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GENETIC DETERMINANTS OF NON-CONTACT MUSCLE INJURY: THE ROLE OF THE CREATINE KINASE, MUSCLE (CKM) RS8111989 POLYMORPHISM IN PHYSICALLY ACTIVE CAUCASIANS

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Abstract The creatine kinase, muscle (*CKM*) rs8111989 polymorphism has been repeatedly linked to athletic performance, yet its role in susceptibility to non-contact muscle injury remains unclear. This study examined the association between *CKM* rs8111989 and the risk of non-contact muscle injury in 269 physically active Caucasian adults. Participants were classified into a study group with a self-reported history of non-contact muscle injury (n=139) and an injury-free control group (n=130). Among injured participants, 25 reported one injury and 114 reported ≥2 injuries. Most participants were engaged in endurance-oriented disciplines, predominantly long-distance running. Genomic DNA was isolated from buccal swabs and genotyped using real-time polymerase chain reaction (real-time PCR). Logistic regression models (dominant, recessive, codominant, overdominant, log-additive) were applied to test associations between rs8111989 and injury status (any injury, one injury, multiple injuries), with age and body mass index (BMI) included as covariates. The rs8111989 alternative-allele frequency was 0.690 overall (controls 0.712; injury group 0.669; 1 injury 0.720; ≥2 injuries 0.658). No statistically significant associations were observed between rs8111989 genotypes and either the presence or number of non-contact muscle injuries after Bonferroni correction for multiple testing. These findings indicate that *CKM* rs8111989 is unlikely to exert a major independent effect on non-contact muscle injury risk in this cohort. Replication in larger, prospectively monitored, and sport-specific samples, ideally within polygenic frameworks, is warranted.

Key words: sports genetics, creatine kinase, muscle, rs8111989, non-contact muscle injury

Introduction

The pursuit of peak athletic performance is a complex interplay of training, environment, and, fundamentally, genetics (Mijaica et al., 2025). While rigorous physical activity is essential for achieving elite status, it also carries an inherent risk of musculoskeletal injury, which can significantly derail an athlete's career and overall well-being (Filbay et al., 2022). Understanding the underlying biological factors that predispose individuals to muscle damage is a critical area of sports medicine and genetics research (Leońska-Duniec, 2025).

Musculoskeletal injury risk is a multifactorial trait influenced by environmental and genetic factors. Previous studies have identified associations between injury susceptibility and genes involved in i) inflammation e.g. interleukin 6 (*IL6*), ii) structural organization of muscle fibers and the extracellular matrix e.g. alpha-actinin-3 (*ACTN3*) and collagen type V alpha 1 chain (*COL5A1*), iii) growth and repair pathways e.g. insulin-like growth factor 2 (*IGF2*), iv) membrane integrity, ion transport, and signaling pathways e.g. caspase 8 (*CASP8*), v) regulators of vascular function and perfusion e.g. angiotensin I-converting enzyme gene (*ACE*), and vi) metabolism and energy homeostasis e.g. adenosine monophosphate deaminase 1 (*AMPD1*) (Leońska-Duniec, 2025; Leońska-Duniec et al., 2025; Lim et al., 2021; Lulińska-Kuklik et al., 2019; Marques et al., 2024; Stastny et al., 2019). Among the numerous genetic markers investigated, the creatine kinase, muscle (*CKM*) gene, given its role in muscle energy metabolism and contraction, has emerged as a compelling candidate influencing both muscle performance and injury susceptibility in physically active populations (Chen et al., 2021; Echegaray & Rivera, 2001; Varillas-Delgado et al., 2023).

The CKM enzyme plays a pivotal role in cellular energy homeostasis, catalyzing the reversible transfer of a phosphate group from phosphocreatine to ADP, thereby rapidly regenerating ATP, particularly in tissues with high and fluctuating energy demands like skeletal muscle (Appel et al., 2021; Baumert et al., 2016). Variations in the *CKM* gene, such as the rs8111989 A/G single nucleotide polymorphism (SNP), are hypothesized to modulate the efficiency of this energy system, consequently affecting muscle function and resilience (Ginevičienė et al., 2021). Indeed, meta-analyses have established a significant association between this polymorphism and athletic phenotype, with the G allele and GG genotype being overrepresented in power athletes compared to the general population, suggesting a beneficial role in strength and power-related performance (Chen et al., 2021).

