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REVIEW

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Genetic variations associated with non-contact muscle injuries in sport: A systematic review

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Introduction: Non-contact muscle injuries (NCMI) account for a large proportion of sport injuries, affecting athletes' performance and career, team results and financial aspects. Recently, genetic factors have been attributed a role in the susceptibility of an athlete to sustain NCMI. However, data in this field are only just starting to emerge.

Objectives: To review available knowledge of genetic variations associated with sport-related NCMI.

Methods: The databases Pubmed, Scopus, and Web of Science were searched for relevant articles published until February 2021. The records selected for review were original articles published in peer-reviewed journals describing studies that have examined NCMI-related genetic variations in adult subjects (17–60 years) practicing any sport. The data extracted from the studies identified were as follows: general information, and data on genetic polymorphisms and NCMI risk, incidence and recovery time and/or severity.

Results: Seventeen studies examining 47 genes and 59 polymorphisms were finally included. 29 polymorphisms affecting 25 genes were found significantly associated with NCMI risk, incidence, recovery time, and/or severity. These genes pertain to three functional categories: (i) muscle fiber structural/contractile properties, (ii) muscle repair and regeneration, or (iii) muscle fiber external matrix composition and maintenance.

Conclusion: Our review confirmed the important role of genetics in NCMI. Some gene variants have practical implications such as differences of several weeks in recovery time detected between genotypes. Knowledge in this field is still in its early stages. Future studies need to examine a wider diversity of sports and standardize their methods and outcome measures.

KEYWORDS

exercise, injury incidence, injury risk, injury severity, polymorphism, recovery time, SNP

1 | INTRODUCTION

Skeletal muscle is the tissue responsible for the movement of an organism. During physical activity or sport, the complex structural organization of skeletal muscle is easily stressed and damaged, leading to frequent injuries. According to the Munich experts' consensus, endorsed by the International Olympic Committee (IOC) and the Union of European Football Association (UEFA), non-contact muscle injuries (NCMI) can be classified into several categories.[1] Accordingly, some NCMI are related to functional muscle disorders without macroscopic evidence of fiber tears, like overexertion-related injuries or neuromuscular muscle disorders. Other NCMI involve structural tissue injury with macroscopic evidence of fiber tears, like partial or (sub)total muscle tear injuries and tendinous avulsions. These different categories can be linked to different degrees of severity.[1] NCMI, especially those affecting the lower extremities, are frequent in many sports, particularly those involving explosive actions such as sprinting, high-speed running, or jumping.[1] Muscles that are frequently injured are often bi-articular[2] or have a more complex architecture, undergo eccentric contraction and contain primarily fast-twitch type 2 muscle fibers.[3,4] NCMI may affect individual as well as team performance, and could compromise an athlete's career or the team's results.[5–7] NCMI account for a large proportion of all kinds of injury. For example, in professional football, muscle/tendon are the most common type of injuries, representing 20–37% of all time-loss injuries at the male professional level (reviewed in Ref. [8]). Between 2007 and 2015, NCMI were found to be the most prevalent type of injury diagnosed during international athletics championships, amounting to 40.9% of all injuries.[6] In 2009, significant correlation was reported between the injury incidence rate and the success of Qatari professional soccer teams. Teams with low injury incidence rates were ranked higher, won more games, and scored more goals.[9] Due to their prevalence, NCMI can also be a considerable economic burden for professional teams. For example, the average cost for a first-team football player injured for 1 month has been estimated at around 500 000 € by the CEO of the Shakhtar Donetsk team.[10] NCMI are related to multiple possible risk factors, age, and history of previous NCMI being considered the most important (reviewed in Refs [11] and [12]). Other factors such as ethnicity,[13,14] increased antagonist peak torque,[14] eccentric strength asymmetry,[15] strength imbalance,[16] and lack of flexibility[13] have been proposed to contribute to the appearance of NCMI. Interestingly, in 2009, Collins and Raleight[17] hypothesized that some genetic variations could likewise represent possible risk factors of the incidence of acute soft-tissue injuries, like those affecting the Achilles tendon, rotator cuff tendons and knee cruciate ligaments. Several further studies were conducted, discovering various candidate genes associated with the incidence of ligament and tendon injuries (reviewed in Ref. [18]). In parallel, other authors also proposed some genetic polymorphisms as possible factors increasing NCMI incidence and severity, and relationships have been detected between NCMI and possible candidate single nucleotide polymorphisms (SNP) in genes responsible for encoding soft-tissue structure and regulatory proteins (detailed in the present review).

Despite the increasing number of studies in the field, our current understanding of the role of genetic components in the incidence and severity of NCMI in sport is still scarce. To date, only one narrative non-systematic review has been conducted on the SNPs involved in the occurrence of hamstring NCMI.[19] More knowledge is needed to understand the role of genetic factors in the multi-factorial phenomenon of NCMI incidence and to improve the efficiency of a predictive model to estimate and reduce the risk of these injuries. The aim of this systematic review was to update current knowledge of genetic variations associated with the incidence and severity of NCMI in sport.

2 | METHODS

2.1 | Search strategy

A literature search was performed in duplicate and independently by three researchers (TL, TY, and CS) in February 2021 to identify all available records of studies examining genetic polymorphisms and NCMI related to sport. The databases searched were Pubmed, Scopus, and Web of Science using the search terms: (polymorphism OR SNP OR "genetic variation") AND (injury) AND (muscle OR sport). The search was limited to articles published from January 1 1985 to February 25 2021. All titles and abstracts were registered in the bibliographic tool Mendeley Desktop Version 1.19.4. Initially, two independent reviewers (TL and TY) checked relevant titles of the studies identified, and then, the same process was used for the selection of the pertinent abstracts. Subsequently, full texts of potentially eligible studies were reviewed in duplicate and independently. In the different stages, any disagreement between reviewers was resolved by a third researcher (CS). Additional studies were identified via a review of the reference lists of relevant papers combined with manual searching.

2.2 | Study selection

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations (PRISMA Statement).[20] Inclusion criteria were as follows: (i) original research

articles in English, Spanish, or French, (ii) article published in a peer-reviewed journal, (iii) studies in human subjects, (iv) participants with diagnosed or reported NCMI, (v) participants practicing sport at any level, and (vi) participant age 17–60 years. Studies whose participants had been diagnosed with some disease were excluded. We also excluded reviews, books, book sections, letters to the editor, opinion articles, theses, film/broadcasts, and congress abstracts.

2.3 | Data extraction

The following data were extracted in duplicate and independently by three researchers from the studies selected: last name of the first author, publication year, study design, number of participants, participant ethnicity, genetic polymorphisms genotyped, and main results related to NCMI risk (% injured vs non-injured; odds ratio [OR]; 95% confidence interval [CI]), NCMI incidence (no. NCMI/season; no. NCMI/1000 hours; mean (±95% CI or standard deviation [SD]); hazard ratio [HR; 95% CI]), recovery time after NCMI (days from the date of injury until return to full training and competition; mean [±95% CI]), and NCMI severity (classification according to recovery days; frequencies, OR [95% CI]).

