to play. *Br J Sports Med*. 2012;46(2):112-7.
9. Hägglund M, Waldén M, Magnusson H, Kristenson K, Bengtsson H, Ekstrand J. Injuries affect team performance negatively in professional football: an 11-year



follow-up of the UEFA Champions League injury study. *Br J Sports Med.*

2013;47(12):738-742.

10. Van Beijsterveldt AM, Port IG, Vereijken AJ, Backx FJ. Risk factors for hamstring injuries in male soccer players: a systematic review of prospective studies. *Scand J Med Sci Sports.* 2013;23(3):253-62.
11. Opar DA, Serpell BG. Is there a potential relationship between prior hamstring strain injury and increased risk for future anterior cruciate ligament injury? *Arch Phys Med Rehab* 2014;95(2):401-5.
12. Røksund OD, Kristoffersen M, Bogen BE, et al. Higher Drop in Speed during a Repeated Sprint Test in Soccer Players Reporting Former Hamstring Strain Injury. *Front Physiol.* 2017;8:25. doi: 10.3389/fphys.2017.00025
13. Askling C. Types of hamstring injuries in sports. *Br J Sports Med.* 2011;45(2):e2-.
14. Woods C, Hawkins RD, Maltby S, Hulse M, Thomas A, Hodson A. The Football Association Medical Research Programme: an audit of injuries in professional football—analysis of hamstring injuries. *Br J Sports Med.* 2004;38(1):36-41.
15. Petersen J, Hölmich P. Evidence based prevention of hamstring injuries in sport. *Br J Sports Med.* 2005;39(6):319-23.
16. Chumanov ES, Heiderscheit BC, Thelen DG. Hamstring musculotendon dynamics during stance and swing phases of high speed running. *Med Sci Sports Exerc.* 2011;43(3):525.
17. Yu B, Queen RM, Abbey AN, Liu Y, Moorman CT, Garrett WE. Hamstring muscle kinematics and activation during overground sprinting. *J Biomech.* 2008;41(15):3121-6.

18. Van Hooren B, Bosch F. Is there really an eccentric action of the hamstrings during the swing phase of high-speed running? part I: A critical review of the literature. *J Sports Sci.* 2017;35(23):2313-21.
19. Ruddy J, Shield A, Maniar N, et al. Predicting hamstring strain injury incidence in elite Australian footballers. *J Sci Med Sport.* 2017;20:10-1.
20. Bourne MN, Timmins RG, Opar DA, et al. An Evidence-Based Framework for Strengthening Exercises to Prevent Hamstring Injury. *Sports Med.* 2018;48(2):251-267
21. Timmins RG, Bourne MN, Shield AJ, Williams MD, Lorenzen C, Opar DA. Short biceps femoris fascicles and eccentric knee flexor weakness increase the risk of hamstring injury in elite football (soccer): a prospective cohort study. *Br J Sports Med.* 2016;50(24):1524-35.
22. Gabbe BJ, Bennell KL, Finch CF. Why are older Australian football players at greater risk of hamstring injury?. *J Sci Med Sport.* 2006;9(4):327-33.
23. Bahr R. Why screening tests to predict injury do not work—and probably never will...: a critical review. *Br J Sports Med.* 2016;50(13):776-80
24. Al Attar WS, Soomro N, Sinclair PJ, Pappas E, Sanders RH. Effect of injury prevention programs that include the Nordic hamstring exercise on hamstring injury rates in soccer players: A systematic review and meta-analysis. *Sports Med.* 2017;47(5):907-916
25. Askling C, Karlsson J, Thorstensson A. Hamstring injury occurrence in elite soccer players after preseason strength training with eccentric overload. *Scand J Med Sci Sports.* 2003;13(4):244-50