Despite the substantial progress in identifying genetic determinants of sports performance, the genetic basis of sports-related injuries remains comparatively underexplored. In contrast to anterior cruciate ligament (ACL) ruptures, which have been the focus of numerous epidemiological and mechanistic studies (Rahim et al., 2016), non-contact muscle injuries, such as strains and tears of the hamstrings, quadriceps, and calf muscles, are poorly characterized at the molecular level (Leońska-Duniec, 2025). Existing research has largely concentrated on extrinsic risk factors (e.g., training load, playing surface, or match congestion) and a limited set of intrinsic factors (e.g., age, previous injury), with relatively few studies addressing the contribution of genetic variation to muscle injury susceptibility (Green et al., 2020; Lim et al., 2021; Marques et al., 2024). Furthermore, most available genetic studies have been conducted in small, highly selective cohorts of elite athletes and frequently emphasize indirect markers of muscle damage (e.g., serum CK activity, delayed onset muscle soreness) rather than non-contact muscle injuries in broader physically active populations (Leońska-Duniec et al., 2025; Varillas-Delgado et al., 2023). This gap highlights the need for well-designed association studies that investigate specific polymorphisms, such as *CKM* rs8111989, in relation to objectively defined outcomes of muscle injury.

However, the relationship between the *CKM* rs8111989 variant and the occurrence of muscle injury is less clear and remains a subject of ongoing debate. Some research has suggested a potential link between this

polymorphism and muscle injury (Maestro et al., 2022; Varillas-Delgado, 2024; Varillas-Delgado et al., 2023). A recent study focusing on high-performance football players found that this polymorphism did not significantly affect the overall injury incidence during training or match exposure. This study, however, did report that players with the heterozygous GA genotype were more prone to experiencing severe injuries and muscle tears compared to homozygotes, suggesting that the polymorphism may influence the type or severity of injury rather than the overall frequency (Varillas-Delgado et al., 2023).

Therefore, the present study aimed to examine the association between the *CKM* rs8111989 A/G polymorphism and the risk of non-contact muscle injury in a cohort of 269 physically active Caucasian individuals. We hypothesize that a specific allele or genotype of this polymorphism will be significantly associated with an altered risk of this kind of sport-related injury.

Materials and Methods

Participants

The Bioethics Committee at the District Medical Chamber in Gdansk (No. KB-8/22) approved the study. The investigation protocols were conducted ethically according to the World Medical Association Declaration of Helsinki and to the Strengthening the Reporting of Genetic Association studies statement (STREGA). Initially, 812 individuals were assessed for eligibility. Participants were excluded if they were underage, failed to submit complete documentation, did not provide consent for genetic testing, reported contact-related injuries, or did not meet the physical activity criteria. Ultimately, a total of 269 unrelated Caucasian individuals were recruited between 2014 and 2020; their characteristics are summarized in Table 1.

The selection of participants for the study and control groups was based on the International Physical Activity Questionnaire (IPAQ), which was used to verify the level and type of habitual physical activity. Most participants were engaged in endurance disciplines, predominantly long-distance running. In addition, a structured survey was administered to collect information on previous injuries, the circumstances in which they occurred, and general health status. All participants were Polish Caucasians, which minimized the risk of ethnicity-related bias and potential problems of population stratification.

The study group comprised 139 physically active individuals with a self-reported history of non-contact muscle injury. The most frequently affected regions were the thigh (61.9%), foot (37.3%), calf (25.2%), upper limb girdle (19.0%), and hip (6.3%). Moreover, 28% of the study group reported additional injuries, such as fractures, dislocations, and sprains. The control group consisted of 130 healthy, unrelated individuals with no reported history of this kind of muscle injury.

Body mass and body composition parameters were assessed using bioelectrical impedance analysis with an electronic scale (Tanita MC-780 P MA, Arlington Heights, Illinois, United States).