2.4 | Study quality assessment

Individual study quality and risk of bias were assessed by two independent researchers according to the McMaster guidelines for Critical Review Form for Quantitative studies.[21] This tool includes 16 items in the nine domains: study purpose, background literature, study design, sample (size, description, justification), outcome (reliable, valid), intervention (description, contamination and cointervention avoided, replicability), results (statistical significance, analysis method, clinical importance), drop-out and conclusion. For every study, 1 point is added for each item completed and 0 points for each item not completed. Due to the design of the included studies, item 10 (contamination and cointervention avoided) could not be assessed; thus, the maximum possible score was 15 points. Scores were calculated based on the 15 item scale and the methodological quality of each study was classified according to score percentages as low (less than 50%), acceptable (50%–64%), high quality (65%–79%), and excellent (80% and over).

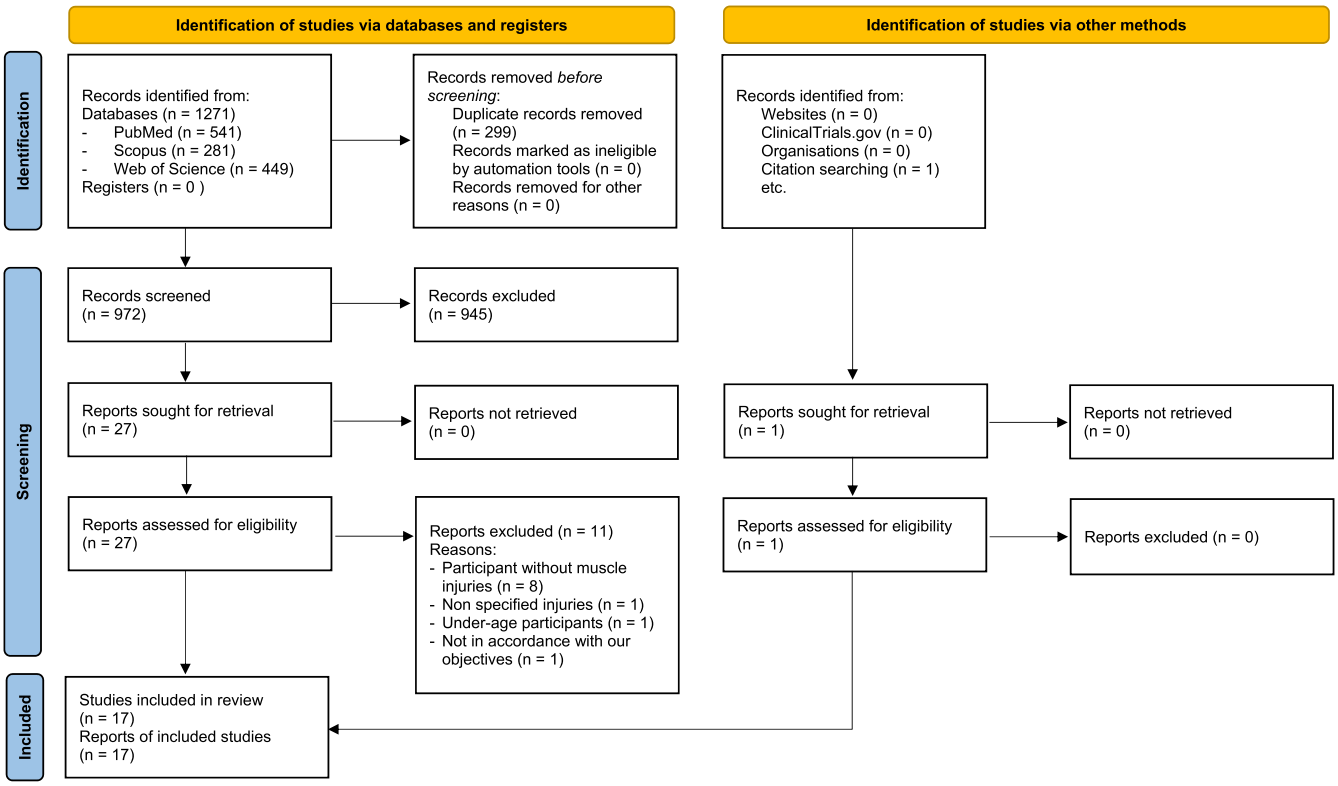

FIGURE 1 Flow diagram. *From*: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

3 | RESULTS

3.1 | Search strategy results

Seventeen studies were finally selected for review. A flow diagram of the different steps of the selection process is provided in Figure 1.

3.2 | Overall study characteristics

The 17 studies reviewed here were observational, including eight longitudinal studies with 3 to 7 years of follow-up,[22–29] seven cross-sectional studies,[30–36] one study combining cross-sectional and longitudinal analysis[37] and one case-control study.[38] The participants of these 17 studies were professional football (soccer) players in ten studies,[22–29,37,38] athletes and sport-students of different specialties and levels in five,[31–35] elite endurance runners in one[30] and experienced amateur marathon runners in the remaining study.[36] In one of the studies by Miyamoto et al., not all subjects met the inclusion criteria; these were physically inactive subjects representing only 9% of participants.[33] Sample sizes ranged from 43 to 2637, and the average age of participants ranged from 19.7 to 41.3 years. While three studies also included children, their results obtained in adult subjects met our inclusion criteria.[26,37,38] Eleven studies included men exclusively,[22–29,33,37,38] one study only females[31] and five both genders.[30,32,34–36] A summary of the study characteristics is provided in Table 1.

Eight studies assessed the link between genetic polymorphisms and NCMI risk (injured subjects vs. non-injured subjects),[30–37] eight studies between genetic polymorphisms and NCMI incidence,[22–27,36,38] 12 between genetic polymorphisms and injury severity,[22–29,35–38] and three between genetic polymorphisms and recovery time.[22,27,28]

All studies used independent candidate gene analysis strategy. Across all 17 studies, 59 polymorphisms affecting 47 genes were assessed. The two most studied polymorphisms *ACTN3 rs1815739*[22,23,30,31,33,36,38] and *COL5A1 rs12722*[23,24,27–29,35] were examined in seven and six of the studies, respectively. *CCL2* rs2857656, *SOX15* rs4227, and *IGF2* rs3213221 were investigated in four studies[23,27–29]; *COL1A1* rs1800012, *TNC* rs2104772, and *TTN* rs2742327 in three[23,28,29]; ACE I/D (rs1799752) in three[23,31,37]; *ELN* rs2289360 in two[28,29]; and *GDF5* rs143383 and *MMP3* rs679620 also in two.[23,27] The remaining polymorphisms examined were only analyzed in one study each (Table 2).

3.3 | Study quality assessment

Methodological quality scores of the studies reviewed ranged from 11/15 to 15/15 on the McMaster scale. This quality was classed as high in one study (6%)[38] and excellent (94%) in the remaining 16 studies.[22–37] However, due to variability of methodologies and data analysis, a meta-analysis was not possible.