26. Petersen J, Thorborg K, Nielsen MB, Budtz-Jørgensen E, Hölmich P. Preventive effect of eccentric training on acute hamstring injuries in men's soccer: a cluster-randomized controlled trial. *Am J Sports Med.* 2011;39(11):2296-303.
27. van der Horst N, Smits DW, Petersen J, Goedhart EA, Backx FJ. The preventive effect of the Nordic hamstring exercise on hamstring injuries in amateur soccer players: a randomized controlled trial. *Am J Sports Med.* 2015;43(6):1316-23.
28. McCall A, Dupont G, Ekstrand J. Injury prevention strategies, coach compliance and player adherence of 33 of the UEFA Elite Club Injury Study teams: a survey of teams' head medical officers. *Br J Sports Med.* 2016;50(12):725-30
29. Ishøi L, Hölmich P, Aagaard P, Thorborg K, Bandholm T, Serner A. Effects of the Nordic Hamstring exercise on sprint capacity in male football players: a randomized controlled trial. *J Sports Sci.* 2017:1-10.
30. Bahr R, Thorborg K, Ekstrand J. Evidence-based hamstring injury prevention is not adopted by the majority of Champions League or Norwegian Premier League football teams: the Nordic Hamstring survey. *Br J Sports Med.* 2015;49(22):1466-71
31. Pickering C, Kiely J. (2017). Understanding personalized training responses: Can genetic assessment help? *The Open Sports Science Journal*, 10.
32. Hubal MJ, Gordish-Dressman HE, Thompson PD, et al. Variability in muscle size and strength gain after unilateral resistance training. *Med Sci Sports Exerc.* 2005;37(6):964-72.
33. Erskine RM, Jones DA, Williams AG, Stewart CE, Degens H. Inter-individual variability in the adaptation of human muscle specific tension to progressive resistance training. *Eur J Appl Physiol.* 2010;110(6):1117-25.

34. Mann TN, Lamberts RP, Lambert MI. High responders and low responders: factors associated with individual variation in response to standardized training. *Sports Med.* 2014;44(8):1113-24.
35. Atkinson G, Batterham AM. True and false interindividual differences in the physiological response to an intervention. *Exp Physiol.* 2015;100(6):577-88
36. Silventoinen K, Magnusson PK, Tynelius P, Kaprio J, Rasmussen F. Heritability of body size and muscle strength in young adulthood: a study of one million Swedish men. *Genet Epidemiol.* 2008;32(4):341-9.
37. Delmonico MJ, Kostek MC, Doldo NA, et al. Alpha-actinin-3 (ACTN3) R577X polymorphism influences knee extensor peak power response to strength training in older men and women. *J Gerontol A Biol Sci Med Sci.* 2007;62(2):206-12.
38. Pereira A, Costa AM, Izquierdo M, Silva AJ, Bastos E, Marques MC. ACE I/D and ACTN3 R/X polymorphisms as potential factors in modulating exercise-related phenotypes in older women in response to a muscle power training stimuli. *Age.* 2013;35(5):1949-59.
39. Hand BD, Kostek MC, Ferrell RE, et al. Influence of promoter region variants of insulin-like growth factor pathway genes on the strength-training response of muscle phenotypes in older adults. *J Appl Physiol.* 2007;103(5):1678-87.
40. Pescatello LS, Kostek MA, Gordish-Dressman H, et al. ACE ID genotype and the muscle strength and size response to unilateral resistance training. *Med Sci Sports Exerc.* 2006;38(6):1074-81.
41. Giaccaglia V, Nicklas B, Kritchevsky S, et al. Interaction between angiotensin converting enzyme insertion/deletion genotype and exercise training on knee extensor strength in older individuals. *Int J Sports Med.* 2008;29(01):40-4.