Table 1. General characteristics of the studied individuals

Group	Number of participants	Number of men	Number of women	Mean age	Mean height (cm)	Mean body mass (kg)	BMI
Main Groups							
Control	130	0	130	21,3	168	60.9	21,7
Individuals with previous muscle injuries	139	113	26	36	175,7	74,1	23,8
Subdivision by Number of Previous Injuries							
One previous injury	25	18	7	35,7	173,6	71,6	23,6
Two or more previous injuries	114	95	19	36,0	176,1	74,6	23,9

* A single participant may be classified into more than one group in the case of multiple injuries; values are presented to three significant figures. BMI – Body Mass Index

Genetic Analyses

DNA was isolated from buccal swabs (Copan FLOQSwabs, Interpath, Murrieta, Australia) collected from each participant, using the High Pure PCR Template Preparation Kit (Roche, Basel, Switzerland) in accordance with the manufacturer's protocol. Genotyping of the *CKM* rs8111989 polymorphism was carried out in duplicate using a TaqMan® Pre-Designed SNP Genotyping Assay (ID: C___3145002_10; Applied Biosystems, Waltham, MA, USA) on a C1000 Touch Thermal Cycler (Bio-Rad, Hercules, CA, USA). Each PCR reaction mixture contained 2.5 µL TaqPath™ ProAmp™ Master Mix (Applied Biosystems), 0.25 µL 10× assay mix, 1.0 µL distilled water, and 1.25 µL genomic DNA, in a final volume of 5 µL. The thermal cycling protocol consisted of a pre-read at 60°C for 30 s, followed by an initial denaturation at 95°C for 5 min, and 40 cycles of 95°C for 5 s and 60°C for 30 s (combined annealing and extension), with a final post-read at 60°C for 30 s. Fluorescence signals were recorded and allelic discrimination was performed using CFX Maestro 4.0 software (Bio-Rad).

Statistical Analysis

The association between the rs8111989 polymorphism in the *CKM* gene and muscle injury occurrence, as well as the analysis of variant frequencies and compliance with Hardy-Weinberg Equilibrium (HWE), was performed using STATISTICA v.13.1 (TIBCO Software Inc., http://statistica.io, accessed on 14.11.2025). Information regarding the characteristics of the studied polymorphism was obtained from the gnomAD database (https://www.nature.com/articles/s41586-020-2308-7, accessed on 14.11.2025).

Before conducting the association analysis, the control group was compared with the study group in terms of additional factors that could influence interactions with genetic variants. For this purpose, the following tests were applied Student's t-test for numerical variables (age, body mass, body height, BMI) and Chi-square test for the categorical variable (sex). Covariates were included in the main association models if their values differed significantly between the control and study groups (nominal p-value <0.05). Body mass index (BMI) was selected as a covariate to avoid excessive correction, since it already accounts for body height and mass.

For each analysis performed, both the nominal p-value and the value adjusted for multiple comparisons using the Bonferroni correction were reported.

Results

The study analyzed the rs8111989 polymorphic site in the *CKM* gene among 269 individuals, including the study group (n=139) and the control group (n=130).

Characteristics of the Groups and Studied Polymorphisms

The characteristics of the control and study groups are presented in Table 1. A preliminary analysis was also performed to compare the control group with the study group in terms of additional factors (covariates). Numerical factors were compared using Student's t-test and categorical variables using the Chi-square test (Table 2). It was shown that all numerical variables (age, height, body mass, BMI) and the categorical variable (sex) differ significantly between the groups.

Table 2. Results of statistical tests comparing the control and study groups in terms of additional factors

Factor	Test	p-value	t/Chi-square Statistic	95% Confidence Interval
Age	Student's t-test	<0,001	19,10	13,14 – 16,14
Height	Student's t-test	<0,001	9,59	6,48 – 9,81
Body Mass	Student's t-test	<0,001	10,61	10,68 – 15,52
BMI	Student's t-test	<0,001	6,78	1,51 – 2,74
Sex	Chi-square	<0,001	179,82	–

* Comparisons yielding nominal p-values <0.05 are shown; odds ratios with 95% confidence intervals (CI) were estimated using generalized linear models.

The study analyzed the polymorphism rs8111989 located in the *CKM* gene, which general characteristics are presented in Table 3.

Table 3. Characteristics of the studied polymorphism

rsID	gnomAD ID	Chromosome	Reference Allele	Alternative Allele	Gene (Location within Gene)	CADD (Variant Deleteriousness)
rs8111989	19-45895457-G-A	19	G*	A*	*CKM*	0,073

* The table presents alleles according to the reference genome and dbSNP, while in the study, alleles of the opposite orientation (C/T) were genotyped. These designations (C/T) are used in subsequent parts of this report.

The frequency of the studied polymorphism for the alternative allele, along with a comparison to population database values (GnomAD), is presented in Table 4.