3.4 | Genes examined

3.4.1 | ACTN3

The links between the *Alpha actinin 3* (*ACTN3*) rs1815739 polymorphism (R577X) and NCMI risk[30,31,33,36] and incidence[22,23,36,38] were examined in four different studies. Clos et al.[22] and Massidda et al.[38] detected significant association between a XX genotype and a higher NCMI incidence. In the case-control study carried out in football players, these last authors[38] reported that players with a XX genotype had a greater NCMI incidence compared to their RX and RR counterparts (OR 2.66 [95% CI: 1.09–6.63]). In addition, Clos et al.[22] found that their XX genotype football players showed a higher injury rate (2.78) than RR (1.51) and RX (0.83) genotypes, respectively ($p = 0.003$). In contrast, Larruskain et al.[23] and Moreno et al.[36] reported no association between the *ACTN3* rs1815739 polymorphism and NCMI incidence, yet did note that amateur marathon runners with a XX genotype were more likely to undergo NCMI compared to RR or RX genotype runners, with an OR of 2.0 (95% CI: 0.51–7.79) and 3.52 (95% CI: 0.91–13.51) ($p = 0.024$), respectively. Conversely, Iwao-Koizumi et al.[31] found that the 577R allele of this gene was more frequent in Japanese university athletes with NCMI than in their non-injured group, with an OR of 2.52 (95% CI: 1.42–4.47) ($p = 0.0015$). Gutiérrez-Hellín et al.[30] and Miyamoto et al.,[33] however, found no associations between any *ACTN3* SNP and NCMI risk in elite endurance runners and university athletes, respectively. The relationship between the *ACTN3* rs1815739 polymorphism and NCMI severity was addressed in four studies, specifically in football player populations.[22,23,36,38] Massidda et al.[38] found that players with an XX or RX genotype carried higher risks of severe NCMI than RR genotype players, OR = 2.13 (95% CI: 1.25–3.74) ($p = 0.0054$) and OR = 1.63 (95% CI: 1.10–2.40) ($p = 0.015$), respectively. However, Clos et al.,[22] Moreno et al.,[36] and Larruskain et al.[23] found no link between *ACTN3* SNP and NCMI severity. Besides, in a study examining the relationship between *ACTN3* rs1815739 and recovery time after a NCMI, Clos et al.[22] detected no significant differences in recovery times between genotypes.

3.4.2 | COL5A1

Three studies[23,24,27] addressed the link between the *Collagen type 5 alpha-1* (*COL5A1*) rs12722 polymorphism and NCMI incidence, and one study its link with NCMI risk,[35] yet no significant differences emerged between genotypes. Six

TABLE 1 Summary of reviewed studies (N = 17 studies)

Autor	Year	Aim investigated	Study design	Participants	Ethnicity	Age (years)	Sporting specialization	Score McMaster
Clos et al. [22]	2019	The association between *ACTN3* rs1815739 and NCMSTIs rate, injury severity and recovery time	Longitudinal (7 years)	43 (M)	European, Black African and Hispanic	27.8 [20–37]	Professional football players	14/15
Gutiérrez-Hellín et al. [30]	2021	The association between *ACTN3* rs1815739 (R577X) and injury epidemiology	Cross-sectional (questionnaire)	89 (M = 48; F = 41)	European (Spanish)	RR: 22.8 ± 4.2; RX: 24.5 ± 10.5; XX: 26.6 ± 7.0	Elite endurance runners	14/15
Iwao-Koizumi et al. [31]	2014	The association between *ACE*, *ACTN3* and *UCPs* SNPs and NCMI	Cross-sectional (questionnaire)	99 (F)	Japanese	19.7 [18–22]	Future professional football, softball, basketball and badminton players	14/15
Kumagai et al. [32]	2019	The association of 2 *ESR1* SNPs (rs2234693, rs9340799) with a history of NCMI	Cross-sectional (questionnaire)	1311 (M = 870; F = 441)	Japanese	Injured: 20.2 ± 1.7; Non-injured: 20.6 ± 2.9	Athletes (national level or more)	13/15
Larruskain et al. [23]	2018	The association between genetic polymorphisms and hamstring injury risk and severity, and create a model to estimate the risk of HMI and test its validity	Longitudinal (6 years)	107 (M)	European (Spanish)	20.0 ± 4.0	Football players (first, reserve and U19 teams)	15/15
Massidda et al. [25]	2015a	The association between *VDR* polymorphisms and NCMI incidence and severity	Longitudinal (4 years)	54 (M)	European (Italian)	25.9 ± 4.3	Professional football players	13/15
Massidda et al. [24]	2015b	The association between *COL5A1* rs12722 and NCMI incidence and severity	Longitudinal (4 years)	54 (M)	European (Italian)	25.9 ± 4.3	Professional football players	13/15
Massidda et al. [26]	2015c	The association between *MCT1* rs1049434 and NCMI incidence and severity	Longitudinal (5 years)	173 (M)	European (Italian)	19.4 ± 5.2	Professional football players (and cadets, juniors, U19 teams)	12/15
Massidda et al. [38]	2017	The association between *ACTN3* rs1815739 SNP and NCMI incidence and severity	Case-control	Case: 169 (M) Controls: 263 (M)	European (Italian)	19.4 ± 5.2	Professional football players (and cadets, juniors, U19 teams)	11/15
Massidda et al. [37]	2020	The association between *ACE* I/D rs4341 and NCMI risk	Longitudinal/ cross-sectional/ meta-analysis	710 (M) Italian: 341 Japanese: 369	European (Italian) and Japanese	Caucasian: 19.9 ± 5.0 Japanese: 20.8 ± 1.4	Professional football players (and cadets, juniors, U19 teams)	13/15

(Continues)

TABLE 1 (Continued)

Autor	Year	Aim investigated	Study design	Participants	Ethnicity	Age (years)	Sporting specialization	Score McMaster
Miyamoto et al. [33]	2018	The association between *ACTN3* rs1815739 and passive muscle stiffness and hamstring injury risk and severity	Cross-sectional (questionnaire)	76 (M)	Japanese	21.2 ± 2.8	University sport science students	13/15
Miyamoto-Mikami et al. [35]	2019	The association between *COL5A1* rs12722 and NCMI risk, ROM and passive muscle stiffness	Cross-sectional (questionnaire)	1559 (M: 1063; F: 496)	Japanese	Injured: 20.1 ± 1.7; Non-injured: 20.5 ± 2.8	Athletes (mixed sport)	13/15
Miyamoto-Mikami et al. [34]	2020	The association between *COL22A1* SNPs and NCMI risk	Cross-sectional (questionnaire)	2637 (M: 1870; F: 767)	Japanese	Injured: 20.2 ± 2.0 Non-injured: 20.2 ± 2.7	Athletes (mixed sport)	13/15
Moreno et al. [36]	2020	The association between *ACTN3* rs1815739 (R577X) and NCMI incidence	Cross-sectional (questionnaire)	139 (M: 119; F: 20)	-	RR: 41.3 ± 10.2; RX: 40.3 ± 8.8; XX: 40.7 ± 9.8	Amateur marathon runners	14/15
Pruna et al. [28]	2013a	The association between genetic polymorphisms and NCMSTIs severity and recovery time	Longitudinal (3 years)	73 (M)	European, Black African and Hispanic	26.2 [19–35]	Professional football players (first and second teams)	13/15
Pruna et al. [29]	2013b	The association between genetic polymorphisms and NCMSTIs severity comparing the ethnicities	Longitudinal (3 years)	73 (M)	European, Black African and Hispanic	26.2 [19–35]	Professional football players (first and second teams)	13/15
Pruna et al. [27]	2016	Identify genetic biomarkers of non-contact injury incidence, severity and recovery time	Longitudinal (5 years)	74 (M)	European, Black African and Hispanic	[19–35]	Professional football players (first and second teams)	13/15