42. Peeters MW, Thomis MA, Beunen GP, Malina RM. Genetics and sports: an overview of the pre-molecular biology era. In: Collins M, editor. Genetics and sports. Karger Publishers; 2009. Vol. 54, pp. 28-42.
43. Thomis MA, Van Leemputte M, Maes HH, et al. Multivariate genetic analysis of maximal isometric muscle force at different elbow angles. *J Appl Physiol.* 1997;82(3):959-67.
44. Tiainen K, Sipilä S, Kauppinen M, Kaprio J, Rantanen T. Genetic and environmental effects on isometric muscle strength and leg extensor power followed up for three years among older female twins. *J Appl Physiol.* 2009;106(5):1604-10.
45. Folland J, Leach B, Little T, et al. Angiotensin-converting enzyme genotype affects the response of human skeletal muscle to functional overload. *Exp Physiol.* 2000;85(5):575-9.
46. Mjølsnes R, Arnason A, Raastad T, Bahr R. A 10-week randomized trial comparing eccentric vs. concentric hamstring strength training in well-trained soccer players. *Scand J Med Sci Sports.* 2004;14(5):311-7.
47. Potier TG, Alexander CM, Seynnes OR. Effects of eccentric strength training on biceps femoris muscle architecture and knee joint range of movement. *Eur J Appl Physiol.* 2009;105(6):939-44.
48. Reeves ND, Maganaris CN, Longo S, Narici MV. Differential adaptations to eccentric versus conventional resistance training in older humans. *Exp Physiol.* 2009;94(7):825-33.
49. Baumert P, Lake MJ, Stewart CE, Drust B, Erskine RM. Inter-individual variability in the response to maximal eccentric exercise. *Eur J Appl Physiol.* 2016;116(10):2055-6.
50. Moeckel-Cole SA, Zambraski E, Gordish-Dressman H, Hoffman E, Devaney J, Clarkson P. A Single Nucleotide Polymorphism (SNP) in Titin (TTN) Decreases

Muscle Soreness and Strength Deficits after Eccentric Exercise in Women. *FASEB*. 2010;24(1 Supplement):806-4.

51. Baumert P, Lake MJ, Stewart CE, Drust B, Erskine RM. Genetic variation and exercise-induced muscle damage: implications for athletic performance, injury and ageing. *Eur J Appl Physiol*. 2016;116(9):1595-625.
52. North KN, Yang N, Wattanasirichaigoon D, Mills M, Eastal S, Beggs AH. A common nonsense mutation results in  $\alpha$ -actinin-3 deficiency in the general population. *Nat Genet*. 1999;21(4):353-4.
53. Vincent B, De Bock K, Ramaekers M, et al. ACTN3 (R577X) genotype is associated with fiber type distribution. *Physiol Genomics*. 2007;32(1):58-63.
54. Pimenta EM, Coelho DB, Cruz IR, et al. The ACTN3 genotype in soccer players in response to acute eccentric training. *Eur J Appl Physiol*. 2012;112(4):1495-503.
55. Ahmetov II, Donnikov AE, Trofimov DY. ACTN3 genotype is associated with testosterone levels of athletes. *Biol Sport*. 2014;31(2):105.
56. Simoneau JA, Bouchard C. Genetic determinism of fiber type proportion in human skeletal muscle. *FASEB*. 1995;9(11):1091-5.
57. Timmons JA. Variability in training-induced skeletal muscle adaptation. *J Appl Physiol*. 2011;110(3):846-53.
58. Douglas J, Pearson S, Ross A, McGuigan M. Chronic adaptations to eccentric training: a systematic review. *Sports Med*. 2017;47(5):917-41
59. Zhang B, Tanaka H, Shono N, Miura S, Kiyonaga A, Shindo M, Saku K. The I allele of the angiotensin-converting enzyme gene is associated with an increased percentage of slow-twitch type I fibers in human skeletal muscle. *Clin Genet*. 2003;63(2):139-44.