Table 4. Frequency of the studied polymorphism for the alternative allele

rsID	GnomAD european (non-Finnish)	Entire Study	Control Group	Study Group	1 Previous Injury	2 or more previous Injuries
rs8111989	0,105	0,690	0,712	0,669	0,720	0,658

Analysis of deviations from HWE

A HWE test was performed, and the results in the form of p-values are presented in Table 5. The test revealed a significant deviation in the entire sample (p=0.049), in the study group (p=0.017), and in the subgroup of participants with multiple injuries (p=0.026). The control group (p=0.727) and the subgroup with one injury (p=0.341) remain in agreement with HWE.

For all individuals included in the study, charts (Figure 1) were also prepared showing the frequency of homozygotes and heterozygotes for the analyzed polymorphism.

Table 5. P-values of tests checking deviations from HWE for each subgroup

rsID	Entire study	Control group	Study group	One previous injury	Two or more previous injuries
rs8111989	0,049	0,727	0,017	0,341	0,026

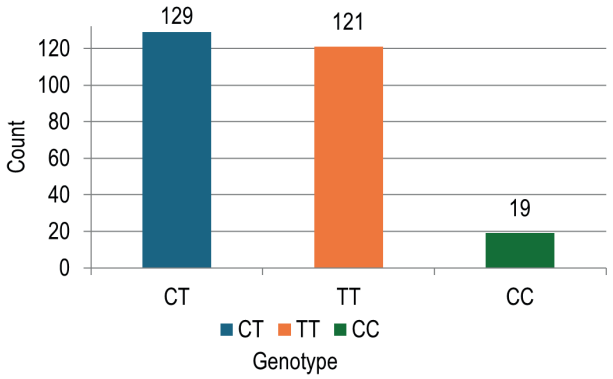


Figure 1. Distribution of homozygotes and heterozygotes for the rs8111989 polymorphism

Association analysis of polymorphism rs8111989 with covariates

For the studied polymorphism, it was examined whether there is a statistically significant association with any of the covariates: age, height, body mass, and BMI. The analysis was conducted using several models: dominant, recessive, codominant, overdominant, and log-additive.

None of the results reached the threshold of statistical significance in the association tests for the rs8111989 polymorphism with covariates (age, height, body mass, BMI) in the study group. The results of the analysis are presented in Table 6.

Table 6. Results of association analysis between additional factors (covariates) and studied variants

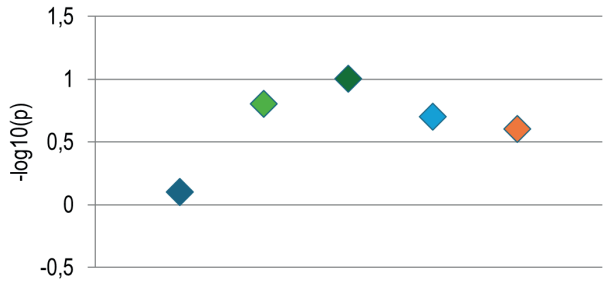
Covariate	Model	p	Adjusted p	Genotype	Mean Difference	95% CI Lower	95% CI Upper
Age	dominant	0,914	1	CT/TT vs CC	-0,38	-7,09	6,34
	recessive	0,949	1	TT vs CT/CC	0,10	-2,85	3,04
	codominant	0,988	1	-	-	-	-
	overdominant	0,902	1	CT vs CC/TT	-0,19	-3,13	2,76
	log-additive	0,927	1	-	-	-	-
Height	dominant	0,136	1	CT/TT vs CC	-2,71	-6,04	0,61
	recessive	0,743	1	TT vs CT/CC	0,44	-2,19	3,07
	codominant	0,523	1	-	-	-	-
	overdominant	0,414	1	CT vs CC/TT	-1,09	-3,68	1,51
	log-additive	0,775	1	-	-	-	-

Covariate	Model	p	Adjusted p	Genotype	Mean Difference	95% CI Lower	95% CI Upper
Body Mass	dominant	0,487	1	CT/TT vs CC	-2,50	-9,29	4,29
	recessive	0,586	1	TT vs CT/CC	1,18	-3,05	5,41
	codominant	0,661	1	-	-	-	-
	overdominant	0,405	1	CT vs CC/TT	-1,75	-5,85	2,35
	log-additive	0,605	1	-	-	-	-
BMI	dominant	0,818	1	CT/TT vs CC	1,59	-11,93	15,12
	recessive	0,467	1	TT vs CT/CC	0,91	-4,12	5,94
	codominant	0,614	1	-	-	-	-
	overdominant	0,407	1	CT vs CC/TT	0,72	-3,45	4,89
	log-additive	0,715	1	-	-	-	-

* Comparisons yielding nominal p-values <0.05 are shown; odds ratios with 95% confidence intervals (CI) were estimated using generalized linear models.