Abbreviation: ACE, Angiotensin I-converting enzyme; ACTN3, Alpha actinin 3; COL5A1, Collagen type 5 alpha-1; COL22A1, Collagen type 22 alpha-1; ESR1, Estrogen receptor 1; HMI, hamstring muscle injury; MCT1, Monocarbocylate transporter 1; NCMI, non-contact muscle injuries; NCMSTIs, non-contact soft musculoskeletal tissue injuries; ROM, Range of Motion; U19, under 19 years; UCP, uncoupling protein; VDR, Vitamin D receptor. Participants (M, male; F, female).

studies[23,24,27–29,35] examined the association between this polymorphism and injury severity. Massidda et al.[24] found the variant accounted for 44% of severity of injuries, with a trend of the TT genotype toward a greater severity than in subjects with the TC or CC genotype ($p = 0.193$, d = 0.22). In their first study in professional football players, Pruna et al.[28] found a tendency of the TC genotype to undergo more severe NCMI ($p = 0.08$). In their subsequent study,[27] they were able to detect significant association between the TC genotype and more severe injuries ($p = 0.042$). Larruskain et al.,[23] Pruna et al., and Miyamoto-Mikami et al.[35] observed no significant difference in injury severity between genotypes. In their two studies, Pruna et al.[27,28] also examined the relationship between the SNP and recovery time after NCMI and observed no significant association. Larruskain et al.[23] also assessed the effects of the *COL5A1* rs16399 polymorphism on NCMI incidence, and found a significant association between a heterozygote ID (insertion-deletion) genotype and a higher incidence of hamstring injuries compared to DD and II genotypes, with a hazard ratio of 1.83 ($p = 0.01$).

3.4.3 | ACE

Two studies[31,37] addressed the impacts of the *Angiotensin I-converting enzyme* (*ACE*) I/D polymorphism (rs1799752). Iwao-Koizumi et al.[31] found a possible relationship between NCMI risk and an *ACE* genotype in Japanese athletes, the DD genotype being less frequent in their non-injured group. Massidda et al.[37] found that the D-allele was associated with the prevalence of NCMI in their Japanese cohort of professional football players (OR = 0.49 [95% CI: 0.24–0.97]) ($p = 0.04$). They confirmed this result in a meta-analysis of data from an Italian cohort of professional football players, showing that the frequency of the D-allele was significantly lower in the injured group compared to the non-injured group, with an OR = 0.61 (95% CI: 0.38–0.98) ($p = 0.04$). In contrast, Larruskain et al.[23] reported no differences between genotypes in *ACE* I/D (rs1799752) and NCMI incidence. Two studies[23,37] reported no significant effects of the polymorphism on injury severity in professional football players.

3.4.4 | CCL2

In football players, the authors of two studies[23,27] found no association between having the *Chemokine CC motif ligand 2* (*CCL2*) rs2857656 polymorphism and NCMI incidence. Four studies[23,27–29] investigated the effect of this polymorphism on injury severity. In their 2013 study, Pruna et al.[28] detected a significant association between the C-allele and less severe NCMI compared to the GG genotype. This result was confirmed in their next study.[27] In contrast, Larruskain et al.[23] found no significant difference in injury severity between genotypes. Further, in their two studies,[27,28] no link was observed between the polymorphism and recovery time. Pruna et al.[27] were also unable to find a significant link between another *CCL2* gene polymorphism rs1860189 and NCMI incidence, severity, and recovery time.

3.4.5 | IGF2

Two studies[23,27] investigated, in a population of football players, the association between the *Insulin-like growth factor II* (*IGF2)* rs3213221 polymorphism and NCMI incidence and detected no significant differences between genotypes. Four studies[23,27–29] examined the effect of this gene variant on injury severity. In their 2013 study, Pruna et al.[28] were able to correlate the GC genotype with less severe NCMI than the GG and CC genotypes. This finding was confirmed in their following study.[27] These authors also found a near-significant association between the *IGF2* rs3213221 genotype and the pattern of NCMI in European players ($p = 0.059$): CC players showed a different pattern to GC/GG players, and a significant association in Hispanic players, with GG players showing a different pattern to GC/CC players.[29] In contrast, Larruskain et al.[23] reported no significant difference in injury severity between genotypes. Pruna et al.[27,28] in two different studies also detected no association between the *IGF2* rs3213221 polymorphism and recovery time.

3.4.6 | SOX15

Two of the studies reviewed here[23,27] examined the link between *SRY-Box 15* (*SOX15*) rs4227 and NCMI incidence in football players. In their 2016 study, Pruna et al.[27] found a significant relationship between the *SOX15* genotype and injury rate, in that carriers of the T allele showed a reduced number of injuries. However, Larruskain et al.[23] found no significant association between *SOX15* SNP and NCMI incidence. In four studies[23,27-29] in which associations with injury severity were looked for, no significant differences were detected between genotypes. The association of this polymorphism with recovery time was explored by Pruna et al. in two different studies,[27,28] again with no significant differences observed between genotypes.

3.4.7 | TNC

Relationships with the *Tenascin C* (*TNC*) rs2104772 variant were explored in four of the studies reviewed here.[23,27–29] Two studies[23,27] examined effects on NCMI incidence in football players. The study by Larruskain et al.[23] found that the A allele

of *TNC* rs2104772 was associated with a higher incidence of NCMI, with a hazard ratio of 1.65 (95% CI: 1.17–2.32) ($p = 0.004$). However, Pruna et al.[27] noted no significant difference between the genotypes. In four studies[23,27–29] and two studies,[27,28] respectively, no associations emerged between the variant and injury severity or recovery time.

3.4.8 | MMP3

Two studies[23,27] examined the polymorphism *Matrix metalloproteinase 3* (*MMP3*) rs679620. Larruskain et al.[23] found that the A allele *MMP3* rs679620 was associated with acute, overuse, severe and recurrent NCMI and with a higher NCMI incidence than the G allele, with a hazard ratio of 1.79 (95% CI: 1.27–2.51) ($p = 0.001$). Pruna et al.[27] found no significant difference among the genotypes in recovery time.

3.4.9 | ELN

In two different studies,[28,29] Pruna et al. investigated the association between *Elastin (ELN)* rs2289360 and NCMI severity and found an association only when analyzing the participants' ethnicity such that Spanish football players carrying the G allele showed a different pattern of NCMI, with less severe injuries than those carrying the A allele.[29] No difference in recovery time[28] was found between genotypes of this gene variant.