60. Bourne MN, Duhig SJ, Timmins RG, et al. Impact of the Nordic hamstring and hip extension exercises on hamstring architecture and morphology: implications for injury prevention. *Br J Sports Med.* 2017;51(5):469-477
61. Stebbings GK, Williams AG, Herbert AJ, et al. TTN genotype is associated with fascicle length and marathon running performance. *Scand J Med Sci Sports.* 2018;28(2):400-406
62. Vincent B, Windelinckx A, Nielens H, et al. Protective role of  $\alpha$ -actinin-3 in the response to an acute eccentric exercise bout. *J Appl Physiol.* 2010;109(2):564-73.
63. Venckunas T, Skurvydas A, Brazaitis M, Kamandulis S, Snieckus A, Moran CN. Human alpha-actinin-3 genotype association with exercise-induced muscle damage and the repeated-bout effect. *Appl Physiol Nutr Metab.* 2012;37(6):1038-46.
64. Beggs AH, Byers TJ, Knoll JH, Boyce FM, Bruns GA, Kunkel LM. Cloning and characterization of two human skeletal muscle alpha-actinin genes located on chromosomes 1 and 11. *J Biol Chem.* 1992;267(13):9281-8.
65. Friden J, Lieber RL (2001). Eccentric exercise-induced injuries to contractile and cytoskeletal muscle fibre components. *Acta Physiol Scand.* 2001;171(3):321-6.
66. Seto JT, Lek M, Quinlan KG, et al. Deficiency of  $\alpha$ -actinin-3 is associated with increased susceptibility to contraction-induced damage and skeletal muscle remodeling. *Hum Mol Genet.* 2011;20(15):2914-27. doi: 10.1093/hmg/ddr196
67. Clarkson PM, Hoffman EP, Zambraski E, et al. ACTN3 and MLCK genotype associations with exertional muscle damage. *J Appl Physiol.* 2005;99(2):564-9.
68. Heled Y, Bloom MS, Wu TJ, Stephens Q, Deuster PA. CM-MM and ACE genotypes and physiological prediction of the creatine kinase response to exercise. *J Appl Physiol* 2007;103(2):504-10.

69. Yamin C, Oliveira J, Meckel Y, et al. CK-MM gene polymorphism does not influence the blood CK activity levels after exhaustive eccentric exercise. *Int J Sports Med.* 2010;31(03):213-7.
70. Deuster PA, Contreras-Sesvold CL, O'Connor FG, et al. Genetic polymorphisms associated with exertional rhabdomyolysis. *Eur J Appl Physiol.* 2013;113(8):1997-2004.
71. Yamin C, Duarte JA, Oliveira JM, et al. IL6 (-174) and TNFA (-308) promoter polymorphisms are associated with systemic creatine kinase response to eccentric exercise. *Eur J Appl Physiol.* 2008;104(3):579
72. Lakka HM, Lakka TA, Rankinen T, et al. The TNF- $\alpha$  G-308A polymorphism is associated with C-reactive protein levels: the HERITAGE Family Study. *Vascul Pharmacol.* 2006;44(5):377-83.
73. Lee J, Goldfarb AH, Rescino MH, Hegde S, Patrick S, Apperson K. Eccentric exercise effect on blood oxidative-stress markers and delayed onset of muscle soreness. *Med Sci Sports Exerc* 2002;34(3):443-8.
74. Miles MP, Andring JM, Pearson SD, et al. Diurnal variation, response to eccentric exercise, and association of inflammatory mediators with muscle damage variables. *J Appl Physiol.* 2008;104(2):451-8.
75. Phillips TR, Childs AC, Dreon DM, Phinney ST, Leeuwenburgh CH. A dietary supplement attenuates IL-6 and CRP after eccentric exercise in untrained males. *Med Sci Sports Exerc.* 2003;35(12):2032-7.
76. DiLorenzo FM, Drager CJ, Rankin JW. Docosahexaenoic acid affects markers of inflammation and muscle damage after eccentric exercise. *J Strength Cond Res.* 2014;28(10):2768-74.



77. Kim J, Lee J. A review of nutritional intervention on delayed onset muscle soreness. Part I. *J Exerc Rehabil.* 2014;10(6):349.
78. Del Coso J, Valero M, Salinero JJ, Lara B, Gallo-Salazar C, Areces F. Optimum polygenic profile to resist exertional rhabdomyolysis during a marathon. *PloS One.* 2017;12(3):e0172965.
79. Del Coso J, Salinero JJ, Lara B, et al. Polygenic Profile and Exercise-Induced Muscle Damage by a Competitive Half-Ironman. *J Strength Cond Res.* 2017 doi: 10.1519/JSC.0000000000002303
80. Posthumus M, September AV, Keegan M, et al. Genetic risk factors for anterior cruciate ligament ruptures: COL1A1 gene variant. *Br J Sports Med.* 2009;43(5):352-6
81. Posthumus M, September AV, O’Cuinneagain D, van der Merwe W, Schwellnus MP, Collins M. The COL5A1 gene is associated with increased risk of anterior cruciate ligament ruptures in female participants. *Am J Sports Med.* 2009;37(11):2234-40.
82. Collins M, Posthumus M, Schwellnus MP. The COL1A1 gene and acute soft tissue ruptures. *Br J Sports Med.* 2010;44(14):1063-4
83. Pruna R, Artells R, Ribas J, et al. Single nucleotide polymorphisms associated with non-contact soft tissue injuries in elite professional soccer players: influence on degree of injury and recovery time. *BMC Musculoskelet Disord.* 2013;14(1):221.
84. Keller HL, St Pierre Schneider B, Eppihimer LA, Cannon JG. Association of IGF-I and IGF-II with myofiber regeneration in vivo. *Muscle Nerve.* 1999;22(3):347-54.
85. Hubal MJ, Devaney JM, Hoffman EP, et al. CCL2 and CCR2 polymorphisms are associated with markers of exercise-induced skeletal muscle damage. *J Appl Physiol.* 2010;108(6):1651-8.