Association analysis of selected variants with muscle injuries

In the association analysis, several models were examined: dominant, recessive, codominant, overdominant, and log-additive. Figure 2 presents p-values (expressed as negative base-10 logarithms) for all models for the main comparison between the group of individuals with previous injuries and the control group. Associations were analyzed using generalized linear models, incorporating age and BMI as covariates. Results of the analysis are presented in Table 7.



The dots on the chart represent the negative base-10 logarithm of the p-values for the association of polymorphism rs8111989 and each model.

Figure 2. Summary chart of the results showing the association of the polymorphism with the occurrence of injuries.

Table 7. Results of associations between the studied variant and muscle injuries

SNP	Comparison	Model	p	Adjusted p	OR	CI Lower	CI Upper
		Dominant	0,8059	1,0000	1,13	0.42	3,08
		Recessive	0,1035	0,5175	0,65	0.38	1,09
	Study vs Control	Codominant	0,2254	1,0000	0,77	0.50	1,18
		Overdominant	0,0814	0,4070	1,59	0,94	2,68
		Log-additive	0,3463	1,0000	0,66	0,28	1,57
		Dominant	0,7099	1,0000	1,50	0,18	12,68
		Recessive	0,8933	1,0000	0,94	0,38	2,32
rs8111989	One injury vs Control	Codominant	0,9694	1,0000	1,01	0,48	2,14
		Overdominant	0,7517	1,0000	1,16	0,47	2,86
		Log-additive	0,9040	1,0000	1,10	0,23	5,22
		Dominant	0,8694	1,0000	1,09	0,39	3,09
		Recessive	0,0492	0,2462	0,57	0,32	0,99
	Multiple injuries vs Control	Codominant	0,1307	0,6536	0,71	0,45	1,11
		Overdominant	0,0417	0,2087	1,78	1,02	3,10
		Log-additive	0,2284	1,0000	0,57	0,23	1,42

* Comparisons yielding nominal p-values <0.05 are shown; odds ratios with 95% confidence intervals (CI) were estimated using generalized linear models.

No significant associations were found between the rs8111989 polymorphism and the risk of muscle injury after applying Bonferroni correction for multiple comparisons. Statistical significance was not observed in any of the analyzed genetic models (dominant, recessive, codominant, overdominant, log-additive) or comparisons (study vs control, 1 injury vs control, multiple injuries vs control).

Discussion

The present study investigated whether the *CKM* rs8111989 polymorphism is associated with the risk of non-contact muscle injury in a cohort of 269 physically active Caucasian adults. Contrary to our initial hypothesis, we did not observe any robust association between rs8111989 and the presence or number of non-contact muscle injuries, regardless of the genetic model applied or the comparison performed (study vs. control, one injury vs. control, multiple injuries vs. control). No statistically significant associations were found in any of the models tested, suggesting that this variant does not have a major independent effect on non-contact muscle injury risk in our cohort. However, these findings should be interpreted with caution and warrant replication in larger samples and in other athletic and physically active populations, ideally with prospective designs and more detailed phenotyping of muscle injuries. Given that injury susceptibility is shaped by multiple biological pathways, including inflammatory processes, muscle and connective tissue integrity, growth and repair, membrane integrity and signaling, vascular function, as well as energy metabolism, *CKM* variation may contribute in combination with other genetic and environmental factors rather than acting as an independent predictor (Leońska-Duniec, 2025). In addition, genetic variation may influence individual trainability, including the possibility of attenuated or adverse adaptations to specific movement patterns or training modalities, as suggested by previous systematic reviews (Petr et al., 2018).