3.4.10 | Other genes

The other SNPs found to be significantly related to NCMI in this review were only detected in single studies. The SNPs associated with NCMI risk were *Collagen type 22 alpha-1* (*COL22A1)* rs11784270 and rs6577958[34] and *Estrogen receptor 1 (ESR1)* rs2234693[32]; those related to NCMI incidence were *COL5A1* rs16399, *Decorin (DCN)* rs516115, *Hypoxia-inducible factor 1 (HIF1A)* rs11549465, *Matrix metalloproteinase 1 (MMP1)* rs1799750, *Matrix metalloproteinase 12 (MMP12)* rs2276109 and *Nitric oxide synthase 3 (NOS3)* rs1799983,[23] *Hepatocyte growth factor (HGF)* rs1011694 and rs5745697,[27] and *Monocarbocylate transporter 1 (MCT1)* rs1049434[26]; those related to NCMI severity were *A disintegrin-like and metalloproteinase with thrombospondin type 1 motif*, *14 (ADAMTS 14)* rs4747096, *Caspase 8 (CASP8)* rs3834129, *Interleukin 1-alpha (IL1A)* rs1800587, *Myosin light chain kinase (MLCK)* rs2700352,[23] and *HGF* rs1011694, rs5745697 and rs5745678,[27] *Vitamin D receptor (VDR)* ApaI[25]; and those related to recovery time were *Rho guanine nucleotide exchange factor 25 (GEFT)* rs11613457 and *HGF* rs5745697 and rs5745678.[27]

4 | DISCUSSION

This review identified 17 articles examining the impacts of polymorphisms affecting 47 different genes on NCMI in different populations of athletes (Table 3). Over half (25/47) of these genes featured polymorphisms found significantly associated with NCMI risk, incidence, severity, and/or recovery time. These findings confirm that genetic variations can be considered risk factors for NCMI, and that their impacts will depend of the combination of various polymorphisms in different genes. We observed that the most relevant genetic variations significantly related to NCMI belonged to three main categories of genes: (i) those involved in the structural/contractile properties of muscle fibers, (ii) those involved in muscle repair and regeneration, and (iii) those involved in muscle external matrix composition and maintenance (Figure 2).

4.1 | Genes related to NCMI risk and incidence

As detailed in Table 3, this systematic review identifies several polymorphisms related to the risk/incidence of NCMI. Firstly, the *ACTN3* R577X (rs1815739) polymorphism showed the strongest links in three studies[22,36,38] in that the XX polymorphism or X allele was associated with a higher risk or incidence of NCMI. Alpha-actinin-3 proteins represent the main structural components of the sarcomere Z-disk in type II muscle fibers, where they anchor thin actin filaments.[39–41] The *ACTN3* 577X allele leads to a premature stop codon during translation and thus to α-actinin-3 protein deficiency in the case of the 577XX genotype. This absence of protein is not pathologic and is relatively frequent (approximately 18% of the world population).[41] This polymorphism is one of the most studied in relation to athletic performance, especially in power/sprint/strength-oriented sports in which the 577XX genotype has been generally linked to lower performance.[42–45] Given the important mechanical role of the protein within the muscle, it is logical that a lack of ACTN3 will determine weaker tissues more likely to suffer injury compared to those of individuals showing the presence of the protein. However, one study[31] found a possible relationship between the 577R allele and a greater risk of NCMI. This study, unlike the other three, was carried out in young Japanese female (university) athletes, which could explain the difference in results.

Other polymorphisms involved in different physiological pathways such as muscle tissue repair and regeneration have been related to the risk or incidence of NCMI: *SOX15* T/G (rs4227), *TNC* A/T (rs2104772), *MMP3* G/A (rs679620), *ACE* I/D (rs1799752), HGF (rs5745697) and (rs1011694), *HIF1A* C/T (rs11549465) and *NOS3* G/T (rs1799983), see Table 3. SRY-Box 15 (SOX15) plays a role in determining

TABLE 2 List of analyzed genetic polymorphisms

			Clos et al. (2019) [22]	Gutiérrez-Hellín et al. (2021) [30]	Iwao-Koizumi et al. (2014) [31]	Kumagai et al. (2019) [32]	Larruskain et al. (2018) [23]	Massidda et al. (2015a) [25]	Massidda et al. (2015b) [24]
ACAN	Aggrecan	rs1516797					●		
ACE	Angiotensin I-converting enzyme	rs1799752 (I/D)			●		●		
ACTN3	Alpha actinin 3	rs1815739	●	●	●		●		
ADAM12	A disintegrin and metalloproteinase domain 12	rs3740199					●		
ADAMTS14	A disintegrin-like and metalloproteinase with thrombospondin type 1 motif, 14	rs4747096					●		
ADAMTS2	A disintegrin-like and metalloproteinase with thrombospondin type 1 motif, 2	rs1054480					●		
ADAMTS5	A disintegrin-like and metalloproteinase with thrombospondin type 1 motif, 5	rs226794					●		
CASP8	Caspase 8, apoptosis-related cysteine protease	rs1045485					●		
		rs3834129					●		
CCL2	Chemokine CC motif Ligand 2	rs1860189							
		rs2857656					●		
CCR2	Chemokine CC motif Receptor 2	rs768539					●		
COL12A1	Collagen type 12 alpha-1	rs970547					●		
COL1A1	Collagen type 1 alpha-1	rs1107946					●		
		rs1800012					●		
COL22A1	Collagen type 22 alpha-1	rs11784270							
		rs6577958							
COL5A1	Collagen type 5 alpha-1	rs16399					●		
		rs12722					●		●
DCN	Decorin	rs516115					●		
DES	Desmin	rs58999456							
		rs60794845							
ELN	Elastin	rs2289360							
EMILIN1	Elastin microfibril interfacer 1	rs2289360					●		
ESR1	Estrogen receptor 1	rs2234693				●			
		rs9340799				●			
GDF5	Growth/differentiation factor 5	rs143383					●		
GEFT	Rho guanine nucleotide exchange factor 25	rs11613457							
HGF	Hepatocyte growth factor	rs1011694							
		rs5745697							
		rs5745678							

Massidda et al. (2015c) [26]	Massidda et al. (2017) [38]	Massidda et al. (2020) [37]	Miyamoto et al. (2018) [33]	Miyamoto-Mikami et al. (2019) [35]	Miyamoto-Mikami et al. (2020) [34]	Moreno et al. (2020) [36]	Pruna et al. (2013a) [28]	Pruna et al. (2013b) [29]	Pruna et al. (2016) [27]	Times analyzed
										1
		●								3
	●		●			●				7
										1
										1
										1
										1
										1
									●	1
							●	●	●	4
										1
										1
										1
							●	●		3
					●					1
					●					1
										1
				●			●	●	●	6
										1
									●	1
									●	1
							●	●		2
										1
										1
										1
									●	2
									●	1
									●	1
									●	1
									●	1

(Continues)

TABLE 2 (Continued)