86. Pruna R, Ribas J, Montoro JB, Artells R. The impact of single nucleotide polymorphisms on patterns of non-contact musculoskeletal soft tissue injuries in a football player population according to ethnicity. *Med Clin*. 2015;144(3):105-10.
87. Muiznieks LD, Weiss AS, Keeley FW. Structural disorder and dynamics of elastin. *Biochem Cell Biol*. 2010;88(2):239-50.
88. Pruna R, Artells R, Lundblad M, Maffulli N. Genetic biomarkers in non-contact muscle injuries in elite soccer players. *Knee Surg Sports Traumatol Arthrosc*. 2017;25(10):3311-8.
89. Massidda M, Voisin S, Culigioni C, et al. ACTN3 R577X Polymorphism Is Associated With the Incidence and Severity of Injuries in Professional Football Players. *Clin J Sport Med*. 2017;16 doi: 10.1097/JSM.0000000000000487.
90. Massidda M, Eynon N, Bachis V, et al. Influence of the MCT1 rs1049434 on Indirect Muscle Disorders/Injuries in Elite Football Players. *Sports Med Open*. 2015;1(1):33.
91. Opar DA, Williams MD, Shield AJ. Hamstring strain injuries. *Sports Med*. 2012;42(3):209-26.
92. Larruskain J, Celorrio D, Barrio I, et al. Genetic variants and hamstring injury in soccer: an association and validation study. *Med Sci Sports Exerc*. 2018;50(2):361-368
93. Bahr R, Krosshaug T. Understanding injury mechanisms: a key component of preventing injuries in sport. *Br J Sports Med*. 2005;39(6):324-9.
94. Hulin BT, Gabbett TJ, Lawson DW, Caputi P, Sampson JA. The acute: chronic workload ratio predicts injury: high chronic workload may decrease injury risk in elite rugby league players. *Br J Sports Med*. 2016;50(4):231-6
95. Sugiura Y, Saito T, Sakuraba K, Sakuma K, Suzuki E. Strength deficits identified with concentric action of the hip extensors and eccentric action of the hamstrings

- predispose to hamstring injury in elite sprinters. *J Orthop Sports Phys Ther.* 2008;38(8):457-64.
96. Jones N, Kiely J, Suraci B, et al. A genetic-based algorithm for personalized resistance training. *Biol Sport.* 2016;33(2):117.
97. Kikuchi N, Nakazato K. Effective utilization of genetic information for athletes and coaches: focus on ACTN3 R577X polymorphism. *J Exerc Nutrition Biochem.* 2015;19(3):157-164
98. Buchheit M. Houston, we still have a problem. *Int J Sports Physiol Perform.* 2017;12(8):1111-4.
99. Varley I, Patel S, Williams AG, Hennis PJ. The current use, and opinions of elite athletes and support staff in relation to genetic testing in elite sport within the UK. *Biol Sport.* 2018;35:13-9.
100. Ekstrand J, Waldén M, Hägglund M. Hamstring injuries have increased by 4% annually in men's professional football, since 2001: a 13-year longitudinal analysis of the UEFA Elite Club injury study. *Br J Sports Med.* 2016;50(12):7