These results are broadly consistent with recent work by Varillas-Delgado and coworkers (2023), who examined the rs8111989 polymorphism in 109 high-performance male football players. In that prospective cohort, *CKM* genotype did not influence overall injury incidence during training or match exposure. However, players with the AG genotype showed a higher frequency of severe injuries and muscle tears than GG or AA homozygotes, hinting at a possible role of rs8111989 in injury severity rather than incidence (Varillas-Delgado et al. 2023). Maestro and colleagues (2022) similarly reported that the AG genotype was more frequent in professional soccer players with musculoskeletal injuries, and particularly in those with severe injuries, compared with non-injured counterparts (Maestro et al., 2022). Our data, obtained in a broader physically active population rather than an elite football cohort, do not replicate a clear heterozygote "risk" pattern, and after correction for multiple comparisons, none of the observed effects reached statistical significance. Taken together, these findings suggest that if rs8111989 does influence muscle injury risk, the effect is modest and may be context-dependent (e.g., specific sport, load profile, or severity definition).

In contrast to the equivocal injury data, the relationship between *CKM* rs8111989 and exercise performance phenotypes is better documented (Ginevičienė et al., 2021; Fedotovskaya et al., 2013). The variant is located in the 3' untranslated region (3' UTR) of the *CKM* gene, a region known to modulate mRNA stability and translational efficiency (Mayr, 2019). Several studies and meta-analyses have shown that the G allele and GG genotype are overrepresented in power or mixed power–endurance athletes, while the A allele is more common among endurance athletes and is associated with more favorable VO□max responses to aerobic training (Chen et al., 2021; Ginevičienė et al., 2021). These data support the notion that rs8111989 contributes to interindividual differences in muscle performance and energy metabolism, even if the underlying molecular mechanisms remain incompletely understood.

From a biological standpoint, it is plausible that a variant affecting *CKM* expression or activity could modulate susceptibility to muscle damage. This gene encodes the muscle-specific isoform, which is densely localized at the M-line of sarcomeres and in proximity to the sarcoplasmic reticulum and mitochondria. This positioning allows CKM to serve as a central hub in the phosphocreatine (PCr) shuttle, rapidly regenerating ATP from ADP using PCr during high-intensity contractions. Efficient CKM activity helps buffer local ATP levels, stabilize ion gradients, and limit the accumulation of ADP, inorganic phosphate, and H□, all of which may contribute to fatigue and structural stress on the muscle fiber (Baker et al., 1994; Guimarães-Ferreira, 2014; Wallimann et al., 1992; Wallimann et al., 2011). In animal models, reductions in CKM activity are associated with impaired force production during high-intensity work and a shift toward more oxidative metabolism, whereas higher CKM activity seems advantageous for short, explosive efforts (Janssen et al., 2003; Steeghs et al., 1997).

The rs8111989 polymorphism, despite being non-coding, is thought to influence *CKM* expression and/or enzyme activity. Some studies suggest that the G variant is associated with lower CKM activity and a more "endurance-like" metabolic profile in skeletal muscle, potentially predisposing carriers to energy depletion and metabolic stress during intense or prolonged exercise (Maestro et al., 2022; Fedotovskaya et al., 2013; Zhou et al., 2006). Others have found that AA homozygotes are overrepresented among individuals with very high post-exercise serum CK responses (high "CK responders") after standardized muscle-damaging protocols, whereas GG homozygotes have been linked to a higher risk of exertional rhabdomyolysis in certain cohorts (Batavani et al., 2017). These apparently contradictory findings highlight that the relationship between rs8111989, CKM activity, and muscle damage is complex and likely modulated by additional genetic and environmental factors.

Conceptually, at least two non-mutually exclusive pathways could link *CKM* variation with non-contact muscle injury. First, intrinsic tissue vulnerability: altered CKM expression may impair ATP buffering during rapid or repetitive contractions, leading to local energy crisis, impaired Ca^{2+} handling, and increased susceptibility of the sarcolemma and cytoskeleton to microtears and Z-line streaming. Recurrent microdamage, if not fully repaired, could accumulate into clinically relevant strains or tears (Proske & Morgan, 2001). Second, exposure-driven risk: genotypes that favor power and sprint performance (e.g., those associated with higher force or rate of force development) may enable athletes to train and compete at higher intensities, thereby increasing mechanical load on muscle-tendon units independently of any intrinsic fragility. In such a scenario, *CKM* variants would influence injury risk indirectly through their impact on performance capacity and behavioral exposure rather than directly via tissue robustness (Leońska-Duniec, 2025; Mijaica et al., 2025).