			Clos et al. (2019) [22]	Gutiérrez-Hellín et al. (2021) [30]	Iwao-Koizumi et al. (2014) [31]	Kumagai et al. (2019) [32]	Larruskain et al. (2018) [23]	Massidda et al. (2015a) [25]	Massidda et al. (2015b) [24]
HIF1A	Hypoxia-inducible factor 1 alpha subunit	rs11549465					●		
IGF2	Insulin-like growth factor 2	rs3213221					●		
IL1A	Interleukin 1-alpha	rs1800587					●		
IL1B	Interleukin 1-beta	rs1143634					●		
IL6	Interleukine 6	rs1800795					●		
IL6R	Interleukine 6 receptor	rs2228145					●		
LIF	Leukemia-inhibitory factor	rs737812							
		rs9290271							
MCT1	Solute carrieur family 16 (Monocarboxylic acid transporter), member 1	rs1049434							
MLCK	Myosin light chain kinase	rs2700352					●		
MMP1	Matrix metalloproteinase 1	rs1799750					●		
MMP12	Matrix metalloproteinase 12	rs2276109					●		
MMP3	Matrix metalloproteinase 3	rs679620					●		
MYF5	Myogenic factor 5	rs1163263							
NOS3	Nitric oxide synthase 3	rs1799983					●		
SOD2	Superoxide dismutase 2	rs4880					●		
SOX15	SRY-Box 15	rs4227					●		
TIMP2	Tissue inhibitor of metalloproteinase 2	rs4789932					●		
TNC	Tenascin C	rs2104772					●		
TNF	Tumor necrosis factor	rs1800629					●		
TTN	Titin	rs2742327					●		
UCP1	Uncoupling protein 1	rs1800592			●				
UCP2	Uncoupling protein 2	rs659366			●				
UCP3	Uncoupling protein 3	rs1800849			●				
VDR	Vitamin D receptor	rs1544410						●	
		rs2228570						●	
		rs7975232						●	
VEGFA	Vascular endothelial growth factor A	rs2010963					●		
Number of SNPs analyzed			1	1	5	2	37	3	1

skeletal muscle cell fate during development[46] and has been shown to be necessary for muscle cell proliferation and muscle tissue regeneration.[47] Tenascin C (TNC) is a glycoprotein that plays an important role in the muscle damage repair cycle, and provides strength and elasticity to resist mechanical forces. It is expressed in regenerating myofibers and in response to mechanical loading in the myotendinous junction, the most vulnerable site of injury.[48] Matrix metalloproteinase 3 (MMP3) plays a key role in the maintenance of myofiber functional integrity by breaking down components of the extracellular matrix and in the regulation of skeletal muscle cell migration, differentiation, and regeneration.[49] Angiotensin I-converting enzyme (ACE) is an essential component of the renin-angiotensin system and tissue kallikrein-kinin system. Higher ACE activity, associated with the D allele of the ACE I/D polymorphism (rs1799752), results in the higher production of angiotensin II and a decreased half-life of bradykinin, both involved in the inflammatory processes that occur following muscle damage.[50] Hepatocyte growth factor (HGF) participates in skeletal muscle development and regeneration by activating quiescent satellite cells and myoblast differentiation into myotubes.[51] Hypoxia-inducible factor 1α (HIF1A) is a transcription factor regulating several genes in response to hypoxia in skeletal muscle, stimulating angiogenesis and

Massidda et al. (2015c) [26]	Massidda et al. (2017) [38]	Massidda et al. (2020) [37]	Miyamoto et al. (2018) [33]	Miyamoto-Mikami et al. (2019) [35]	Miyamoto-Mikami et al. (2020) [34]	Moreno et al. (2020) [36]	Pruna et al. (2013a) [28]	Pruna et al. (2013b) [29]	Pruna et al. (2016) [27]	Times analyzed
										1
							●	●	●	4
										1
										1
										1
										1
									●	1
									●	1
●										1
										1
										1
										1
									●	2
									●	1
										1
										1
							●	●	●	4
										1
							●	●		3
										1
							●	●		3
										1
										1
										1
										1
										1
										1
1	1	1	1	1	2	1	8	8	16	-

glycolytic metabolism. It can be induced by mechanical loading, and is an important component of matrix remodeling and skeletal myogenesis.[52,53] Nitric oxide synthase 3 (NOS3) is the rate-limiting enzyme for nitric oxide production. Nitric oxide has many relevant biological functions in muscle, such as, regulation of blood flow, muscle contractility, mitochondrial respiration, and skeletal muscle injury repair.[54] Accordingly, these polymorphisms could affect the ability of muscle to quickly recover from exercise-induced damage produced by repeated sessions of training and competition, and could thus be related to a higher risk of NCMI in the long term for athletes. However, the number of studies and subjects available to address this issue are still scarce, and more studies are needed to better understand these aspects.

Further, the other category of variant genes found related to the incidence of NCMI are genes involved in the maintenance and remodeling of the connective tissue extracellular matrix surrounding the muscle cells and spindles: *COL5A1* I/D (rs16399), *DCN* A/G (rs516115), *MMP1* I/D (rs1799750), *MMP3* G/A (rs679620), and *MMP12* A/G (rs2276109). Collagen type 5 alpha-1 (COL5A1) encodes the α1 chain of type V collagen, which forms part of the extracellular matrix in skeletal muscle. COL5A1 interacts with COL1A1 and has an important functional role in regulating

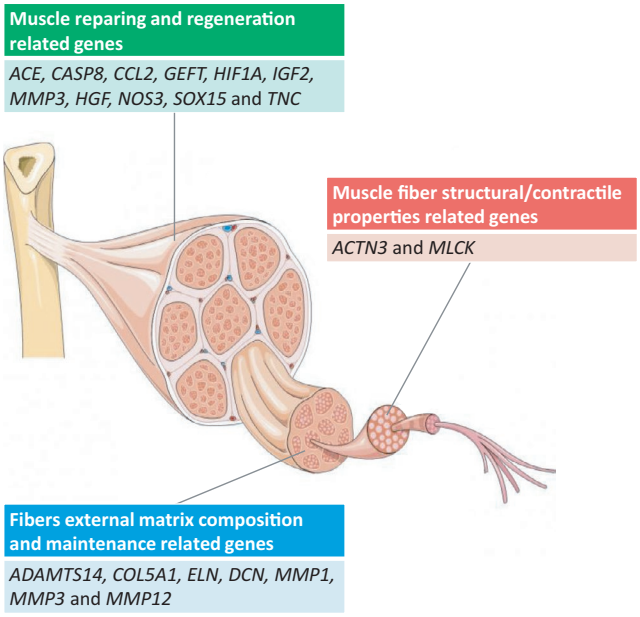

FIGURE 2 Functional categories of the genes significantly related with NCMI risk, incidence, recovery time or severity

collagen fiber diameters and their assembly, thus modulating fibrillogenesis.[55,56] Further, the inclusion of decorin proteoglycan (DCN) during fibrillogenesis of type I collagen increases the modulus and tensile strength of resulting collagen gels, improving their mechanical properties. Like MMP3, MMP1 and MMP12 are matrix metallopoteinases responsible for the maintenance of the extracellular matrix, degrading proteins (collagen) and components and playing a role in muscle cell-matrix interactions.[57,58] It also seems logical that these polymorphisms could affect the quality and strength of the different connective tissue matrices surrounding the muscle cells and spindles, as well as the quality of cell-matrix interactions and anchoring, and could be thus related to weaker muscle tissues promoting higher NCMI rates. However, once again this topic has only just started to be explored, and many more studies are needed to confirm the role played by genetic polymorphisms in these traits.

4.2 | Genes related to NCMI severity and recovery time

Several studies have investigated possible polymorphisms linked to NCMI severity. Rather than measuring NCMI severity through clinical or imaging tests, these studies have determined the number of days from the date of injury until return to full training and competition to establish categories of severity. However, while these categories are not homogeneous among some of the studies, all of them considered the highest severity category more than 28–30 days of recovery time.

TABLE 3 Details of polymorphisms significantly linked to NCMI

Role	Polymorphism (rs)	Study	Injury risk	Injury incidence	Injury severity	Recovery time
Structural/contractile properties of the muscle fibers	***ACTN3*** R577X (rs1815739), exon (OMIM: 102574)	Clos et al. (2019) [22]		↑ XX	ns	ns
		Gutiérrez-Hellín et al. (2021) [30]	ns			
		Iwao-Koizumi et al. (2014) [31]	↑ R			
		Larruskain et al. (2018) [23]		ns	ns	
		Massidda et al. (2017) [38]		↑ XX	↑ X	
		Miyamoto et al. (2018) [33]	ns			
		Moreno et al. (2020) [36]	↑ XX	ns	ns	
	MLCK C/T (rs2700352), 5′ UTR (OMIM: 600922)	Larruskain et al. (2018) [23]		ns	↑ TT	

(Continues)

TABLE 3 (Continued)

Role	Polymorphism (rs)	Study	Injury risk	Injury incidence	Injury severity	Recovery time
Muscle tissue repair and regeneration	***ACE*** I/D (rs1799752, rs4341), intron (OMIM: 106180)	Iwao-Koizumi et al. (2014) [31]	ns			
		Larruskain et al. (2018) [23]		ns	ns	
		Massidda et al. (2020) [37]	↓ D		ns	
	CASP8 I/D (rs3834129), intron (OMIM: 601763)	Larruskain et al. (2018) [23]		ns	↑ DD + II	
	CCL2 G/C (rs2857656), intron (OMIM: 158105)	Larruskain et al. (2018) [23]		ns	ns	
		Pruna et al. (2013a) [28]			↓ C	ns
		Pruna et al. (2016) [27]		ns	↓ C	ns
	GEFT G/A (rs11613457) (OMIM: 610215)	Pruna et al. (2016) [27]		ns	ns	↓ GG
	HGF T/C (rs5745678), intron (OMIM: 142409)	Pruna et al. (2016) [27]		ns	↓ T	↓ T
	HGF A/C (rs5745697), intron	Pruna et al. (2016) [27]		↓ CC	↓ A	↓ A
	HGF A/T (rs1011694), intron	Pruna et al. (2016) [27]		↓ AA	↓ T	ns
	HIF1A C/T (rs11549465), exon (OMIM: 603348)	Larruskain et al. (2018) [23]		↑ CC	ns	
	IGF2 C/G (rs3213221), intron (OMIM: 147470)	Larruskain et al. (2018) [23]		ns	ns	
		Pruna et al. (2013a) [28]			↓ GC	ns
		Pruna et al. (2016) [27]		ns	↓ GC	ns
	LIF C/T (rs929071), intron (OMIM: 159540)	Pruna et al. (2016) [27]		ns	ns	↓ TT
	MMP3 A/G (rs679620), exon (OMIM: 185250)	Larruskain et al. (2018) [23]		↑ A	↑ A	
		Pruna et al. (2016) [27]		ns	ns	ns
	NOS3 T/G (rs1799983), exon (OMIM: 163729)	Larruskain et al. (2018) [23		↑ G	ns	
	SOX15 G/T (rs4227), 3' UTR (OMIM: 601297)	Larruskain et al. (2018) [23]		ns	ns	
		Pruna et al. (2013a) [28]			ns	ns
		Pruna et al. (2016) [27]		↓ T	ns	ns
	TNC A/T (rs2104772), exon (OMIM: 187380)	Larruskain et al. (2018) [23]		↑A	ns	
		Pruna et al. (2013a) [28]			ns	ns

(Continues)

TABLE 3 (Continued)

Role	Polymorphism (rs)	Study	Injury risk	Injury incidence	Injury severity	Recovery time
Maintenance and remodeling of extracellular connective tissue	***ADAMTS14*** A/G (rs4747096), exon (OMIM: 607506)	Larruskain et al. (2018) [23]		ns	↑ AG	
	COL5A1 C/T (rs12722), 3' UTR (OMIM: 120215)	Larruskain et al. (2018) [23]		ns	ns	
		Massidda et al. (2015b) [24]		ns	↑ TT	
		Miyamoto-Mikami et al. (2019) [35]	ns		ns	
		Pruna et al. (2013a) [28]			ns	ns
		Pruna et al. (2016) [27]		ns	↑ TC	ns
	COL5A1 I/D (rs16399), 3' UTR	Larruskain et al. (2018) [23]		↑ DI	ns	
	COL22A1 A/C (rs11784270) (OMIM: 610026)	Miyamoto-Mikami et al. (2020) [34]	↑ A			
	COL22A1 T/C (rs6577958)	Miyamoto-Mikami et al. (2020) [34]	↑ T			
	DCN A/G (rs516115), intron (OMIM: 125255)	Larruskain et al. (2018) [23]		↑ A	ns	
	ELN A/G (rs2289360), intron (OMIM: 130660)	Pruna et al. (2013a) [28]			ns	ns
		Pruna et al. (2013b) [29]			↑ AA (in Hispanics)	
	MMP1 I/D (rs1799750) (OMIM: 120353)	Larruskain et al. (2018) [23]		↑ DD + DI	ns	
	MMP12 A/G (rs2276109), intron (OMIM: 601046)	Larruskain et al. (2018) [23]		↑ A	ns	
Other	***ESR1*** T/C (rs2234693), intron (OMIM: 133430)	Kumagai et al. (2019) [32]	↓ C			
	IL1A C/T (rs1800587) (OMIM: 147760)	Larruskain et al. (2018) [23]		ns	↑ CT	
	MCT1 A/T (rs1049434), exon (OMIM: 600682)	Massidda et al. (2015c) [26]		↓ TT	ns	
	VDR ApaI C/A (rs7975232), intron (OMIM: 601769)	Massidda et al. (2015a) [25]		ns	●	

↓: reduced risk, incidence, severity or recovery time, ↑: increased risk, incidence, severity or recovery time, ns: not significant, ●: significant results but not detailed.