Our findings do not provide strong support for either mechanism acting in isolation in a general physically active population. The lack of a clear association between rs8111989 and injury status, even in models adjusted for age and BMI, suggests that any effect of this polymorphism on non-contact muscle injury risk is small relative to more proximal determinants such as training load, previous injury, strength imbalance, flexibility, and neuromuscular control (Massidda et al., 2024; Varillas-Delgado, 2024). It is also notable that studies in elite footballers have reported genotype associations primarily with injury severity or etiology (e.g., muscle tear vs. other injuries), rather than with overall incidence, whereas our study classified participants based on the presence and number of self-reported non-contact muscle injuries without detailed grading of severity (Maestro et al., 2022; Varillas-Delgado et al., 2023). This phenotypic difference may partly explain the absence of concordant signals.

Recent research has shifted from single-variant analyses toward polygenic approaches, recognizing that musculoskeletal injury risk is likely influenced by the combined effect of multiple SNPs of small effect (Leońska-Duniec, 2025). Maestro et al. (2022) and Massidda et al. (2024) showed that total genotype scores integrating several "injury-related" polymorphisms, including *ACTN3*, collagen type I alpha 1 chain (*COL1A1*), *COL5A1*, *AMPD1*, and *CKM*, better discriminated between injured and non-injured players than any single variant alone (Maestro et al., 2022; Massidda et al., 2024). In this context, *CKM* rs8111989 may act as one modest contributor within a broader polygenic architecture of muscle injury susceptibility, with its effect size too small to detect reliably in a cohort of our size when considered in isolation.

Several methodological aspects of our study warrant consideration. First, the sample size (n=269) provides reasonable power to detect moderate effects but remains underpowered for small odds ratios (e.g., OR<1.4), especially after correction for multiple testing and stratification by number of injuries. Second, injury history was self-reported and retrospective, which introduces the risk of recall bias and misclassification, particularly for less severe injuries. However, the questionnaire specifically targeted non-contact muscle injuries, which individuals generally recall better than minor contusions or transient soreness. Nevertheless, we could not verify the reported injuries against medical records or imaging, and the retrospective design limited the standardization of injury diagnosis and severity grading. Consequently, some degree of misclassification (e.g., injury type, timing, or recurrence) cannot be ruled out. In addition, the study and control groups differed in key characteristics (notably sex and age distribution), and although age and BMI were included as covariates, residual confounding cannot be fully excluded. Third, the cohort included participants from various endurance-dominant disciplines, with relatively few athletes from pure power sports; if rs8111989 interacts with specific mechanical or metabolic demands (e.g., sprinting and repeated accelerations typical of football), its effect might be diluted in a more heterogeneous physically active sample. Fourth,

we observed deviations from HWE for rs8111989 in the overall sample and in the injury subgroups, while the control group remained in equilibrium. Genotyping was performed in duplicate using a validated TaqMan assay, which reduces the likelihood of systematic genotyping error, but selection bias and chance related to modest subgroup sizes cannot be excluded. Finally, we focused on a single *CKM* polymorphism. Given the regulatory complexity of this gene locus and its integration into broader metabolic networks, future work should examine additional *CKM* variants and their interactions with other genes involved in excitation–contraction coupling, extracellular matrix organization, and inflammation.

Despite these limitations, the study has several strengths. We specifically targeted non-contact muscle injuries, a clinically relevant but comparatively under-investigated phenotype in genetic research, and included a physically active, but not exclusively elite, cohort, which increases the generalizability of the findings beyond professional athletes. The use of standardized genotyping methods and consideration of key covariates (age, BMI, sex) in the association models also strengthens the internal validity of the results.

In summary, our data do not support a major role of the *CKM* rs8111989 polymorphism as an isolated determinant of non-contact muscle injury risk in physically active Caucasians. These findings align with previous reports showing no effect of rs8111989 on overall injury incidence in football players, while still being compatible with a small, context-dependent contribution to injury severity or etiology (Maestro et al., 2022; Varillas-Delgado et al., 2023). Future studies should prioritize larger, prospectively monitored cohorts, more granular injury phenotyping, and polygenic approaches that integrate *CKM* variants into broader genetic profiles. Such work will be essential to clarify whether *CKM* genotyping can meaningfully contribute to individualized injury risk stratification or whether its primary relevance remains confined to modulation of exercise performance rather than injury susceptibility.

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