The *ACTN3* gene, which is thought to play an important role in NCMI incidence, has generated controversial findings regarding NCMI severity in the 3 studies that have examined this relationship.[22,23,38] In 169 professional football players, Massidda et al.[38] detected clinically interesting odds ratios in favor of more severe injuries in players carrying at least one X allele than in those with the RR genotype (OR = 2.13 [1.25–3.74], $p = 0.0054$, for XX vs. RR); and (OR = 1.63 [1.10–2.40], $p = 0.015$, for RX vs RR). Based on their figures, we estimated a mean of around 28 days of recovery for athletes carrying the XX genotype vs. ~21 days and ~15 days for RX and RR, respectively. However, Clos et al. and Larruskain et al.[22,23] found no significant differences between genotypes of this variant in 43 and 107 football players, respectively. Interestingly, in one study,[23] another gene polymorphism linked to the structural properties of skeletal muscle fibers emerged as related to NCMI severity. This determined that elite football players with the TT genotype for the *MLCK* (rs2700352) polymorphism showed a higher risk of severe injury, with a hazard ratio of 8.69 [95%CI: 2.42–31.18] ($p = 0.001$). The *MLCK* gene codes for the myosin light chain kinase which is activated by Ca2+/calmodulin to phosphorylate the regulatory light chain of myosin in fast-twitch muscle fibers, producing increases in force development during skeletal muscle contraction[59] as well as the ability to resist muscle strain.[60]

In addition, several polymorphisms affecting genes related to physiological aspects of muscle tissue repair and regeneration also appear to play a role in NCMI severity. In the study of Pruna et al.,[27] *CCL2* G/C (rs2857656) and *IGF2* G/C (rs3213221) appeared significantly related to NCMI severity but not in the study by Larruskain et al.[23] The polymorphisms *CASP8* I/D (rs3834129), *MMP3* G/A (rs679620), and *HGF* (rs5745678, rs5745697, and rs1011694) have also been significantly linked to NCMI severity. Furthermore, Pruna et al.[27] obtained some interesting results in that elite football players with the CC genotype for the polymorphisms *HGF* rs5745678 and rs5745697 needed a mean of 7 days more of recovery than player with the CT/TT and CA/AA genotypes, respectively ($p = 0.009$ and $p = 0.02$). Even more interesting from a practical perspective, these authors also found that elite football players with the GG genotype of the *GEFT* rs11613457 polymorphism took a mean of 27 days less to recover from their NCMI than players carrying the GA polymorphism ($p = 0.004$). The Rho guanine nucleotide exchange factor (GEFT) belongs to the Rho family of small GTPases involved in diverse cell processes, including actin cytoskeleton regulation, cell polarity, microtubule dynamics, membrane transport pathways, and transcription factor activity, and seem key regulators of the skeletal myogenic program.[61] Further, Bryan et al.[62] found that human GEFT promoted skeletal muscle regeneration in cardiotoxin-injured mouse tibialis anterior muscle following gene transfer.

Finally, it seems that variants of genes that play a role in extracellular matrix composition and maintenance also show an appreciable impact on NCMI severity. Hence, the *COL5A1* T/C (rs12722) polymorphism has been related to NCMI severity in different studies, although so far results have been conflicting. Pruna et al.[27] found that the heterozygous TC genotype could be associated with a greater NCMI severity ($p = 0.042$), while Massidda et al.[24] noted the TT genotype was possibly related to this factor ($p = 0.193$, $d = 0.22$). The G allele of the *ELN* (rs2289360) polymorphism of the gene that codes for the elastin emilin, one of the main components of the extracellular matrix, was linked to a lower NCMI severity in the Hispanic population of study by Pruna et al. 2013b,[29] although this was not confirmed in their study of the same year.[28] Further, Larruskain et al.[23] observed that football players with the AA genotype of the *ADAMTS14* (rs4747096) polymorphism showed a lower risk of severe NCMI, with a hazard ratio of 4.49 (95%CI: 1.18–17.15) ($p = 0.03$). ADAMTS14 is a procollagen N-peptidase intervening during the synthesis of collagen fibers.[63]

4.3 | Limitations

This systematic review is a meticulous update of the evidence available regarding the genetic impact on NCMI. Despite the general good quality of the studies reviewed, there are still several limitations. Firstly, our review reveals that few polymorphism analyses have been replicated by several research groups. Only two polymorphisms have been frequently examined in relation to NCMI: *ACTN3* R577X rs1815739 and *COL5A1* C > T rs12722. Further, while the variant *ACTN3* R577X rs1815739 seems to be associated with NCMI risk, incidence and severity, the *COL5A1* C > T rs12722 variant of a gene known to play a role in ligament and tendon injuries,[64] does not seem to be very relevant for NCMI incidence. Future studies are needed to expand the existing body of knowledge, for example by confirming the effects of interesting polymorphisms identified in this review. Further, the main analysis strategy used to analyze relationships between genetic profiles and NCMI was to examine individual SNPs in candidate genes. It could be of interest to examine possible combinations between these different genes, as well as to develop next-generation sequencing strategies to help screen for the different genetic variants linked to NCMI. A further limitation is that participants of most of the studies reviewed (10 out of 17) were professional football (soccer) players. Although we consider football a very good model to explore NCMI incidence and severity because of the high incidence of injuries sustained by these athletes (estimated at 10–35 per 1000 h of exposure[65]), more research is needed to compare and analyze other sport modalities and levels of physical activity. Moreover, football was more represented in

this review, because two research groups working in the field of football NCMI and genetics were the most productive (5 publications from the University of Cagliari[24–26,37,38] and 4 from FC Barcelona Medical Services/S.M. Genomics[22,27–29]). Another possible limitation was that many of the studies analyzed together results obtained in people of different ethnicity. It is known that each polymorphism gives rise to different genotype frequencies and there could be ethnic-specific genetic profiles associated with sport-related NCMI. More studies are needed to clarify these possible ethnic-related genetic profiles. Finally, the most important limitation of the data available is the lack of homogeneity of analyzed variables and measurements, precluding any possible meta-analysis of data. We propose that future studies should follow the model developed by UEFA for the study of injuries in football players[66] recommending that studies should at least provide: (i) the number of injuries per 1000 h of participation, and (ii) raw numbers of days of absence from participation.

In conclusion, the findings of this review reveal that, so far, the data available regarding the relationship between genetic factors and NCMI are based on good quality observational studies. Our review confirmed that genetic variations play an important role in NCMI risk, incidence, severity, and recovery time. Notably, some genetic variations resulted in a difference of several weeks of "absence from participation" between the subjects). We observed that genetic variations significantly related to NCMI affected categories of genes involved in muscle fiber structural/contractile properties, muscle repair and regeneration, and muscle external matrix composition and maintenance. This systematic review also highlights that NCMI-related genetics is a new emerging field of research and that we are still far from developing a predictive model to estimate and reduce NCMI risk based on genetics. We recommend future studies should try to expand the sports and physical activities analyzed, and also strive for a greater homogeneity of methods and outcome measures to allow for accurate meta-analysis of results.

4.4 | Perspectives

Recently, genetic factors have been attributed an important role in the risk of having a non-contact muscle injury, as well as in its incidence, severity, and recovery time. While several reviews have been conducted of genetic variations associated with injuries of the tendons and ligaments, knowledge of the genetic factors related to skeletal muscle tissue injuries is still scarce and, to date, this is the first systematic review conducted on this topic. In our systematic review, we found that current knowledge in this field is still at a very early stage and that much more work is needed. Nevertheless, 28 reviewed polymorphisms have been found significantly associated with the risk, incidence and recovery time and/or severity of non-contact muscle injury. Some polymorphisms showing very promising results, for example presenting a difference in weeks in the time needed to recover from an injury.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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